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CLINICAL REVIEW(S)

CLINICAL REVIEW

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(Proposed) Trade Name Probuphine
Therapeutic Class Partial mu-opioid receptor
agonist
Applicant Titan Pharmaceuticals, Inc.
(Braeburn Pharmaceuticals)

Formulation(s) Subdermal Implant
Dosing Regimen 4 80-mg implants every 6
months
Indication(s) Maintenance treatment of
opioid dependence
Intended Population(s) Clinically stable patients with
opioid dependence, on $\leq$ 8 mg
of a Subutex or Suboxone SL

buprenorphine equivalent

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 204442 for Probuphine (buprenorphine) implant is recommended for approval, exclusively for use in a narrow, defined subpopulation of patients with opioid dependence. The subpopulation includes only those patients with opioid dependence (opioid addiction) who have achieved and sustained clinical stability as evidenced by “behavioral stability,” and have been maintained long-term on a buprenorphine-containing transmucosal product at a dose of no more than 8 mg/day as a Subutex tablet or Suboxone tablet equivalent.

1.2 Risk Benefit Assessment

Probuphine[®] (buprenorphine) implant is an implantable formulation of buprenorphine designed to provide sustained delivery of buprenorphine for six months. For each six-month treatment cycle, four Probuphine implants, or rods, are inserted into the inner surface of the upper arm in an outpatient surgical procedure, and later removed in another in-office procedure at the end of six months.

Benefit Assessment for Probuphine

Buprenorphine in transmucosal form (i.e., sublingual and buccal formulations) is currently approved for the maintenance treatment¹ of opioid dependence. The target dose for maintenance treatment is 16 mg once daily as a Subutex or Suboxone tablet equivalent. Based on a steady-state comparison between Probuphine and the approved treatment at 16 mg/day, the plasma buprenorphine exposure associated with four Probuphine implants (320 mg total buprenorphine hydrochloride) is 31% of the steady-state plasma level associated with sublingual buprenorphine tablets, based on the mean AUC₀₋₂₄, and provides a level that approximates the trough plasma level associated with sublingual buprenorphine tablets 8 mg/day. Transmucosal buprenorphine products increasingly have been targets of abuse, misuse, and diversion, and have been implicated in incidents of accidental pediatric exposure. Because it is implanted surgically, Probuphine is intended to be less vulnerable to these risks.

This New Drug Application (NDA) Resubmission, NDA 204442, is intended to provide evidence of efficacy and safety to support the use of Probuphine for maintenance treatment of opioid dependence, in a subpopulation of patients with opioid dependence, when used as part of a complete treatment program to include counseling and

¹ Most of the transmucosal buprenorphine-containing products are also indicated for initial treatment, or induction.

psychosocial support. This review finds that Probuphine (buprenorphine) implant has a favorable benefit-risk profile for use in a select group of stable opioid-dependent patients. The safety and efficacy data in the NDA submission provide evidence that supports that Probuphine is an appropriate option for patients who have achieved and sustained clinical stability and have been maintained on a transmucosal form of buprenorphine at doses that provide comparable buprenorphine exposures to that yielded by Probuphine (i.e., 8 mg/day or less of a Subutex or Suboxone equivalent). Some clinically stable patients meeting these dosing parameters may prefer to transfer from daily dosing of a transmucosal product to an alternate delivery system, such as Probuphine, which provides sustained, long-term delivery of buprenorphine. Probuphine may offer these patients conveniences such as reduced risk of accidental exposure for children who may be in the home, curtailing the need to take or remember to take medication on a daily basis for long-term and even lifelong maintenance, or the need to travel with bottles, as well as offering an overall measure of discreetness with respect to treatment for their medical condition.

In describing the subpopulation for whom Probuphine may be appropriate, it must be simultaneously emphasized that a favorable risk-benefit profile has not been demonstrated for Probuphine for any other opioid-dependent patients aside from the subpopulation described herein. Probuphine should **not** be used in new entrants to treatment who have not achieved clinical stability, who are better served by a product that can be titrated to effect, and who may require higher doses for blockade.

The initial submission proposed use of Probuphine in a broader population of patients with opioid dependence. However, review of the initial submission concluded that the observed differences between the plasma levels delivered by Probuphine and those associated with the target dose for sublingual buprenorphine, coupled with the results of the clinical trials, suggested that the dose was too low to be effective for new entrants to treatment. Based on this determination, the review team could not conclude that the benefits of treatment outweighed the risks in the studied population of new entrants to treatment, and the application received a Complete Response.

After the Complete Response action, the Applicant conducted a 24-week, double-blind, double-dummy, Phase 3 safety and efficacy trial, PRO-814, to evaluate the efficacy of Probuphine for the maintenance of treatment of opioid dependence in a subpopulation of patients with opioid dependence. PRO-814 specifically enrolled patients who were deemed clinically stable by their treating healthcare provider, and had been successfully maintained on a dose of no more than 8 mg/day of sublingual buprenorphine as a Subutex and Suboxone tablet equivalent. There are many approaches that would be considered reasonable for presenting the findings from this trial. The Agency's preferred analysis concluded that 66% of patients treated with Probuphine could be considered responders vs. 64% of patients receiving usual care, with the lower bound of the 95% confidence interval for non-inferiority at -0.13. This demonstrated that Probuphine is not unacceptably less effective than usual care with sublingual

buprenorphine. Probuphine provides an alternative treatment option for clinically stable patients – and again, clinical stability must be stressed – who may value the aforementioned conveniences that Probuphine offers. Additionally, Probuphine reduces the risk of misuse, abuse, and accidental pediatric exposure; however, these could occur if the implants come out accidentally or are removed, so it must be emphasized that it does not eliminate this risk.

Risk Assessment for Probuphine

The major safety risk for the product is related to procedural safety. Probuphine requires an outpatient surgical procedure for insertion of the implants, or rods, and another in-office procedure for removal of the rods. There are similarities between the outpatient procedures for insertion and removal of Probuphine, and the procedures for the implantable contraceptives, particularly Norplant. Norplant's marketing history has been typified by a number of removal complications, which led to declines in usage. Other serious and severe complications for Norplant have included reported cases of disability, primarily nerve damage, and implant migration, with one case involving migration to the pulmonary vasculature. Subsequent evolutions of implantable contraceptives have yielded products that require fewer implants, offer improved insertion devices, and require simpler procedures compared to Norplant. Nevertheless, complications are still reported, although clinicians providing implanted contraceptive treatment must undergo specific training (in addition to typically being surgically trained).

The Probuphine procedural safety database is limited, especially when placed in context with the pre-approval safety databases for the implantable contraceptives. The procedural-related adverse events observed in the Probuphine clinical trial database were not worrisome overall, although the rate of complications associated with removal, as well as bleeding and infection rates in this small database, is considered relatively high. Because the database is small, however, it should be noted that it may not have allowed for full characterization of procedural safety concerns. It is believed, however, that with appropriate training and if enough procedures are performed, the implanting clinician can become adept at the procedures and safely insert and remove the implants. Additionally, procedural safety will be under monitoring through required implementation of a program of enhanced pharmacovigilance. Finally, a Risk Evaluation and Mitigation Strategy (REMS) will be instituted for this product to mitigate the risk of complications of migration, protrusion, expulsion, and nerve damage associated with the improper insertion and removal of Probuphine and to mitigate the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin.

Overall Risk-Benefit Assessment for Probuphine

In summary, for properly-selected patients, Probuphine offers an alternative to daily transmucosal buprenorphine treatment and is not unacceptably inferior to this treatment. The benefits to the patients, including convenience, privacy, and reduced

risk of theft or accidental exposure of household contacts are augmented by the potential benefits to public health of a reduced risk of misuse, abuse, diversion, and accidental pediatric exposure which are associated with transmucosal buprenorphine products. These benefits outweigh the potential risks of the product, which are primarily associated with the potential for procedural complications. Risks of misuse, abuse, and accidental exposure may occur if the implants come out of the implant site, as a consequence of implant site complications (or, potentially, deliberately). A REMS which ensures that clinicians performing the procedures are appropriately qualified will be aimed at mitigating the risks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Probuphine will have a Risk Evaluation and Mitigation Strategy (REMS) in place 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. The Applicant submitted a proposed REMS as part of the NDA Resubmission. At the time of this writing, the final REMS is still being negotiated, and is being informed by recommendations of the panel of experts at a Psychopharmacologic Drugs Advisory Committee (PDAC) meeting held on January 12, 2016, as well as recommendations from proceduralist and risk analysis experts.

1.4 Recommendations for Postmarket Requirements and Commitments

Postmarket Requirements recommended for Probuphine include the following:

1. Reuse of Previously-Used Sites of Implantation

Because opioid addiction is a chronic, relapsing disorder, it is conceivable that long-term or even life-long pharmacologic treatment will be necessary for some patients. In the Probuphine clinical development program, reinsertion of Probuphine into previously-used anatomic sites has never been formally evaluated. Consequently, the impact that reuse of previously used implant sites may have on procedural complications, e.g., as a result of scarring at the site, is unknown. Currently, there are a maximum of four anatomic sites available for Probuphine administration. Evaluation of previously-used implant sites is necessary to provide more definitive guidance about the use of Probuphine after a maximum of four treatment cycles.

2. Identification of Alternate Anatomic Sites

Again, as opioid addiction is a chronic, relapsing disorder, long-term or even lifelong treatment may be necessary for some. Accordingly, it is important to identify additional anatomic sites where Probuphine can be administered, to prevent treatment constraints as a result of diminishing available sites, if continued treatment is desired.

3. Procedural Safety Enhanced Pharmacovigilance Program

The Probuphine procedural safety database is small compared to other implantable drug products. Additionally, the training program includes a meat model; however, the insertion and removal procedures are not readily modeled. A dedicated pharmacovigilance program is recommended to garner procedural safety information on insertions and removals to augment the available safety information, and to better characterize the procedural safety profile of the Product in practice.

4. QT prolongation

As described in the April 30, 2013, Complete Response Letter, the Applicant is again being required to evaluate the effect of Probuphine on cardiac conduction.

2 Introduction and Regulatory Background

Probuphine[®] is a combination product consisting of drug and device components. The drug component refers to the subdermally implantable formulation of the active ingredient buprenorphine hydrochloride (buprenorphine) in a solid matrix of ethylene vinyl acetate (EVA) polymer molded into implants, or rods. The device component is the applicator that is used for subdermal insertion of the implants into the inner surface of the upper arm. The packaging of the implants and applicator is also considered an element of the device component.

Probuphine is intended to be used for maintenance treatment of opioid dependence in a subpopulation of patients with opioid addiction. Specifically, it is intended to be used in those patients with opioid dependence who have achieved and sustained clinical stability (“behavioral stability”), and have been maintained on low-to-moderate doses of a buprenorphine-containing transmucosal product², i.e., no more than 8 mg/day of a Subutex or Suboxone sublingual (SL) tablet equivalent. Four individual Probuphine implants, or rods, are administered per treatment cycle and are designed to provide sustained delivery of buprenorphine for six months. The Probuphine New Drug Application (NDA) Resubmission, the subject of this review, is intended to support this narrow indication that restricts use of Probuphine to a circumscribed subpopulation.

Braeburn Pharmaceuticals, on behalf of Titan Pharmaceuticals, the Applicant, resubmitted the Probuphine NDA (NDA 204442) on August 27, 2015. The original Probuphine NDA was initially submitted on October 31, 2012. The Probuphine NDA received a Complete Response, upon review of the initial submission, because of concerns about efficacy of the product for a broad population of adults with opioid dependence, and safe use of the product as it relates to the insertion and removal procedures required for drug administration. The NDA Resubmission is intended to support a limited indication, relative to the initial submission, for use of Probuphine in

² Buprenorphine-containing products for opioid addiction treatment, administered by sublingual and/or buccal routes, distinct from an enteral route of administration, are collectively referred to as having transmucosal routes of administration, and called buprenorphine-containing transmucosal products.

clinically stable patients with opioid dependence, on low-to-moderate doses of a buprenorphine-containing transmucosal product, and to address the outstanding concerns regarding insertion and removal of the implants.

The Probuphine NDA (NDA 204442) is a 505(b)(2) application³, relying in part on the Agency's previous findings of safety and efficacy for Subutex SL tablets (NDA 020732) and Suboxone SL tablets (NDA 020733), which are indicated for treatment and maintenance treatment of opioid dependence, respectively. Both Subutex and Suboxone have been removed from the US market by the manufacturer, but generics remain available. Agency determinations that Subutex and Suboxone were not withdrawn from the market for reasons of safety or effectiveness were announced on February 13, 2015 and June 6, 2013, respectively.

The present Probuphine NDA Resubmission is the first submission following the Complete Response action for the NDA, and represents the second review cycle for this application. For the purposes of this review, the original submission in October 2012 will be referred to as the initial submission, or first cycle review, interchangeably, while the present August 27, 2015, submission will be referred to as the Resubmission, or second cycle review, also interchangeably.

2.1 Product Information

Probuphine[®] (buprenorphine implant) is a subdermal implantable formulation of the active ingredient buprenorphine hydrochloride (buprenorphine) in a solid matrix of ethylene vinyl acetate polymer (EVA) shaped into implants or rods. Probuphine is formulated using the ProNeura drug delivery technology.

The drug component of the drug product is the rod, or implant, which each contain 80 mg of buprenorphine hydrochloride USP (i.e., 74.2 mg of buprenorphine, equivalent to 80 mg of buprenorphine hydrochloride) in EVA copolymer matrix. The matrix formulation of the implants results in a steady-state delivery of buprenorphine that maintains a stable plasma level of the drug for 6 months.

Each Probuphine implant measures 26 mm in length and 2.5 mm in diameter, with a total weight of 112 mg. Implants are individually packaged into laminated foil pouches. The pouches are terminally sterilized using gamma irradiation. The immediate container closure for each implant is a laminated foil pouch. The packaging configuration with implants and applicators is four individually pouched implants in a carton with an applicator. The implants will be labeled for storage at 15-30°C (57-86°F).

³ A 505(b)(2) application is one for which one or more of the investigations relied upon by the Applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" (21 U.S.C. 355(b)(2)). <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm079345.pdf>

Four implants are administered subdermally in the inner side of the patient's upper arm per six-month treatment cycle. Probuphine must be removed by the end of the sixth month and may be replaced by new implants at the time of removal, if continued treatment is desired. The new implants should be inserted into another location that has not been previously used, on the opposite arm, if available.

Buprenorphine, the active ingredient in Probuphine, is a partial agonist⁴ at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect. The agonist effects of buprenorphine increase linearly with increasing doses of the drug until at moderate doses they reach a plateau and no longer continue to increase with further increases in dose—the “ceiling effect.” Thus, buprenorphine carries a lower risk of certain adverse effects compared to full opioid agonists.

Buprenorphine has dose-dependent activity. At low doses, buprenorphine produces sufficient agonist effect to enable individuals with opioid addiction to discontinue use of opioids without experiencing withdrawal symptoms. In fact, in high doses and under certain circumstances, buprenorphine can actually block the effects of full opioid agonists, and can precipitate withdrawal symptoms if administered to an individual with opioid addiction and physical dependence while a full agonist is in the bloodstream.⁵

It should be noted also that the dose of buprenorphine necessary to treat symptoms of withdrawal is much lower than the dose necessary to block the effects of exogenous opioids. The dose of sublingual buprenorphine recommended in labeling is based on the blocking dose, in order to provide both the reinforcing agonist effects and to provide disincentive to continue illicit opioid use.

Probuphine clinical trial data suggest that Probuphine may provide a dose sufficient to palliate the symptoms of withdrawal and potentially the subjective urge to use illicit opioids, but not a dose that blocks exogenous opioids. Therefore, it is conceivable that Probuphine is not appropriate for those newly initiating treatment, as was evidenced by the observation that many patients persisted in regular drug use while on Probuphine in the clinical trials supporting the first cycle review that evaluated Probuphine for a broad population. In contrast, Probuphine may be appropriate for clinically stable patients on doses of transmucosal buprenorphine comparable to, or lower than, the amount of buprenorphine provided by Probuphine, who are at the stage in treatment where behavioral changes have been ingrained and the blocking properties may not be as fundamental for management.

⁴ This means that although buprenorphine is an opioid, and thus can produce typical opioid agonist effects and side effects such as euphoria and respiratory depression, its maximal effects are less than those of full agonists like heroin and methadone. <http://buprenorphine.samhsa.gov/about.html>

⁵ <http://buprenorphine.samhsa.gov/about.html>

Product Information Summary

Trade name:	Probuphine®
Drug established name:	buprenorphine implant
Chemical name:	21-Cyclopropyl-7 α -[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14- <i>endo</i> -ethano-6,7,8,14-tetrahydrooripavine hydrochloride
Drug class:	Mu-opioid receptor partial agonist and kappa-opioid receptor antagonist
Proposed indication:	Maintenance treatment of opioid dependence (Although maintenance treatment of opioid dependence is the proposed indication, the more appropriate indication given the population studied in PRO-814 is maintenance treatment of opioid dependence in opioid-dependent patients who have achieved and sustained clinical stability and have been maintained on a transmucosal form of buprenorphine at a dose of no more than 8 mg/day [$\leq$ 8 mg/day] as a Subutex SL tablet or Suboxone SL tablet equivalent.)
Dose and Administration:	• Four 80-mg implants for six months • Implants are to be inserted into the inner side of the patient's upper arm by a qualified and trained health care professional during an in-office surgical procedure • Implants are to be removed by a qualified and trained health care professional six months after insertion of the four implants in another in-office surgical procedure
Age groups:	• Adults only ○ Full waiver granted for pediatric studies

2.2 Tables of Currently Available Treatments for Proposed Indications

CURRENTLY AVAILABLE TREATMENTS FOR OPIOID DEPENDENCE			
Generic/Chemical Name	Trade Name	Sponsor(s)	Dosage form(s)
Buprenorphine	Subutex and generics (n.b., Subutex no longer marketed by manufacturer in US)	Reckitt Benckiser	• Sublingual tablet
Buprenorphine/naloxone	Suboxone and generics (n.b., Subutex no longer marketed by manufacturer in US)	Reckitt Benckiser	• Sublingual tablet
Buprenorphine/naloxone	Suboxone	Reckitt Benckiser	• Sublingual and buccal film
Buprenorphine/naloxone	Zubsolv	Orexo	• Sublingual tablet
Buprenorphine/naloxone	Bunavail	Biodelivery Sciences International	• Buccal film
Methadone HCl	Methadose (also generic) Dolophine (also generic) Diskets	Mallinckrodt Roxane	• Oral solution • Bulk powder • Tablet • Dispersible tab • Oral concentrate
Naltrexone HCl	ReVia (also generics)	Duramed	• Tablet
Naltrexone HCl	Vivitrol	Alkermes	• Suspension for intramuscular injection

2.3 Availability of Proposed Active Ingredient in the United States

Buprenorphine in sublingual tablet and sublingual and buccal film formulations is approved in the US for treatment of opioid dependence. Buprenorphine is available as a sublingual tablet (Subutex)⁶ and currently generic formulations are being marketed. Buprenorphine is also available in combination with naloxone as a sublingual tablet (Suboxone⁷ and Zubsolv) and generic formulations of Suboxone are also being marketed. Buprenorphine is available in combination with naloxone as a film formulation (Suboxone and Bunavail). Parenteral and transdermal formulations of buprenorphine have been approved for analgesia.

⁶ Subutex SL tablets are no longer marketed.

⁷ Suboxone SL tablets are no longer marketed.

2.4 Important Safety Issues With Consideration to Related Drugs

Buprenorphine is a partial mu-opioid receptor agonist having mixed agonist-antagonist properties. Important safety issues to consider with respect to related drugs are those safety issues observed in association with pure opioid agonists. Buprenorphine produces typical opioid agonist effects, but they are limited by a ceiling effect. Thus, buprenorphine is not anticipated to carry with it the same risks of overdose as seen with other opioid agonists, although it can cause respiratory depression and has been associated with fatal overdose when combined with other CNS depressants (*in particular, benzodiazepines*). Key safety concerns related to the drug substance buprenorphine have included hepatic effects, allergic reactions, and potential cardiac conduction effects. The sublingual drug products have been subject to abuse and misuse, and have been implicated in cases of accidental pediatric poisonings.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Initial Probuphine NDA Submission – October 31, 2012

The Probuphine NDA was initially submitted on October 31, 2012 to support an indication of maintenance treatment of opioid dependence. The application was supported by two Phase 3 efficacy and safety trials in new entrants to treatment that were near identical in design. Briefly, these new entrants initially received four implants after first undergoing treatment with sublingual buprenorphine tablet to reach a target dose of 12–16 mg/day for three consecutive days. There was an option for a dose increase with a fifth rod. Supplemental buprenorphine use was permitted, and used in the treatment failure definition. Subjects were defined as experiencing “treatment failure” and withdrawn from the trial if they met protocol-specified criteria defined by the amount of supplemental buprenorphine dosing given in response to scores on measures of withdrawal or “craving,” or investigator discretion. The criteria for providing supplemental doses did not include ongoing drug use, to which the investigators were blind. There were separate definitions for “treatment failure” (which resulted in removal from the study) and the assessment of “treatment response.” Although used to define treatment failure, supplemental use was not taken into account when determining treatment response, which was assessed based only on drug use pattern, and did not include the measures of withdrawal or “craving,” or supplemental buprenorphine use.

The efficacy evaluation was based on urine toxicology and self-report. Urine toxicology was collected three times per week to improve detection. The window of detection for many opioids is up to three days, so this frequency in urine sampling helps to avoid urine samples being classified as negative, simply because use of an illicit opioid was outside of the detection window for a particular urine sample. Urine toxicology findings were taken along with self-report of illicit opioid use occurring around the time the urine samples were collected to adjudicate a urine sample as positive or negative. If either the urine toxicology or self-report was positive, the sample was considered positive. Investigators were blinded to urine toxicology findings during the trial.

Because the goal was to evaluate individual treatment response, a response profile was used for the analysis. In this case, the cumulative distribution function (CDF), of the percent of opioid-negative urines was evaluated to assess treatment response. Missing urines were considered positive for the purposes of the analysis. Once withdrawn from the study, patients' urine samples were considered positive from the point of discontinuation and on. At the same time, a high rate of placebo dropout could be anticipated for this trial. New entrants to treatment reached a target dose of SL buprenorphine 12 to 16 mg/day, and placebo patients were then abruptly discontinued in being switched to placebo. It is anticipated that these subjects would likely need supplemental buprenorphine in this context, which, in turn, was used to determine treatment failure. The placebo "treatment failures" resulting in placebo dropout, would likely drive a high rate of opioid-positive urines among this arm, because after dropout, all the urines were considered positive after the point of dropout.

As noted above, treatment failure was defined entirely by supplemental use, but urine toxicology samples (which were blinded) were not accounted for when determining whether supplemental buprenorphine was required. It seems likely that had investigators been aware of the continued use of illicit opioids observed by the subjects who remained on study, supplemental buprenorphine use is likely to have been considered warranted and many of these patients would have met the protocol-specified criteria for "treatment failure." This feature of study design rendered interpretation of the reported rate of "treatment failure" essentially meaningless. Moreover, the great majority patients who remained in the study persisted in regular drug use throughout the six month treatment period. Further details about the results of the trials are in the original reviews of the application.

The application received a Complete Response on April 30, 2013. The clinical benefit of the minor changes in drug-taking behavior – a surrogate endpoint – observed in the trials had not been established. In short, the buprenorphine exposures associated with Probuphine, which are approximately one-third that yielded by the target maintenance dose of the transmucosal products, appeared too low, particularly if the product was intended for use in new entrants to treatment. There were also concerns about the comprehensiveness of the safety evaluation for the insertion and removal procedures, the training program, which had not been validated, and the associated proposed Risk Evaluation and Mitigation Strategy. The Applicant was advised to evaluate higher doses of Probuphine and/or conduct an opioid blockade study, and to conduct a validation study for the training program.

Post-Action Discussions and Development Activities

A Post-Action Meeting was held with the Applicant on November 19, 2013. Over the course of the discussions, the Applicant, in acknowledging that four Probuphine implants yield buprenorphine concentrations similar to those observed with 4 to 8 mg/day of sublingual buprenorphine based on average exposure (e.g., mean AUC

values) or concentration, proposed a revised indication for Probuphine, namely *for the treatment of patients stabilized on sublingual buprenorphine at doses of 8 mg/day or less*. The Applicant proposed identifying a population for whom the Probuphine dose may be suitable, in lieu of evaluating higher doses of Probuphine, or demonstrating the product's opioid blockade properties. It should be noted that the study results for the initial submission were discussed at a meeting of the Psychopharmacologic Drugs Advisory Committee on March 21, 2013, at which time, 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. The Division agreed that, with adequate support, the revised indication may be suitable for a subset of patients, particularly bearing in mind the public health benefit that Probuphine could potentially offer related to decreased misuse, abuse, and accidental pediatric exposure. The Division deemed some level of flexibility to be warranted in light of the growing public health crisis surrounding opioid addiction and abuse.

Following the Post-Action meeting and a subsequent follow-up teleconference, there were a series of communications regarding the design and conduct of Study PRO-814, the trial designed and conducted by the Applicant to assess the efficacy of Probuphine in this new limited population.

2.6 Other Relevant Background Information

PRO-814 is entitled "A Randomized, Double-Blind, Double-Dummy, Active-Controlled Multicenter Study of Adult Outpatients With Opioid Dependence Transitioned From a Daily Maintenance Dose of 8 mg or Less of Sublingual Buprenorphine or Buprenorphine/Naloxone to Four Probuphine® Subdermal Implants." PRO-814 was a double-blind, double-dummy, active control (generic sublingual buprenorphine tablet), non-inferiority trial comparing four Probuphine implants to sublingual buprenorphine for maintenance treatment in adult patients with opioid dependence who are considered clinically stable, and maintained on low-to-moderated doses of a buprenorphine-containing transmucosal product, i.e., no more than 8 mg/day as a Subutex or Suboxone tablet equivalent.

Certain aspects of the study design for PRO-814 were novel. Customarily, studies of drugs to treat opioid addiction have featured frequent visits for collection of urine toxicology tests to reflect the window of detection for opioid use to ascertain abstinence from illicit drug use. However, because stable patients already in established buprenorphine treatment would not ordinarily be seen thrice-weekly, or possibly, 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, and that less-frequent urine toxicology testing could be used, along with patient self-report of use, to determine whether patients returned to illicit drug use. Although it might be argued that a passive-compliance formulation such as Probuphine 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.

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.

Because of these uncertainties regarding a non-inferiority design in this setting, the Division informed the Applicant that the determination regarding whether a study meeting the proposed primary endpoint, augmented by the secondary endpoints, would provide adequate evidence of efficacy to support a label for “the treatment of patients stabilized on sublingual buprenorphine at doses 8 mg/day or less with four Probuphine subdermal implants” would be a matter for review. The Applicant was further informed that the review would quantitatively and qualitatively assess the analysis of the primary endpoint and the clinical meaningfulness of the trial findings to make such a determination.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Inspection of the case report forms and line listings by the reviewer revealed no major concerns about data quality or integrity. Overall, the submission was organized and generally did not present any major barriers to review. When needed, clinical information requests were sent to the Applicant in order to clarify information in the submission and to provide new information to facilitate the review. Datasets were not always assembled in a fashion that was intuitive, but overall, were in a format that allowed for the reviewer to evaluate and reproduce findings.

3.2 Compliance with Good Clinical Practices

According to the Applicant, PRO-814, the main trial supporting this application, was conducted in accordance with the International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) guidelines and all applicable regulations, including, where applicable, the Declaration of Helsinki. The Applicant also documented that the trial was conducted in keeping with applicable national and local laws and regulations.

The Office of Scientific Investigations (OSI) was consulted to inspect four sites: Site 2, Site 5, Site 7, and Site 11. These sites had a large number of protocol violations reported in the submission pertaining to inappropriate handling of the (infrequent) urine samples for this trial. Additionally, supplemental buprenorphine use was concentrated among two sites, i.e., Site 7 and Site 11, which contributed a disproportionate number of patients who required frequent and ongoing supplemental sublingual buprenorphine relative to the other 19 sites. Ongoing and frequent use of supplemental sublingual buprenorphine was not anticipated for this clinically stable population, and called into question the suitability of the candidates enrolled into the trial at those two sites. OSI reported that there were no significant findings on inspection. Three of the sites will receive NAIs, or No Action Indicated assessments. One site, Site 7, will receive a VAI, or Voluntary Action Indicated. According to the OSI Review, a Form FDA 483 was issued for this site for minor GCP deficiencies.

3.3 Financial Disclosures

The Applicant's submission included the completed "Certification: Financial Interests and Arrangements of Clinical Investigators" form (Form FDA 3455). The Applicant indicated that the investigators at each site are certified as having no Financial Arrangement as defined in 21 CFR 54.2, except for two sub-investigators, (b) (6) who received payments in excess of \$25,000. (b) (6) received payment for services rendered (b) (6). In response to an Information Request, the Applicant provided updated financial disclosure information (b) (4)

[REDACTED]

As such, these significant payments are not anticipated to materially impact interpretation of the efficacy findings, although it could conceivably have an impact on procedural safety reporting. (b) (6)

Procedural complications appear to have been documented for the procedures performed.

Refer to the completed Clinical Investigator Financial Disclosure Review template form in the Appendix of this review for further details.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the human factors validation study, and information related to labels and labeling to assess their suitability from a medication error perspective. DMEPA considered the following items for their review: Product Information/Prescribing Information; Previous DMEPA Reviews; the Human Factors Study; ISMP Newsletters; ISMP Newsletters; FDA Adverse Event Reporting System (FAERS); DMEPA Information Request and Applicant's Response; Human Factors Deficiencies in Complete Response Letter; Labels and Labeling; Prescribing Information. Based on their review, DMEPA provided comments on the proposed Instructions for Use (IFU), proposed labeling, and proposed Training Program and Slides, and associated training items.

4.1 Chemistry Manufacturing and Controls

The Probuphine product consists of drug and device components.

The Chemistry, Manufacturing, and Controls (CMC) Reviewer concluded that the Applicant provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The referenced DMF 16419 and (b) (4) were found adequate to support the NDA. The CMC Reviewer also reported that the application received an "acceptable" recommendation from the Office of Compliance on January 28, 2016. The CMC Reviewer determined that the NDA is recommended for approval from the CMC perspective.

The Center for Devices and Radiologic Health (CDRH)/Office of Drug Evaluation (ODE) was consulted to review the device component of the product, specifically for an assessment of the acceptability of any additional changes to the device since the Complete Response action in April 2013. CDRH had been consulted during the initial review cycle, and found the performance data adequate to support approval at that time. For this NDA Resubmission, through interaction with the Applicant via Information Requests, device-related review issues that were identified were adequately resolved, and the CDRH consultant recommends that there is adequate information for approval.

Refer to the respective CMC and CDRH reviews for further details.

4.2 Clinical Microbiology

No new clinical microbiology data were included in this NDA Resubmission. The CMC Review refers to the earlier product quality microbiology review for the evaluation of microbiology.

4.3 Preclinical Pharmacology/Toxicology

On review of the initial NDA submission, the Nonclinical Review Team recommended approval of the NDA from a nonclinical pharmacology/toxicology perspective, based on the information submitted at that time. With the present submission, the Applicant provided data to address a nonclinical comment in the April 30, 2013, Complete Response Letter, related to labeling, specifically for the pregnancy, carcinogenicity, and fertility sections of labeling, and the need for justification of the safety margins for Probuphine relative to the reference sublingual label. The Nonclinical Reviewer reviewed the submitted nonclinical bridging studies to support nonclinical labeling of Probuphine doses for pregnancy, carcinogenicity, and fertility. Refer to the Nonclinical Pharmacology/Toxicology Review for the NDA Resubmission for details.

4.4 Clinical Pharmacology

No new clinical pharmacology information was submitted with this NDA Resubmission. The premise underlying this Resubmission is that four Probuphine implants yield buprenorphine plasma exposures that are comparable to the plasma exposure levels associated with 8 mg/day or less of sublingual buprenorphine (as a Subutex or Suboxone tablet equivalent).

4.4.1 Mechanism of Action

Mechanism of action information for the buprenorphine drug substance in the implantable formulation, Probuphine, will derive from the labels for Subutex and Suboxone tablets, the reference products.

4.4.2 Pharmacodynamics

Information on pharmacodynamics for the buprenorphine drug substance in the implantable formulation, Probuphine, will derive from the labels for Subutex and Suboxone tablets, the reference products.

In addition to the pharmacodynamic properties currently described in labeling for the reference products, and in understanding Probuphine's specific pharmacologic activity,

it should be noted that the pharmacodynamic effects exhibited by buprenorphine are dose-dependent. Buprenorphine produces both *withdrawal suppression, at low doses, and blockade of the effects of exogenously-administered opioids at much higher doses*. While research is ongoing to precisely correlate buprenorphine's distinctive actions with buprenorphine plasma exposure levels, and by extension, dose, evidence to date from the published literature suggests that doses in the range of 2 to 4 mg of buprenorphine provide relief of withdrawal symptoms. Conversely, doses at least as high as 16 mg are needed for buprenorphine's blockade properties to be exhibited. Notably, for new entrants to treatment, 16 mg is the target daily dose, which may reinforce declines in drug-taking behavior.

Studies in literature of the relationship between plasma buprenorphine levels, opioid receptor occupancy, and the clinical effects of withdrawal suppression and blockade of clinically relevant doses of opioids of abuse feature heterogeneity in the challenge doses used, the interpretation of the term "blockade" (to mean either any detectable attenuation of agonist effect, or complete prevention of agonist effect), and in the doses, route, and timing of the buprenorphine administration. However, although the literature does not support a consistent conclusion about the PK/PD relationships, and the plasma level necessary to provide effective blockade of exogenous opioids at clinically-relevant doses has not been definitively established, it appears likely to be in the range of 2–3 ng/ml.^{8,9 10,11, 12}

Additionally, the literature confirms that the relationship between buprenorphine plasma levels and the effects of opioid blockade are different from the relationship between buprenorphine levels and withdrawal suppression. A recent article¹³ reviewed the scientific data on buprenorphine-induced changes in mu-opioid receptor (μ OR) availability, pharmacokinetics and clinical efficacy. The authors concluded that "Opioid withdrawal suppression appears to require $\leq 50\%$ μ OR availability which is associated with buprenorphine plasma concentrations ≥ 1 ng/ml; for most patients, this may require single daily buprenorphine doses of 4 mg or lower divided doses. Blocking opioid reinforcement requires $< 20\%$ μ OR availability, or BUP plasma levels ≥ 3 ng/ml for most individuals, this may require single daily BUP doses > 16 mg..."

⁸ Comer SD, Walker EA, Collins ED. Buprenorphine/naloxone reduces the reinforcing and subjective effects of heroin in heroin-dependent volunteers. *Psychopharmacology* 2005; 181 (4): 664-675

⁹ Strain EC, Walsh SL, Bigelow GE. Blockade of hydromorphone effects by buprenorphine/naloxone and buprenorphine. *Psychopharmacology* 2002; 159:161-166.

¹⁰ Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE. Buprenorphine: dose-related blockade of opioid challenge effects in opioid dependent humans. *J Pharmacol Exp Ther.* 1988 Oct; 247(1):47-53.

¹¹ Schuh KJ, Walsh SL, Stitzer ML. Onset, magnitude and duration of opioid blockade produced by buprenorphine and naltrexone in humans. *Psychopharmacology (Berl)*. 1999 Jul; 145(2):162-74.

¹² Mello NK, Mendelson JH, Kuehnle JC. Buprenorphine effects on human heroin self-administration: an operant analysis. *J. Pharmacol. Exp. Ther.*, 223 (1982), pp. 30–39

¹³ Greenwald MK, Comer SD, Fiellin DA. Buprenorphine maintenance and mu-receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. *Drug And Alcohol Depend.* 2014 November 1; 0: 1-11.

To the extent that blockade of exogenous opioids plays a role in efficacy for addiction treatment, it must be noted that Probuphine is not expected to provide this effect. However, lower plasma levels are required to provide relief of withdrawal symptoms. The exposure provided by Probuphine may be sufficient for this purpose in some patients.

4.4.3 Pharmacokinetics

Buprenorphine in transmucosal form is currently approved for the maintenance treatment of opioid dependence. The target dose for maintenance treatment is 16 mg once daily as a Subutex or Suboxone tablet equivalent. Based on a steady-state comparison between Probuphine and the approved treatment at 16 mg/day, the plasma buprenorphine exposure associated with Probuphine implants [320 mg total buprenorphine] is 31% of the steady-state plasma level associated with SL buprenorphine tablets [16 mg once daily], based on the mean AUC₀₋₂₄, and provides a level that approximates the trough plasma level associated with SL buprenorphine tablets 8 mg/day.

5 Sources of Clinical Data

For this NDA Resubmission, a single clinical trial, PRO-814, was conducted and included in this submission to provide efficacy data (evidence) to support the use of Probuphine in clinically stable patients with opioid dependence, who are maintained on 8 mg/day or less of a buprenorphine-containing transmucosal product. A human factors evaluation was undertaken to validate the training program for the insertion and removal procedures.

The original submission included two Phase 3 safety and efficacy trials, PRO-805 and PRO-806, two safety extension trials, PRO-807 and PRO-811, that were extension trials to PRO-805 and PRO-806, respectively. There were also two clinical pharmacology studies, TTP-400-02-01, a pharmacokinetic trial evaluating 2 rods and 4 rods, and PRO-810, a comparative bioavailability study that compared 4 Probuphine implants to Suboxone (buprenorphine/naloxone) sublingual tablets (16 mg). Safety data from the two Phase 3 clinical trials, the two safety extension studies, and the clinical pharmacology studies were combined with the safety data for PRO-814 and comprise the Probuphine safety database for this NDA Resubmission. The Human Factors Evaluation provides data related to procedural safety.

5.1 Tables of Studies/Clinical Trials

PRO-814 is the trial the Applicant is using to provide efficacy and safety data to support the use of Probuphine in clinically stable patients with opioid dependence on low-to-moderate doses of a buprenorphine-containing transmucosal product.

Probuphine studies and trials completed to support the initial submission combined with the PRO-814 trial to form the Probuphine safety database.

Table 1 Table of Probuphine Studies/Clinical Trials

Study No. & Title	Design/ Status	Study Treatments	Population	Duration	Location/ # of Centers
Probuphine NDA Resubmission (2nd Review Cycle)					
PRO-814 A Randomized, Double-Blind, Double-Dummy, Active-Controlled Multicenter Study of Adult Outpatients With Opioid Dependence Transitioned From a Daily Maintenance Dose of 8 mg or Less of Sublingual Buprenorphine or Buprenorphine/Naloxone to Four Probuphine® Subdermal Implants	P3, DB, double-dummy, active-controlled (SL buprenorphine tablets), non-inferiority trial First subject enrolled: June 26, 2014 Last subject completed: May 18, 2015	<u>Group A:</u> SL buprenorphine tablets 8 mg/day or less & 4 placebo implants <u>Group B:</u> 4 Probuphine subdermal implants & placebo SL tablets <u>All:</u> supplemental SL BPN as needed	N=177 opioid-dependent subjects who were clinically stable on 8 mg/day or less of a buprenorphine-containing transmucosal products • SL BPN (Group A) n = 89 • Probuphine (Group B) n=87	24 weeks	US 21 centers
Initial Probuphine NDA Submission (1st Review Cycle)					
P3 S&E Trials					
PRO-805 A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study of Probuphine in Patients with Opioid Dependence	P3, DB, R, PC trial with 2:1 randomization Probuphine to placebo Initiated: Apr 2, 2007 Completed: Jun 19, 2008	4 Probuphine subdermal implants (80 mg buprenorphine per implant) (5 if protocol-specified criteria met) 4 Placebo subdermal implants (5 if protocol-specified criteria met) <u>All:</u> supplemental SL BPN as needed	N = 163 opioid-dependent subjects • Probuphine: n= 108 • Placebo: n=55 Median age: 35 (19 – 62) Gender: 69% male	Single dose; 24 weeks	US 23 centers
PRO-806 A Randomized, Placebo and Active-Controlled, Multi-Center Study of Probuphine in Patients	P3, DB, R, PC and OL AC trial with 2:1:2 randomization Probuphine, placebo, SL	4 Probuphine subdermal implants (5 if protocol-specified criteria met)	N = 301 opioid-dependent subjects (301 enrolled; 287 received study drug)	Single dose; 24 weeks	US 20 centers

Clinical Review
 Rachel Skeete, MD, MHS
 NDA 204442 (Class 2 Resubmission)
 Probuphine (buprenorphine) implant

Study No. & Title	Design/ Status	Study Treatments	Population	Duration	Location/ # of Centers
with Opioid Dependence	BPN Initiated: Apr 22, 2010 Completed: May 12, 2011	4 Placebo subdermal implants (5 if protocol-specified criteria met) SL BPN 12–16 mg once daily All: SL BPN as needed	• Probuphine: n= 114 • Placebo 4 implants: n=54 • SL BPN n=119 Median age: 33 (18 – 60) Gender: 61% male		
P3 Extension Trials					
PRO-807 (PRO-805 extension)	Open-label; Extension Initiated: Mar 20, 2008 Completed: Feb 19, 2009	4 Probuphine subdermal implants (5 if protocol-specified criteria met) All: SL BPN as needed	N = 62 opioid-dependent subjects Median age: 37 range (20 – 62) Gender: 71% male	Single dose; 24 weeks	US 15 centers
PRO-811 (PRO-806 extension)	Open-label; Extension 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 Median age: 37 (19 – 61) Gender: 66% male	Single dose; 24 weeks	US 18 centers
Clinical Pharmacology Studies					
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 • 2 Probuphine implants n=6 • 4 Probuphine implants n=6 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	16 mg SL buprenorphine; cross-over to 4	N = 9 opioid-dependent subjects	Single dose 8 weeks	US 1 center

Study No. & Title	Design/ Status	Study Treatments	Population	Duration	Location/ # of Centers
	bioavailability of Probuphine implants versus sublingual buprenorphine tablet Initiated: Sep 29, 2008 Completed: Dec 23, 2008	Probuphine implants (80 mg buprenorphine per implant, single dose, subdermal insertion) All subjects: sublingual buprenorphine as needed	Median age: 44 (25 – 63) Gender: 67% male		

Human Factors Evaluation

A Human Factors evaluation of the training program for the Probuphine insertion and removal procedures was conducted under the protocol entitled “Human Factors Evaluation of the Probuphine Subdermal Implant Training Program.” The Human Factors evaluation was undertaken to address a deficiency outlined in the April 30, 2013, Complete Response Letter. The Applicant was to demonstrate that the training program is adequate to impart the necessary skills to a variety of providers, who may not all have surgical experience (non-proceduralists) as well as to validate the proposed training program’s design and materials.

Although the original intent was to validate the training program and subsequently market the product under a clinical model where both proceduralists and non-proceduralists could perform the insertion and removal procedures, based on data observed across several studies with the non-proceduralists, the Applicant decided to only request approval for proceduralists. The Applicant considered physicians and midlevel providers to be “proceduralists” if they had completed a medical residency or fellowship in a “procedural specialty” and currently practiced in that specialty, or if they had performed a sterile procedure in the last 3 months. The Applicant explained that it was determined that non-proceduralists likely require both more hands-on training (mostly due to their lack of basic surgical experience) and supervised procedures before being able to perform successfully on their own.

The Applicant initially undertook formative human factors efforts, including clinical trial user interviews/ethnography, heuristic evaluations, risk analysis, and an Instructions for Use (IFU) and video comprehension study, to inform and refine the training program and procedures, prior to the summative validation study. For the summative human factors study, a total of 15 proceduralists completed the training program and validation study. The study components included the training, the IFU, quick guides¹⁴ and the

¹⁴ The Quick Guides, two guides, one each for insertion and removal, are intended to support users in following the required order of steps during the insertion and removal procedures. These quick guides were each a single sheet of paper that contained step-by-step instructions with no graphics. These quick guides pulled from the same language included in the IFU.

insertion and removal kit components. There were two primary procedures of interest, each of which has several subtasks: 1) Insertion, and 2) Removal. The Applicant trained proceduralists on the proper insertion and removal technique for Probuphine using pork tenderloins to simulate the human arm. The training program consisted of: classroom lecture/presentation; Master Trainer demonstration; practice session with time for questions and answers; and certification exam (consisting of multiple choice questions only, and no final evaluation of participant performance). Upon completion of the training program, participants were given a one-hour break to simulate a training decay period (e.g., for Probuphine, six months would elapse between the insertion and removal procedures, and the training would likely have been taken prior to the insertion procedure, long before the proceduralist would be performing a removal procedure). Participants then independently performed the insertion and removal procedures without assistance from trainers or study moderators, and were evaluated on their performance of tasks.

5.2 Review Strategy

For the efficacy evaluation, data from the Phase 3, double-blind, double-dummy, active-controlled, safety and efficacy, non-inferiority trial, PRO-814 were examined. The PRO-814 trial was intended to establish non-inferiority relative to sublingual buprenorphine tablets, at low-to-moderate doses. The efficacy information that was reviewed was primarily from the PRO-814 study report and accompanying datasets. Analyses of these data were performed by the primary Statistics Reviewer, James Travis, PhD, who reproduced the Applicant's analyses to ensure that they were replicable and conducted additional analyses deemed important for efficacy ascertainment and for arriving at a better understanding of the clinical relevance of the findings.

For the safety evaluation, data from the Phase 3, double-blind, safety and efficacy trials, PRO-814, and the previous trials, PRO-805 and PRO-806, were pooled. The data from the Phase 3, open-label, extension studies, PRO-807 and PRO-811 (PRO-805 and PRO-806 extension trials, respectively) were also evaluated with an emphasis on major safety results. Additionally, limited safety data were available from the clinical pharmacology studies TTP-400-02-01 and PRO-810, and were used to supplement and complement safety data provided by the major contributors to the safety database, i.e., the Phase 3 double-blind and extension studies. The safety information that was reviewed was primarily from the PRO-814 trial and the Integrated Summary of Safety (ISS) Addendum. Safety information included in the individual study reports for the respective studies was referenced when additional detail beyond that included in the ISS Addendum was needed.

A Psychopharmacologic Drugs Advisory Committee (PDAC) meeting was held on January 12, 2016 to discuss aspects of the Probuphine NDA Resubmission pertaining to the efficacy findings, procedural safety, and the proposed REMS. Recommendations

made by the Advisors and Consultants during the AC meeting are discussed throughout the review where applicable.

5.3 Discussion of Individual Studies/Clinical Trials

PRO-814 was the trial conducted to support the NDA Resubmission. PRO-814 is discussed in detail in this section. The discussion is based on the last protocol version, or amendment, which is considered the final version, and supersedes earlier versions.

PRO-814

Title:	A Randomized, Double-Blind, Double-Dummy, Active-Controlled Multicenter Study of Adult Outpatients with Opioid Dependence Transitioned from a Daily Maintenance Dose of 8 mg or Less of Sublingual Buprenorphine or Buprenorphine/Naloxone to Four Probuphine® Subdermal Implants	
Protocol & Amendment Dates:	• Protocol PRO-814; Original Protocol • Amendment 1 • Amendment 2 • Amendment 3	May 14, 2014 August 14, 2014 September 24, 2014 March 30, 2015
Study Initiation & Completion Dates:	• First subject enrolled: • Last subject enrolled: • Release date of clinical study report:	June 26, 2014 May 18, 2015 July 31, 2015 (FINAL)

PRO-814 Objective/Rationale:

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

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

Comment: The 8 mg/day or less of SL BPN criterion refers specifically to 8 mg/day or less of a sublingual Subutex or Suboxone tablet equivalent.

PRO-814 Overall Study Design

This was a multicenter, randomized, double-blind, double-dummy active controlled, non-inferiority study that evaluated the safety and efficacy of 4 Probuphine implants compared to SL BPN tablets 8 mg/day or less (pre-randomization dose) in patients with

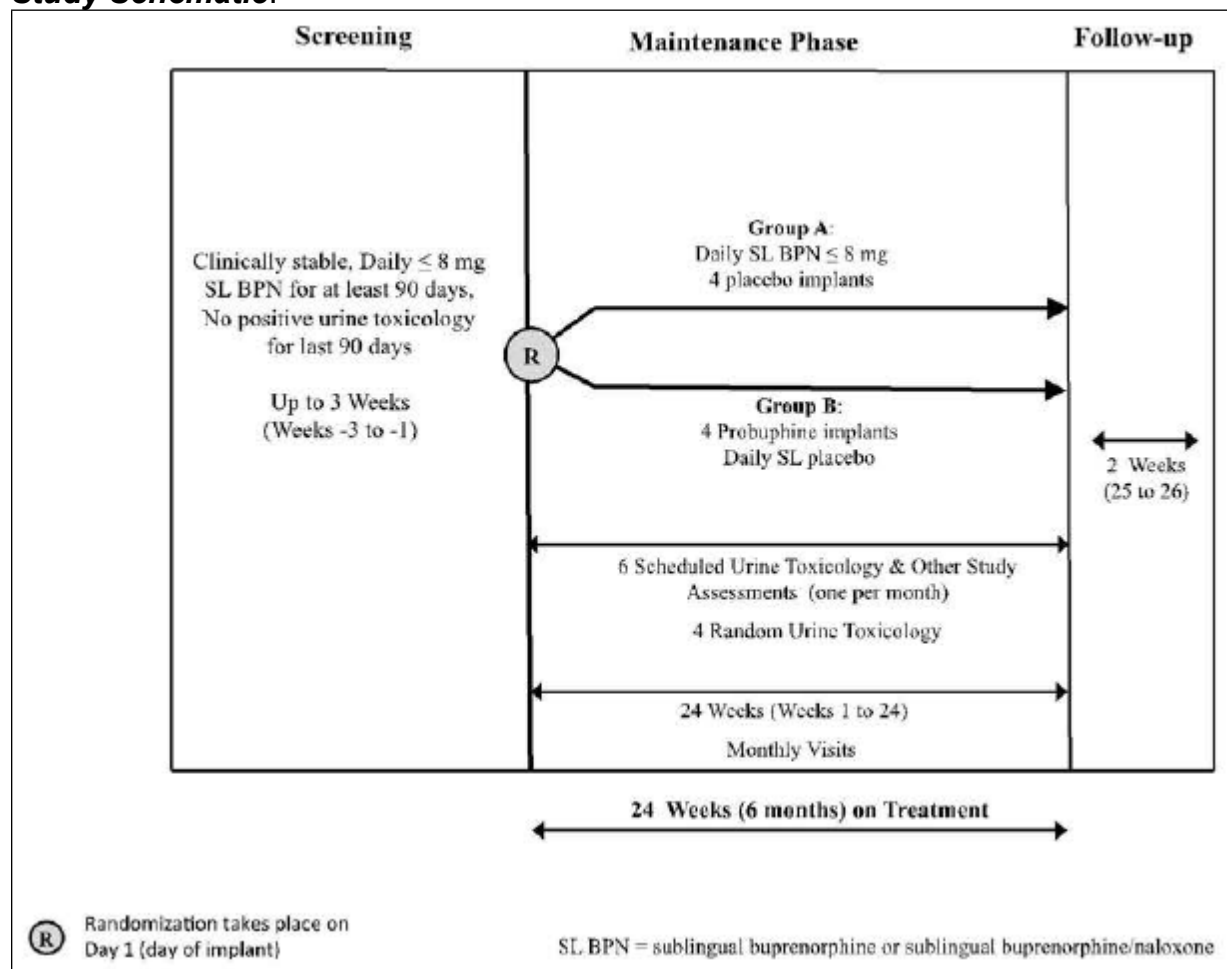
opioid dependence who were clinically stable and on no more than 8 mg/day of sublingual buprenorphine (as a Subutex or Suboxone tablet equivalent).

Subjects were randomized in a 1:1 ratio to 1 of 2 treatment groups on Day 1 and received daily doses of SL BPN tablets (≤ 8 mg per day) plus 4 placebo implants OR daily SL placebo tablets plus 4 Probuphine implants for 24 weeks. Subjects randomized to SL BPN tablets plus placebo implants were transitioned to the same dose of SL BPN on which they were previously maintained. Subjects randomized to SL placebo tablets and 4 Probuphine implants were transitioned to 4 Probuphine implants.

After Day 1, subjects were to return to the site for 7 scheduled Maintenance Phase visits. Scheduled visits during the 6-month Maintenance Phase occurred at Week 1 (Post-Implant Follow-Up Visit) and then monthly from Week 4 through Week 24 (End of Treatment [EOT] Visit). Subjects were also to present to the study site 4 other times during the Maintenance Phase to provide random urine toxicology samples. A Post-Treatment Telephone Contact (Week 25) and a Follow-Up Visit (Week 26) were to occur 1 week and 2 weeks after the EOT Visit, respectively. Implants were removed at the EOT Visit.

During the Maintenance Phase, a total of 10 urine toxicology samples were to be collected, 6 at regularly scheduled monthly visits and 4 at randomly scheduled visits.

Study Schematic:



Source: PRO-814, Version: Final4.0, 30-March-2015, p. 24 of 72

PRO-814 Study Population: The planned randomization goal was at least 180 subjects who met the following entry criteria:

Inclusion criteria:

- Adults, ages 18–65 years, with primary diagnosis of opioid dependence (DSM-IV-TR)
- Considered clinically stable by their treating healthcare provider and confirmed by the following criteria at time of randomization:
 - On SL BPN treatment for at least 6 months (≥ 24 weeks)
 - On stable SL BPN dose ≤ 8 mg daily for at least the last 90 days
 - No positive urine toxicology for illicit opioids in last 90 days
- Free from significant withdrawal symptoms (COWS score ≤ 5)
- Reliable method of contraception

REVIEWER COMMENT: The definition of “clinically stable” for the opioid-dependent population (DSM-IV criteria) is not well-established and there are not criteria that are universally understood to define clinical stability. During communications with the Applicant, the Agency

stressed that in defining a population for the study, it was important to note that being on a stable dose of SL buprenorphine is not synonymous with being clinically stable. In defining the population and responder definition for the trial, the Applicant reviewed existing literature on patients whose clinical picture appeared consistent with clinical stability on buprenorphine treatment. Additionally, the Applicant conducted a survey of 18 addiction experts.

The criteria to establish clinical stability were not operationalized as was anticipated based on the communications about the design of PRO-814. Both the literature and physician survey data explored by the Applicant in formulating a responder definition described patients who were on buprenorphine treatment for at least six consecutive months. However, although the protocol for PRO-814 stipulated that patients needed to have been on “sublingual buprenorphine treatment for at least 6 months (at least 24 weeks) at time of randomization,” and six months already is a relatively short duration to deem a patient clinically stable, the Applicant did not include measures in the protocol to ensure that only patients with at least six consecutive months of buprenorphine treatment would be enrolled. Instead, the criterion was apparently interpreted by investigators to mean cumulative lifetime duration of buprenorphine treatment. Regarding buprenorphine treatment history, according to the case report forms (CRFs), patients were asked:

- In your lifetime:
 - How long have you been treated with Buprenorphine? (This was entered as the total number of years and months on buprenorphine in their lifetime.)
 - How many times have you entered Buprenorphine treatment?

As a result, patients could have had less than 6 consecutive months on buprenorphine treatment, if across their lifetime they were ever on buprenorphine for 6 or more months cumulatively.

The other clinical stability criterion related to buprenorphine treatment history was: “Subject must have been on a SL BPN dose of 8 mg or less daily for at least the last 90 days at time of randomization.” This was envisioned as a sublingual buprenorphine dose of 8 mg or less daily, as a Subutex or Suboxone tablet equivalent. However, additional buprenorphine-containing transmucosal products have come on the market after the trial was being designed, or underway. Across the products there are differences in bioavailability as evidenced by the disparate doses seen in the table of available strengths and corresponding doses below. It also bears mentioning that although the corresponding doses for the Suboxone tablet and the Suboxone film are nominally the same, the Suboxone film provides higher buprenorphine exposures at the same nominal dose. This is most pronounced for the higher dose strengths, i.e., the 8 mg buprenorphine/2 mg naloxone and 12 mg buprenorphine/3 mg naloxone film strengths.

Table 2 Buprenorphine-Containing Transmucosal Products and Available Dosage Strengths

Subutex (Buprenorphine sublingual tablets), including generic equivalents:	2 mg buprenorphine 8 mg buprenorphine
Suboxone (Buprenorphine and naloxone sublingual tablets), including generic equivalents:	2 mg buprenorphine / 0.5 mg naloxone 8 mg buprenorphine / 2 mg naloxone
Zubsolv (Buprenorphine and naloxone sublingual tablets):	1.4 mg buprenorphine / 0.36 mg naloxone 2.9 mg buprenorphine / 0.71 mg naloxone 5.7 mg buprenorphine / 1.4 mg naloxone 8.6 mg buprenorphine / 2.1 mg naloxone 11.4 mg buprenorphine / 2.9 mg naloxone
Suboxone sublingual film (Buprenorphine and naloxone sublingual film):	2 mg buprenorphine / 0.5 mg naloxone 4 mg buprenorphine / 1 mg naloxone 8 mg buprenorphine / 2 mg naloxone 12 mg buprenorphine / 3 mg naloxone
Bunavail (Buprenorphine hydrochloride and naloxone hydrochloride buccal film):	2.1 mg buprenorphine / 0.3 mg naloxone 4.2 mg buprenorphine / 0.7 mg naloxone 6.3 mg buprenorphine / 1 mg naloxone

Source: Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) Risk Evaluation and Mitigation Strategy (REMS), 08/2015 modification

Table 3 Buprenorphine-Containing Transmucosal Products and Available Dosage Strengths

Corresponding doses of buprenorphine products that contain naloxone			
Suboxone sublingual tablets, including generic equivalents	Suboxone sublingual films	Zubsolv sublingual tablets	Bunavail buccal films
2 mg buprenorphine/ 0.5 mg naloxone	2 mg buprenorphine/ 0.5 mg naloxone	1.4 mg buprenorphine/ 0.36 mg naloxone	
	4 mg buprenorphine/ 1 mg naloxone	2.9 mg buprenorphine / 0.71 mg naloxone	2.1 mg buprenorphine/ 0.3 mg naloxone
8 mg buprenorphine/ 2 mg naloxone	8 mg buprenorphine/ 2 mg naloxone	5.7 mg buprenorphine/ 1.4 mg naloxone	4.2 mg buprenorphine/ 0.7 mg naloxone
	12 mg buprenorphine/ 3 mg naloxone	8.6 mg buprenorphine/ 2.1 mg naloxone	6.3 mg buprenorphine/ 1 mg naloxone
		11.4 mg buprenorphine/ 2.9 mg naloxone	

Source: Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) Risk Evaluation and Mitigation Strategy (REMS), 08/2015 modification

Subjects had to be on the sublingual buprenorphine dose of less than 8 mg/day or less for at least three months. As such, it is conceivable that patients could have been tapered to a dose of 8 mg/day or less three months prior to entry in the study in order to be eligible. Prescribed doses of buprenorphine prior to the three months required for study entry apparently were not captured, to allow for an appraisal of patients who may have fallen into this category.

Finally, the treating health care providers completed and signed a clinical stability checklist, attesting to their patient’s clinical stability and indicating the clinical criteria on which they were judging their patients to be stable. The clinical stability checklist is reproduced below.

Figure 1 Clinical Stability Checklist

PRO-814 Checklist for Clinical Stability

A potential study subject must be considered clinically stable by their treating healthcare provider and confirmed by the following attestation:

Patient Name _____ Treating Physician Name _____
Treating Physician Address _____

I consider this patient clinically stable based on the following (please check all that apply)

- a. Patient has not reported any illicit opioid drug use in the past 90 days _____
- b. Patient has a stable living environment _____
- c. Patient participates in a structured activity/job that contributes to the community _____
- d. Patient has not reported significant withdrawal symptoms in the past 90 days _____
- e. Patient has consistently participated in recommended cognitive behavioral therapy/peer support program _____
- f. Patient has been consistently compliant with clinic visit requirements _____
- g. Patient has reported low to no desire/need to use illicit opioids in the past 90 days _____
- h. No episodes of hospitalizations (addiction or mental health issues), emergency room visits, or crisis interventions in the previous 90 days
- i. Please describe any other indicators of clinical stability that you have observed _____

Treating Physician Signature _____

Source: PRO-814 Manual of Procedures, 2.1 Clinical Stability Checklist

Exclusion criteria:

- Current AIDS diagnosis
- Current chronic pain syndrome diagnosis requiring chronic opioid treatment, or conditions associated with acute episodic flares that require opioid treatment
- Substance dependence on any other psychoactive substances other than opioids or nicotine
- Significant symptoms or other factors which, in investigator opinion, would preclude compliance with protocol, subject safety, adequate cooperation in the study, or obtaining informed consent
- Current medical conditions such as severe respiratory insufficiency that may prevent subject from safely participating in study
- AST or ALT $\geq 3 \times \text{ULN}$; Tbili $\geq 1.5 \times \text{ULN}$; Creatinine $\geq 1.5 \times \text{ULN}$
- Clinically significant low platelet count
- Coagulopathy within past 90 days and/or current anticoagulant therapy
- Use of agents metabolized through CYP 3A4
- Recent scarring or tattoos on upper arms, or history of keloid scarring
- Hypersensitivity or allergy to EVA-containing substances or naloxone
- Exposure to any investigational drug within 8 weeks prior to Screening
- Pregnancy or lactation
- Pending legal action that could prohibit participation or compliance in the study

PRO-814 Study Procedures: Screening, Maintenance Phase, and Follow-Up

Subjects were to be seen for a total of approximately 14 visits:

- 1 Screening visit
- 12 main study visits:
 - 8 Maintenance Phase visits, including
 - 1 Baseline and Initiation of Study Drugs Visit (post-randomization Implant Day [Day 1]),
 - 1 Post-Implant Follow-up Visit
 - 6 additional monthly Maintenance Phase visits, including the End of Treatment Visit at Week 24
 - 4 Random urine toxicology visits
 - A total of 10 urine toxicology samples were to be collected across the Maintenance Phase, during the six monthly scheduled maintenance Phase visits and four random toxicology visits
- A Post-Treatment Telephone Contact will occur 1 week after the End of Treatment Visit (~1 week prior to the Follow-Up Visit).
- 1 Follow-Up Visit (2 weeks after the End of Treatment Visit)

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

Screening

Screening was to occur within 3 weeks¹⁵ of the first Maintenance Phase visit and include the following procedures: standard medical screening procedures; complete

medical/psychosocial history; VS; clinical laboratory tests; ECG; MINI; medication history; urine toxicology; detailed substance use and treatment history, using a timeline follow-back type of interview; and additional procedures as outlined in the Schedule of Assessments (below). Data on urine toxicology results for the duration of historical stable maintenance dosing (e.g., at least 90 days at time of randomization¹⁶), and the treating Health Care Practitioner's documentation on the patient's clinical stability¹⁷ (including the length of time that they have judged the patient to be stable) was to be obtained via the clinical stability form (provided in the MOP¹⁸).

REVIEWER COMMENT: The length of time that the health care provider judged the patient to be stable was not reported, and instead, on the Clinical Stability Checklist (See above), the providers were asked only about the previous 90 days for some items.

Maintenance Phase

Following the Screening phase, eligible participants were to participate in a Maintenance Phase, and a subsequent Follow-up phase. Eligibility for randomization was to be confirmed after the Screening visit and prior to implantation on Day 1 (Baseline and Initiation of Study Drugs Visit).

Following confirmation of eligibility, subjects were to be randomized to one of two treatment groups in a 1:1 ratio:

- Treatment **Group A: SL BPN tablets (≤ 8 mg/daily)** + four placebo implants ("Treatment as Usual Arm")
- Treatment **Group B: Four 80-mg Probuphine implants¹⁹** + daily SL placebo tablets

Subjects in Treatment Group A were to be transitioned to the same dose of SL BPN on which they were previously maintained (pre-randomization dose of no more than 8 mg/day or less). Subjects in Treatment Group B were to be transitioned to four Probuphine implants that the Applicant noted are expected to yield BPN plasma concentration within a range of approximately 0.5 to 1 ng/mL, comparable to the average of those observed following a daily dose of 8 mg or less of SL BPN.

¹⁵ Screening period increased from 2 to 3 weeks in Amendment 1.

¹⁶ At time of randomization vs. prior to Screening per Amendment

¹⁷ In addition to being on a stable dose for at least 90 days, clinicians will also attest to their patients' clinical stability as characterized by absence of withdrawal symptoms and no evidence of positive urine toxicology tests for illicit opioids in the previous 90 days. Other elements of clinical stability include social, emotional and psychological stability (i.e., stable family/home life and employment, treated emotional/psychological issues), compliance to clinic visits, and ongoing counseling.

¹⁸ In various places, the protocol refers to information that can be found in the Manual of Procedures (MOP).

¹⁹ The dose of 4 Probuphine implants for this study was selected by the sponsor based on efficacy, safety, and PK data from Studies PRO-805, PRO-806, TPP-400, and PRO-810 (two P3 S&E trials, PK study, and BA study, respectively). Four implants yield BPN plasma concentrations comparable to a SL BPN dose of ≤ 8 mg/day.

During the first month, subjects were required to attend 3 scheduled visits:

1. Baseline and Initiation of Study Drugs Visit (Probuphine/placebo implant insertion and SL BPN/SL placebo administration [Day 1])

On Day 1, Probuphine and placebo implants were to be implanted by a trained Implant Clinician at the clinical study site.²⁰ Prior to randomization on Day 1, it was recommended that subjects discontinue their prior sublingual buprenorphine and have implants inserted subdermally within 12–24 hours after their last sublingual buprenorphine dose. Insertion under the skin of the upper arm was performed using a specialized applicator provided by the Applicant, (which the Applicant describes as similar in design to commercially-approved applicators used for the insertion of other implantable drugs). Subjects were to be monitored closely for AEs and vital signs for at least 30 minutes following insertion by medically qualified personnel.

2. Post-Implant Follow-up Visit (to occur within 5 days after implantation) to conduct implant site examination and any additional safety assessments
3. Week 4 First Study Assessment Visit (evaluation of outcome measures and safety assessments)

During Months 2 to 6, subjects were to return for monthly study visits for evaluation of outcome measures and safety assessments as described in the Schedule of Assessments table (See below). Subjects were to be provided with sufficient take home medication for the daily dose of SL BPN or placebo for the subsequent month, as appropriate.

In order to assess the number of opioid-free months throughout the 6 months (24 weeks) of treatment, patients were to attend a total of 6 monthly study visits (6 scheduled monthly urine toxicology samples) and 4 random visits (4 random urine samples throughout the 6 months) where urine samples were to be obtained for each subject. During the 6 scheduled visits where urine samples were to be collected, self-reports of illicit opioid use (and other drugs of abuse) were also to be recorded.

In scheduling random urine toxicology visits, sites were advised to utilize their standard clinical process for scheduling the 4 random urine drug testing visits. It was recommended, however, that no more than one random urine test be conducted between two scheduled visits. Each of the random visits was to occur within 48 hours after speaking directly with the subject. Investigators were privy to the urine toxicology test results during the trial, and generally received the results 7 to 10 days from the date the sample was received by the central laboratory.

²⁰ The clinicians who inserted the Probuphine rods across the trial sites included 8 Family Medicine, 6 Obstetrics & Gynecology, 3 General Surgery, 3 Anesthesiology, 1 Neurology and Psychiatry, and 1 Radiation Oncology physicians, and 1 Family Practice Nurse Practitioner.

Subjects were also to be encouraged to contact their investigator for unscheduled visits if they experienced any signs of inadequate treatment.

Investigators were instructed to treat additional symptoms (e.g., withdrawal, desire/need to use, etc.) as they usually would under normal clinical practice, including additional counseling sessions, supplemental SL BPN, or other pharmacological interventions (other than those identified as prohibited). Subjects were to be told that their study dose of BPN is comparable to the dose they have been stable on and is expected to be adequate to maintain stability. Therefore, it was generally not anticipated that they would need any additional SL BPN (b) (6)

but additional counseling and other pharmacological interventions were available at the discretion of the investigator. Any additional interventions that the subjects received were to be recorded.

REVIEWER COMMENT: Because the study dose of buprenorphine both in the sublingual form and as Probuphine was to be comparable to the dose they had been stable on, it was expected to be adequate to maintain stability in patients who were considered to have achieved and sustained clinical stability. This was in keeping with a trial evaluating Probuphine, a drug product that is a fixed dose product that cannot be titrated. Thus this product does not permit dose adjustments as part of its inherent properties. This is in contrast to treatment as usual with the transmucosal products, which allow for titration and dose adjustments when the patient's observed clinical status dictates. Because sporadic and infrequent use of supplemental sublingual buprenorphine was anticipated for clinically stable patients who were deemed to have sustained clinical stability for some time, use of supplemental buprenorphine was not considered in the responder definition.

Final outcome measures were to be collected at the final treatment visit at Week 24 (End of Treatment Visit) and implants were to be removed as described below.

Follow-up Phase

Additional post-implant removal and other assessments were to be performed on Week 25 to 26 as outlined in the Schedule of Assessments table (Appendix). Following Week 24, subjects were to be re-transitioned back to usual care (pretrial), as needed. During Week 25, telephone contact was to be made with all subjects, 1 week ($\pm$ 3 days) after the End of Treatment Visit to capture any AEs that may have occurred. Week 26 ($\pm$ 3 days) was to include an on-site visit to the clinic for final follow-up assessments (Follow-up Visit).

PRO-814 Study Procedures:

**Study Treatments and Administration
Procedures**

Patients were to receive SL BPN or placebo SL BPN, and 4 Probuphine or placebo implants during the Maintenance Phase:

- Treatment **Group A:** **SL BPN & 4 placebo implants**
- Treatment **Group B:** **4 Probuphine implants & placebo SL BPN**

The following summarizes the treatment and administration procedures that were undertaken for the trial for the Probuphine and placebo implants and the sublingual buprenorphine or placebo sublingual buprenorphine tablets.

- PROBUPHINE & PLACEBO IMPLANTS: IMPLANT INSERTION AND REMOVAL PROCEDURES
All Probuphine and placebo implants were to be inserted and removed by trained clinicians. The Applicant was to institute the Probuphine Clinical and Procedure Training and Evaluation program to ensure that clinicians who performed the implant insertion and removal procedures met competency standards. The Applicant was also to provide an Implant Insertion/Removal Instruction for Use slide deck, training DVD, as well as live training on the instructions for aseptic subdermal insertion and removal of Probuphine or placebo implants.

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

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

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

- The Implanting Clinician and any other staff involved in the implant insertion and removal procedures *must not* participate in subject efficacy evaluations nor discuss with other study staff any information regarding the implants in reference to the subjects.
 - In order to keep the subjects blinded, appropriate steps must be taken to ensure that the subject is unable to view the implant insertion or removal procedures at any time (e.g., by draping the surgery table to obstruct subject's view of the procedure, etc.).
 - The study staff *must not* ask the Implanting Clinician or any other staff involved in the implant insertion and removal procedures for information regarding subject group assignment that might inadvertently unblind the study staff.
- SUBLINGUAL BUPRENORPHINE
Daily Treatment Dose: Subjects were required to take daily SL BPN (BPN/naloxone) or placebo during the Maintenance Phase. These products were to be supplied by the Applicant or designee. Matching SL placebo tablets were to be provided for each dosage strength.

The sublingual BPN tablets used during the study were to have a nearly-matching placebo. Due to minor potential differences between active and placebo SL tablets, subjects were to be told that clinical supplies of SL BPN have been specifically developed for the trial and may look or taste different than commercially available products they may have been treated with previously. Subjects were also to be told that they should not interpret these differences as indicative of whether they were receiving SL active or placebo tablets.

Sublingual BPN (buprenorphine/naloxone) as the comparator was manufactured by (b) (4). The sublingual placebo tablets were manufactured by (b) (4).

Subjects were to be advised to not eat or drink anything until the tablet(s) were completely dissolved. To ensure consistency in bioavailability, subjects were supposed to follow the same manner of dosing for the duration of the study. Subjects were to be instructed to place SL BPN or placebo tablets under the tongue until dissolved. For dosages requiring more than one SL tablet, it was advised that tablets should be placed in different areas under the tongue at the same time.

Supplemental SL BPN: For potential supplemental SL BPN needs, a different brand of SL BPN was to be utilized to prevent the unblinding of study drug. The manufacturer of supplemental sublingual buprenorphine for the trial was (b) (4)

Investigators were to be instructed to treat additional symptoms as they would usually, including additional counseling sessions, supplemental SL BPN, or other pharmacological interventions. However, as noted previously, subjects were also to be told that while additional counseling and other pharmacological interventions could be available, their current dose of BPN was expected to be adequate to maintain stability and their physician did not expect that they would need any additional supplemental SL BPN. (b) (6)

Any supplemental SL BPN provided by the Investigator was to be recorded, along with the reasons for determining the need for any supplemental interventions.

- PSYCHOSOCIAL COUNSELING

All subjects were to receive manual-guided drug counseling during the study, as outlined in the Schedule of Assessments Table (below) and as was to be described in more detail in the Individual Drug Counseling Manual (provided in the Study MOP)²¹. Additional counseling was permitted to be provided as clinically indicated; however, all additional counseling, visits or phone calls had to be recorded.

PRO-814 Study Procedures: Study Assessments and Procedures

Study assessments and procedures include the following, to occur as outlined in the Schedule of Assessments table (See below):

Urine Toxicology	- <u>Opioids</u> : Collected at each visit using a urine collection cup containing a temperature sensor. Specimen authenticity verified at site. ²² Direct observation approach was to be an option if deemed necessary. In addition, it was recommended that the scheduled assessment visits take place on Mondays to potentially improve detection of illicit opioid use that may have occurred over the weekend. Urine samples were to be logged and numbered and then sent to the central laboratory for quantitative analysis (via LC-MS/ MS methods) of opioids (codeine, morphine, hydrocodone, oxycodone, hydromorphone, oxycodone, methadone, dihydrocodeine, and fentanyl) and opioid metabolites

²¹ Cited reference: Mercer D, Woody G. Individual Drug Counseling: adapted from the Naltrexone and Fluoxetine for Heroin Addiction Study; Philadelphia Veterans' Affairs Medical Center.

²² Specimen authenticity verified at site using the sensor to measure urine temp immediately following collection. If test results outside temp ranges (32.2° to 37.7° C [90° to 100 F]) within 4 minutes, subject asked to provide another urine sample. If 2nd sample outside of temperature range, sample will be counted as 'missing', and should not be sent for analysis per protocol.

	(EDDP [methadone metabolite], and norfentanyl). - <u>Other Drugs of Abuse</u> : Urine was to be tested for other drugs of abuse (e.g., cocaine, benzodiazepines, barbiturates, amphetamines, phencyclidine and cannabinoids [THC]) using qualitative (immunoassay) methods. Positive results were not to be confirmed using quantitative methods.
Self-reported Illicit Drug Use	Illicit or prescription opioids and other drugs of abuse self-report was to be recorded using a timeline follow-back type of interview.
Measures of Desire and Need to Use	<i>Desire to Use VAS & Need to Use VAS</i> Desire to Use and Need to Use were to be administered using unipolar 100 mm VAS (“Since your last scheduled assessment visit, indicate your worst or strongest desire/need to use opioids, where 0=No desire to use and 100 mm=Strongest possible desire, and from 0=No need to use and 100 mm=Strongest possible need, respectively). <i>A separate VAS was to be provided for each Desire to Use and Need to Use, and measurements must be taken separately (i.e., separated in time or by other procedures).</i>
Measures of Withdrawal	- Subjective Opioid Withdrawal Scale (SOWS) - Clinical Opioid Withdrawal Scale (COWS)
Supplemental Visits, Medication and Counseling	Supplemental SL BPN use was allowed. Subject-requested or physician-directed supplemental visits, phone calls or additional counseling, or other pharmacological interventions, along with the reason(s) for supplemental visits, phone calls or additional counseling or other pharmacological interventions, were to be recorded.

Refer to the Schedule of Assessments table below for the timing of assessments.

PRO-814 Study Procedures: Study Subject Withdrawal

Subjects were to be discontinued from the study for the following reasons:

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

Subjects may also have been discontinued from the study for the following reasons:

- Subject refusal or inability to adhere to study protocol
- Protocol violation
- Requirement for continual use of opioid analgesics for >7 days or requirement for general anesthesia for surgery
- Pregnancy – The protocol stated that subjects who become pregnant may withdraw their consent and discontinue the study and be referred back to the care of their

usual provider. Follow-up information was to be obtained where possible (with the consent of the participant or their partner) regarding the course and outcome of the pregnancy, including any post-natal sequelae in the infant.

Reason(s) for study discontinuation were to be documented. Subjects were to be required to return for, at minimum, the End of Treatment Visit to remove the implants. All efforts should have been made by the Investigator to continue collection of urine samples at the protocol-defined study visit intervals (monthly and random), concomitant medications, and adverse events in subjects that discontinued study drugs, unless the subject withdrew his/her consent at time of early discontinuation. The Investigator should also have asked the subject to return for the Follow-up assessments (i.e., Week 26 assessments), provided that the subject had not withdrawn consent for those assessments. If a subject refused to complete early termination procedures and/or Follow-up, this information was to be recorded.

PRO-814 Study Procedures: Schedule of Assessments

Study Period/Phase:	Screening	Maintenance Phase					Follow-up	
Month:	-	Month 1 Visits		Month 2 to 5 Visits		Month 6/ End of Treatment Visit	-	
Week: ^a	-3 to -1	Week 1	Week 4	Week 8, 12, 16, 20		Week 24	Week 25	Week 26
Day:	-	Day 1 ^b	Post-Implant ^c	-	-	-	-	-
Informed Consent ^d	X							
Eligibility Criteria Review ^e	X	X						
Medical and Medication History / Substance Abuse and Treatment History	X							
DSM-IV-TR, MINI, v 6.0	X							
Physical Examination ^f	X							
Abbreviated Review of Systems		X						
Vital Signs ^g	X	X ^h	X	X	Monthly	X ^h		X
EKG	X					X		
Chemistry, Hematology, Urinalysis and Coagulation Profile	X					X		

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

^b Baseline and Initiation of Study Drugs Visit.

^c Post-Implant Visit.

^d Subjects must voluntarily provide written informed consent prior to any study-related procedures being performed.

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

^f A complete physical exam of all major body systems will be performed at the Screening Visit.

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

^h Vital signs (temperature, blood pressure, pulse rate, and respiration rate) will be measured just prior to implant insertion/removal, and then 15 minutes and 30 minutes after implant insertion/removal.

Clinical Review
 Rachel Skeete, MD, MHS
 NDA 204442 (Class 2 Resubmission)
 Probuphine (buprenorphine) implant

Study Period/Phase:	Screening	Maintenance Phase					Follow-up	
		Month:	Month 1 Visits		Month 2 to 5 Visits	Month 6/ End of Treatment Visit	-	
Week: ^a	-3 to -1	Week 1	Week 4	Week 8, 12, 16, 20	Week 24	Week 25	Week 26	
Day:	-	Day 1 ^b	Post-Implant ^c	-	-	-	-	
Pregnancy test ^d	X	X		X	Monthly	X		
Hepatitis B/C, HIV ^e	X							
Implant Site Examination ^b			X	X	Monthly	X	X	
Dispense Treatment Identification Card		X						
Urine Toxicology	X			X	Monthly	X		
Random Urine Toxicology		4 Random Urine Toxicology Tests						
Illicit Drug Use Self-Report	X			X	Monthly	X		
Withdrawal and Desire to Use/Need to Use (SOWS, COWS, VAS)	X	X		X	Monthly	X		
SL BPN or placebo dispensing		X		X	Monthly			
Probuphine or placebo [four (4) implants] Insertion		X ^f						
Implant removal procedure						X ^g		
Additional interventions ^h				X				

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

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

^c The implant site will be visually inspected and palpated.

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

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

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

Study Period/Phase:	Screening	Maintenance Phase					Follow-up	
		Month:	Month 1 Visits		Month 2 to 5 Visits	Month 6/ End of Treatment Visit	-	
Week: ^a	-3 to -1	Week 1	Week 4	Week 8, 12, 16, 20	Week 24	Week 25	Week 26	
Day:	-	Day 1 ^b	Post-Implant ^c	-	-	-	-	
Implant Insertion Procedure Assessment		X						
Implant Removal Procedure Assessment						X		
Psychosocial Counseling				X	Monthly	X		
Adverse Events ^{d,e,f}	X	X	X	X	Monthly	X	X	
Concomitant Medications/Procedures	X	X	X	X	Monthly	X	X	
Wound Care Information Sheet ^g		X				X		
Telephone Contact				X (As Needed)		X		

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

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

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

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

^e A Wound Care Information Sheet will be given to the subject after each insertion/removal procedure.

Source: PR0-814 Protocol, Amendment 3, p. 250–252

PRO-814 Statistical Considerations

Study Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was a responder rate analysis. The pre-specified responder definition was a patient with no more than 2 of 6 months with any evidence of illicit opioid use. Evidence of illicit opioid use was defined as a positive opioid urine toxicology result or self-reported illicit opioid use. The responder definition was developed based on the Applicant's interpretation of their Clinician Survey (a survey of addiction specialists), and limited information from the literature, as outlined below. A primary analysis was agreed upon, but the Division noted that exploratory analyses would be undertaken.

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

Secondary efficacy endpoints included:

<u>Measures of desire/need to use:</u>	<u>Measures of withdrawal:</u>	<u>Illicit Opioid Use Measures²³</u>
• Desire to Use VAS • Need to Use VAS	• Clinical Opiate Withdrawal Scale (COWS) • Subjective Opioid Withdrawal Scale (SOWS)	• Illicit Opioid Use by Month by opioid urine toxicology and self-reported illicit drug use • Time to first Evidence of Illicit Opioid Use

Exploratory Efficacy Variables

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

Statistical Analysis

Analysis Populations

- Randomized Population: All subjects randomized into Maintenance Phase
- Intent-to-Treat (ITT) Population: All subjects who have been randomized and have received an implant and/or received SL BPN/placebo. Analyses based on this population were to group subjects according to the treatment they were randomized to receive, regardless of actual treatment received. The **ITT population was to be the PRIMARY ANALYSIS POPULATION**.

REVIEWER COMMENT: The Statistical Analysis Plan (SAP) defined the ITT population as all subjects who have been randomized and have received an implant and/or received SL BPN/placebo and provided some baseline efficacy data. The ITT population as defined in the protocol is considered the more appropriate definition, rather than the SAP definition, which the Applicant used for their efficacy analyses.

- Safety Population: All subjects who are randomized and treated with implants or who received any dose of SL BPN/placebo in the Maintenance Phase. Analyses based on this population were to group subjects according to the treatment they actually received regardless of the treatment they were randomized to receive. All safety analyses were to use the safety population.
- Per Protocol Population: All subjects in the ITT population with no major protocol violations. Major protocol violation criteria were to be established prior to the database lock.

Analysis of Primary Endpoint

A test of non-inferiority in the rate of responders between the two treatments arms was to be conducted. A non-inferiority margin of $\delta=20\%$ was to be employed to define non-inferiority.²⁴ Let

²³ Secondary efficacy endpoints based on illicit opioid use were added in Amendment 2.

²⁴ See Clinical Review dated May 20, 2014 for the rationale the Sponsor provided for the 20% non-inferiority margin.

π_C and π_T be the rate of response at 24-weeks on the control arm and experimental treatment arm, respectively. The null hypothesis (H_0) of inferiority is

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

The alternative hypothesis (H_A) of non-inferiority is

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

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

The Applicant explained its rationale for selection of the 20% margin as follows:

The Applicant contended that the 20% margin was appropriate from a scientific validity perspective as well as meeting FDA guidelines for non-inferiority margin selection (FDA, 2010)²⁵. In this study with 180 subjects, the observed data that met the statistical 20% margin, the Applicant continued, would meet scientific face-validity for the equivalency of the treatment arms. The Applicant provided the table below summarizing the required Probuphine Treatment Group's response rate (% of responders) to satisfy non-inferiority based on the 20% margin and the sample size of 90 subjects per group at the two-sided 5% significance level for a range of observed SL BPN arm's response rate (Note: due to discreteness some percentages are not possible).

Observed SL BPN Arm's Response Rate (% of Responders)	Required Minimum Observed Probuphine Arm's Response Rate (% of Responders) to Satisfy Non-inferiority (%)
90	81.1
84.4	76.7
80	73.3
74.4	67.8
70	64.4
64.4	58.9
60	54.4

Source: PRO-814 Protocol, Table 4, p. 269

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

Although there is little literature on SL BPN treatment in long-term stabilized maintenance subjects, the Applicant contended that there is some empirical information available to lend credence to the 20% non-inferiority margin, and summarized the following as justification:

²⁵ <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM202140.pdf> cited.

1. With patients on longer term BPN or methadone treatment, blinded taper (detoxification) studies indicate rates of continued opioid abstinence following complete withdrawal of about 18 to 31%. Although little data are available on abrupt withdrawal, published survey data indicate an abstinence rate of about 15%. (An excerpted summary of the sponsor's summary of literature to support the non-inferiority margin from the standpoint of placebo effect, is provided in the Section 6).
2. A survey of addiction experts was performed by the Applicant to estimate the proportion of patients, who have been on a stable dose of 8 mg or less of SL BPN, expected to maintain abstinence after abrupt discontinuation of the SL BPN. (The survey questions and the summary of responses as reported by the Applicant are included in the Appendix).
 - a. The results demonstrated that clinicians would expect that a median of only 25% of clinically stabilized patients would not relapse (i.e., maintain clinical stability) to illicit opioid use if these patients were taken off their stable dose of 8 mg or less of SL BPN. The FDA Draft Guidance would suggest a 37.5% margin to be appropriate, based on an estimate of 75% effect size (i.e., assuming all patients being stable at Baseline). However, the Sponsor acknowledges that a 37.5% margin, estimating 50% preservation of the effect size may not be clinically acceptable. The proposed 20% margin would estimate preserving >70% of the effect and, the Sponsor states, should be considered clinically acceptable.
3. Finally, the FDA Draft Guidance notes that circumstances might support a less conservative choice for the margin, including:
 - a. *Pharmacologic properties of the test drug that are very similar to those of the active control* – Probuphine is an alternative dosage form of the same active entity with the expectation of similar overall plasma concentrations to the SL BPN arm;
 - b. *Use of a persuasive biomarker* – responder definition in this trial will include the standard and well-accepted objective urine toxicology results to confirm treatment success;
 - c. *If the drug has been shown to be effective in closely-related clinical settings* – Probuphine has already been shown to be effective relative to placebo in two trials in harder-to-treat populations;
 - d. *If the test drug were shown to have some important advantage (e.g., on safety or on a secondary endpoint)* – The safety issues associated with abuse of SL BPN are well-known; the Drug Abuse Warning Network confirmed an increasing trend to adverse medical outcomes associated with BPN abuse, i.e., a total of 21,483 emergency department visits related to abuse/misuse were reported in 2011 (DAWN, 2013). Probuphine has the potential to reduce misuse/abuse associated with SL BPN and have a significant positive public health impact, in addition to potentially increasing adherence. (Above description of analysis of primary endpoint found in PRO-814 protocol, pp. 56 – 58).

REVIEWER COMMENT: Note that for item 3b, the Division's view is that urine toxicology tests are a biomarker for recent drug use and not a "persuasive biomarker" for clinical benefit. A sustained pattern of drug use, as documented in such measures as toxicology tests, might be a surrogate for clinical benefit but urine toxicology by itself is not. For items 3c and 3d, although statistical significance was demonstrated in the referenced trials for Probuphine as compared to placebo, the clinical benefit of the minor changes in drug-taking behavior observed in the clinical trials has not been established.

Moreover, because of the continued use of SL BPN use throughout the trials, the safety advantages are also called into question.

Based on the above, the Applicant concluded that the overall data and circumstances associated with this study support the use of a 20% non-inferiority margin.

REVIEWER COMMENT: Although the Applicant pre-specified a 20% non-inferiority margin for the PRO-814, when this aspect of the study design was discussed at the January 12, 2016, Psychopharmacologic Drugs Advisory Committee, there was consensus that this non-inferiority margin was too permissive, and Committee members thought that a narrower non-inferiority margin would be more appropriate, with one member suggesting a margin as small as 5%.

Handling of Dropouts or Missing Data

Imputation methods to handle dropouts and/or missing data were to be detailed in the SAP.

Sensitivity Analyses

The following sensitivity analyses were to be performed:

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

Additional sensitivity analyses were to be conducted as outlined in the SAP for this study.

Analysis of Secondary Efficacy Endpoints

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

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

Determination of Sample Size

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

PRO-814 Key Protocol Amendments

The protocol as summarized above in this section is a review of the protocol as it stands following the protocol amendments. Amendments were made to the protocol August 14, 2014, September 24, 2014, and March 30, 2015. The study initiation date, or the date of first subject enrollment, was June 26, 2014.

- **Amendment 1**, August 14, 2014
 - Duration of the Screening Phase was changed from 2 weeks to 3 weeks, resulting in an additional revision to change the study duration for each subject from 28 weeks to 29 weeks.
 - Text stating that subjects should discontinue NSAID or aspirin containing medications during the week prior to implant insertion or removal was repeated for consistency.
 - The timing for serum pregnancy testing was changed from the Screening and Follow-Up
- **Amendment 2**, September 24, 2014
 - The 3 entry criteria used by the treating healthcare provider to confirm clinical stability of the subject were changed to read as follows:
 - On SL BPN treatment for 6 months (at least 24 weeks) at time of randomization.
 - On a SL BPN dose of 8 mg or less daily for at least the last 90 days at time of randomization.
 - Had no positive urine toxicology results for illicit opioids in the last 90 days at time of randomization.

REVIEWER COMMENT: Essentially, the phrase “at time of randomization” was added for clarity.
 - Two secondary efficacy endpoints were added: urine illicit opioid use by month and time to first evidence of illicit opioid use.
 - A requirement was added for the investigator to make every effort to continue urine collection at the protocol-defined study visit intervals (monthly and random) and continue monitoring of concomitant medications and AEs for subjects who discontinued study drugs, unless the subject withdrew his/her consent at the time of early discontinuation.
- **Amendment 3**, March 30, 2015
 - Text describing statistical methods for the secondary efficacy analyses was replaced by statements that secondary efficacy analyses would be described in detail in the SAP.
 - Redefined the secondary efficacy endpoints and exploratory efficacy endpoints.

The amendments all occurred after the first subject was enrolled. These amendments are not anticipated to materially impact interpretation of the findings.

PRO-814 Study Outcome

Study Subject Enrollment: A total of 211 subjects were screened and 177 were randomized into the study. During the January 12, 2016, AC meeting, when a concern was raised about the clinical stability of the recruited patients, the Applicant asserted that the participants were primarily pre-existing patients at the clinics at the various study sites, and were not newly-recruited patients treated for the minimum period of

time solely for the purposes of attaining eligibility for the trial. Of the randomized subjects, 176 subjects received study medication, including 87 subjects randomized to treatment with Probuphine, and 89 subjects randomized to sublingual buprenorphine (SL BPN) treatment (tablets at a dose equivalent to their pre-randomization buprenorphine dose). One subject (007-027) was randomized to the sublingual buprenorphine arm, but on Day 1, after being randomized, revealed that she was scheduled to undergo surgical removal of a tumor the following week and surgery had the potential to be major. As a result, the investigator felt that the subject was not a suitable subject for the study and the subject was withdrawn from the study, never having received any study medication.

Enrollment by Center: PRO-814 was conducted in the US and randomized patients at 21 sites. Enrollment was distributed among centers as shown in the table below.

Table 4 Enrollment by Center – PRO-814

Site №	Institution Name and Site Investigators	Enrollment
001	North County Clinical Research Oceanside, CA PI: Dr. Valentin Isacescu Sub-I: • Brett Barnes • Mark Meldon, DO • Timothy E. Lindamood, MD* • Tristin Smith • Olga Johnson *Implant Clinician† (Family Medicine)	N = 4 patients • Probuphine: n = 2 • SL BPN: n = 2
002	Maryhaven Institute Columbus, OH PI: Dr. Paul W. Schkolnik Sub-I: • Dr. Gregory Brigham • Bryan N. Feldman, DO* • Elizabeth B. Lottes, DO • Tiffany Madden • Lee Ann Williams *Implant Clinician (Family Medicine)	N = 6 patients • Probuphine: n = 2 • SL BPN: n = 4
003	Saint Luke's Roosevelt Hospital Center New York, NY PI: Dr. Richard Rosenthal (Also trial PI?) Sub-I: • Abigail Herron, DO • Navjot Khinda, MD • Allegra Cummings, MD* • Joann Gomez	N = 1 patients • Probuphine: n = 1 • SL BPN: n = 0

Site No	Institution Name and Site Investigators	Enrollment
	Hart Nicholas Hopple-Perry, MD *Implant Clinician (Obstetrics & Gynecology)	
004	Novex Clinical Research LLC New Bedford, MA PI: Dr.Mohammd Munir Sub-I: - Mushtaque A. Chachar, MD* - Paula DeAlmeida *Implant Clinician (Neurology and Psychiatry)	N = 6 patients - Probuphine: n = 3 - SL BPN: n = 3
005	Wellness and Research Center Belvidere, NJ PI: Dr. John V. Bernard Sub-I: - Vijay Rastogi, MD* - Lea Baylor - Ruth Eldred - Chelsea Markopoulos *Implant Clinician (General Surgery)	N = 29 patients - Probuphine: n = 15 - SL BPN: n = 14
006	PsychCare Consultants Research St Louis, MO PI: Dr. Mohd A. Malik Sub-I: - Maheen Malik, MD - Shazia Malik, MD - Kausar Nazir, MD* - Syed Hadi Zaidi, - Aneel Kumar, - Vikram Datta, - Assad Mukhtar - Steve May *Implant Clinician (Family Medicine)	N = 10 patients - Probuphine: n = 4 - SL BPN: n = 6
007	Amit Vijapura, MD Jacksonville, FL PI: Dr. Amit Vijapura Sub-I: - Kamalesh Pai, MD - Loren Guzman - John Hunt, MD* - Jaimie Recore - Hemant Shah, MD* - Raina Dave - Cecilia Langford - Laurel Rutter - Peter Mehta	N = 26 patients - Probuphine: n = 13 - SL BPN: n = 13

Site №	Institution Name and Site Investigators	Enrollment
	*Implant Clinician (Anesthesiology [Hunt & Shah])	
008	Carolina Clinical Trials, Inc Charleston, SC PI: Dr. Eduardo Cifuentes Sub-I: • Steven G. Lopez, MD • Karen Slawson • Ashley Dayson • Courtney Cadden • Harry Wade Boatwright, MD* • Sandi Zurlo • Ashley King	N = 3 patients • Probuphine: n = 2 • SL BPN: n = 1
	*Implant Clinician (Obstetrics & Gynecology)	
010	University of Pennsylvania Health System, Treatment Research Center Philadelphia, PA PI: Dr. Kyle M. Kampman Sub-I: • Brenda J. Beitler • Laurie Allan Downing • Elmer Yu, MD* • Gail Kaempf • Lauren Rodriguez • Margo E. Hendrickson • Michael P. Frost, MD • Karah Williams • Elizabeth Mahoney	N = 2 patients • Probuphine: n = 0 • SL BPN: n = 2
	*Implant Clinician (General Surgery)	
011	Parkway Medical Center Birmingham, AL PI: Dr. James G. Sullivan Sub-I: • Stephanie M. Hightower, MD* • Jack Whites, MD	N = 20 patients • Probuphine: n = 9 • SL BPN: n = 11
	*Implant Clinician (Family Medicine)	
012	Scientific Clinical Research, Inc. North Miami, FL PI: Dr. Scott Segal Sub-I: • Olga Marie Lapeyra, MD • Steven E. Chavoustie, MD* • Melissa S. Vinson, PhD • Mara Bailey, PsyD • Nestor Morillo	N = 3 patients • Probuphine: n = 2 • SL BPN: n = 1

Clinical Review
 Rachel Skeete, MD, MHS
 NDA 204442 (Class 2 Resubmission)
 Probuphine (buprenorphine) implant

Site No	Institution Name and Site Investigators	Enrollment
	• Jennydsa (Jenny) Rojas • Swanzetta Palmer • Diana Leyva • William Gerson, DO • Salika Mansuri *Implant Clinician (Obstetrics & Gynecology)	
013	University of California Los Angeles Los Angeles, CA PI: Dr. Walter Ling Sub-I: • Larissa Mooney, MD • Garth Terry, MD • Albert Hasson • Jessica Jenkins • Sandra MacNicoll • Erendida Cano • Jasmin Hernandez • Daniel Dickerson, DO • Cole Marta, MD • Lynn Yen, MD • Matthew Torrington, MD* • Claudia Gonzalez *Implant Clinician (Family Medicine)	N = 2 patients • Probuphine: n = 1 • SL BPN: n = 1
014	University of Vermont Medical Center Burlington, VT PI: Dr. Stacey Sigmon Sub-I: • Elisabeth Wegner, MD* • Lisa Smith, RN • Heather Stein, MD* • John Brooklyn, MD • Thomas White, PhD • Karen Brown • Magen Phillips • David Segel • Maria Newell *Implant Clinician (Obstetrics & Gynecology [Wegner] & Family Medicine [Stein])	N = 4 patients • Probuphine: n = 3 • SL BPN: n = 1
015	Innovative Clinical Research, Inc. North Miami, FL PI: Dr. Rishi Kakar Sub-I: • David Howard Flaherty, DO • Steven E. Chavoustie, MD, CCRP* • Erin L. Tireman, PsyD • Paul A. Martin	N = 8 patients • Probuphine: n = 3 • SL BPN: n = 5

Clinical Review
 Rachel Skeete, MD, MHS
 NDA 204442 (Class 2 Resubmission)
 Probuphine (buprenorphine) implant

Site No	Institution Name and Site Investigators	Enrollment
	• Kadian Watson • Adriana Drada • Denise Pichardo *Implant Clinician (Obstetrics & Gynecology)	
016	Stanley Street Treatment and Resources, Inc Fall River, MA PI: Dr. Genie Bailey Sub-I: • David Carter, MD* • Michelle Rapoza • Tamara Freitas, RN • Susan St. Amour, NP • Kristy Rapoza, CNA • Doris Merrill, RN • Denise Wright, RN • Jacqueline Roy, RN • Crystal Cote-Campos, LMHC • Frederick Rocco, PhD • Julie Charest *Implant Clinician (Family Medicine)	N = 7 patients • Probuphine: n = 6 • SL BPN: n = 1
017	Altea Research Institute Las Vegas, Nevada PI: Dr. Jelena Kunovac Sub-I: • Mustafa Rawaf, DO • Mader Y. Abdelsayed, MD* • Martin Fakiel, MD *Implant Clinician (Obstetrics & Gynecology)	N = 1 patients • Probuphine: n = 1 • SL BPN: n = 0
018	Altea Research Institute Las Vegas, Nevada PI: Dr. Michael Frost Sub-I: • Thomas Foley III • Raymond Bobb, DO* *Implant Clinician (Anesthesiology)	N = 3 patients • Probuphine: n = 1 • SL BPN: n = 2
019	TRY Research Maitland, FL PI: Dr. Kent Hoffman Sub-I: • Kathleen Luise Todd, DO* • Carrie S. Herbert • Samantha Kelly Carver • Steven E. Chavoustie, MD^δ • Julie Diane Eberwein, PhD	N = 13 patients • Probuphine: n = 7 • SL BPN: n = 6

Site No	Institution Name and Site Investigators	Enrollment
	*Implant Clinician (Family Medicine)	
020	Haleyville Clinical Research, LLC Haleyville, AL PI: Dr. Boyde J. Harrison Sub-I: • Deborah K. Dyar, RN* • Karen Louise Moore, RN • Kathy Lynn Bell, RN • Jeff L. Ryan, MD* • Stephen Grady Sanders, MD *Implant Clinician (Certified Nurse Practitioner, Family Medicine [Dyar] & General Surgery [Ryan])	N = 14 patients • Probuphine: n = 4 • SL BPN: n = 10
021	University of Kentucky Center on Drug & Alcohol Research Lexington, KY PI: Dr. Michelle Lofwall Sub-I: • Jonathan Michael Feddock, MD* • Sharon Lynn Walsh, PhD • Paul Sloan, MD • Stacey Conley, RN *Implant Clinician (Radiation Medicine, Oncology)	N = 7 patients • Probuphine: n = 4 • SL BPN: n = 3
023	Boyett Health Services Inc Hamilton, AL PI: Dr. Brent Boyett Sub-I: • Sandra Diane Boyett, • Clayton Cockrell II, NP • Douglas Michael Turner, Jr., MD* • Ashley Howell *Implant Clinician (Obstetrics & Gynecology)	N = 8 patients • Probuphine: n = 4 • SL BPN: n = 4

† Implant Clinician is a descriptor meant to refer to the proceduralist(s) at the site who were responsible for the Probuphine insertion and removal procedures. Per protocol, the implant clinician was not to be responsible for any other study-related activities. The site Implant Clinician(s) are denoted by an asterisk (*), with the clinician's specialty in parentheses.

° At site 019 on one day only to videotape a single removal procedure for an instructional videotape. He was included in the site's delegation log as a sub-investigator and explanter because he performed the explant procedure on this one specific occasion. The site did not designate sub-investigator as an implanter and so he was not included in the listing of implanting clinicians by specialty and site.

Source: Generated from a Response to an Information Request for an enrollment by site summary, and Response to Information Request for the Proceduralists' specialty.

PRO-814 Major Protocol Violations

Major protocol deviations from entry criteria and treatment compliance were summarized. The criteria used for determining a major protocol violation were as follows:

- Study procedures/assessments
- Missing endpoint assessments
- Other protocol deviation
- Study treatment compliance
- Study treatment/administration/dispensing
- Visit scheduling

The Applicant summarized the major protocol violations for the ITT population. Note that the Applicant’s definition of the ITT population excluded 3 subjects on Probuphine who were randomized and received study medication, but never returned following post-baseline efficacy assessments.

Subject ID	Assigned Treatment Group	Reason for exclusion
(b) (6)	Probuphine	Lost to follow-up [after Day 1]
	Probuphine	Other (The subject is incarcerated [after Day 1]. The subject is not able to complete any of the study visits)
	Probuphine	Lost to follow-up [after Day 1]
	SL BPN	Requirement for continual use of opioid analgesics >7 days or requirement for general anesthesia for surgery ^a

a. On Day 1, after being randomized, the subject revealed that she was scheduled to undergo surgical removal of a tumor the following week and surgery had the potential to be major. As the results, the investigator felt that it was not a suitable subject for the study and the subject was withdrawn from the study.

Source: NDA 204442 Resubmission, August 27, 2015, Listing 16.2.3 Subjects Excluded From the Efficacy Analysis

The following is a summary of the major protocol deviations for the ITT population.

Category ^a	SL BPN N=89	Probuphine N=84	Total N=173
Number of Subjects with at Least 1 Major Protocol Violation	17 (19.1)	20 (23.8)	37 (21.4)
Study Procedures/Assessments	11 (12.4)	16 (19.0)	27 (15.6)
Missing Endpoint Assessments	4 (4.5)	5 (6.0)	9 (5.2)
Other protocol deviation	0	2 (2.4)	2 (1.2)
Study treatment compliance	2 (2.2)	1 (1.2)	3 (1.7)
Study treatment/administration/dispensing	1 (1.1)	0	1 (0.6)
Visit Scheduling	1 (1.1)	0	1 (0.6)

Abbreviations: ITT, intent-to-treat; SL BPN, sublingual buprenorphine

^a Subjects may have had a major protocol violation in >1 category.

Source: PRO-814 CSR, Table 5.

An imbalance in the number of patients with major protocol violations is observed for this study, with more occurring in the Probuphine arm, for Study Procedures / Assessments, missing endpoint assessments, and other protocol violations, specifically. These violations included missed visits, missed urine toxicology samples, and improper handling of urine toxicology samples. Some of the exploratory analyses performed during the review of the Resubmission, examined the impact that these types of violations could have on the ability to conclude that non-inferiority was established. Also included among the protocol violations were protocol deviations, such as psychosocial counseling not being provided for some patients at some visits.

Probuphine Clinical Trials – Initial NDA Submission (submitted October 31, 2012)

As discussed previously, the initial Probuphine NDA submission was supported by two Phase 3 safety and efficacy trials, PRO-805 and PRO-806, two safety extension trials, PRO-807 and PRO-811, that were extension trials to PRO-805 and PRO-806, respectively. There were also two clinical pharmacology studies, TTP-400-02-01, a pharmacokinetic trial evaluating 2 rods and 4 rods, (conducted outside of the US and not under IND) and PRO-810, a comparative bioavailability study that compared 4 Probuphine implants to Suboxone (buprenorphine/naloxone) sublingual tablets. Safety data from the two Phase 3 clinical trials, the two safety extension studies, and the clinical pharmacology studies were combined with the safety data for PRO-814 and comprise the Probuphine safety database for this NDA Resubmission. Clinical pharmacology data from these studies were used in justifying the proposal that Probuphine may be appropriate for patients who have achieved and sustained clinically stability and are maintained on doses of 8 mg/day or less of a buprenorphine-containing

transmucosal product. This line of inquiry was then evaluated in PRO-814, the trial that supports this NDA Resubmission.

An integrated summary of the protocols for the trials and studies that were intended to support the initial submission is provided here in brief.

INTEGRATED SUMMARY OF PROTOCOLS

The trials in the Probuphine clinical development program had a number of parallels. The studies are described collectively, and specific protocol elements that differ across the studies are emphasized.

All studies enrolled opioid-dependent patients who received sublingual buprenorphine either before enrollment or as open-label treatment during an induction phase of the study. Once a target dose of sublingual buprenorphine was achieved either on entry to the study or for three consecutive days during an induction phase, sublingual buprenorphine was discontinued, and Probuphine (or placebo) implants were inserted into the upper arm in an in-office surgical procedure. Implants were intended to remain indwelling for 24 weeks and removed in another in-office surgical procedure at the end of the 6-month treatment cycle.

Study Population

All studies enrolled opioid-dependent adults. Patients with dependence on any other psychoactive substances besides opioids or nicotine (e.g., alcohol, sedatives) were excluded. In general, patients who received treatment for opioid dependence within the previous 90 days, candidates for only short-term opioid treatment or detoxification therapy, and patients with chronic pain requiring opioids for treatment were also excluded from participation.

Outpatient Induction with SL Buprenorphine

The studies included an induction period with SL buprenorphine treatment in the form of sublingual (SL) Subutex tablets or Suboxone tablets to ensure tolerability, safety, and adequate control of opioid withdrawal symptoms and “cravings” in subjects who had not received pharmacotherapy for opioid dependence for at least 90 days prior to screening. SL Subutex tablets were used for induction during a portion of Study PRO-805 and SL Suboxone was used otherwise in the studies. Subjects had to successfully complete induction in order to be transitioned to either Probuphine implants, placebo implants or, in the case of Study PRO-806, to a defined starting dose of 12–16 mg of SL buprenorphine. All studies included in the pooled data defined successful induction as achieving a stable 12–16 mg daily SL buprenorphine dose for a minimum of 3 consecutive days within 8–16 days of having started the induction process after Screening. Subjects in TTP-400-02-01 were maintained on a dose of 8 mg to 16 mg SL Subutex prior to enrollment; this was an eligibility criterion.

24-week Treatment Period

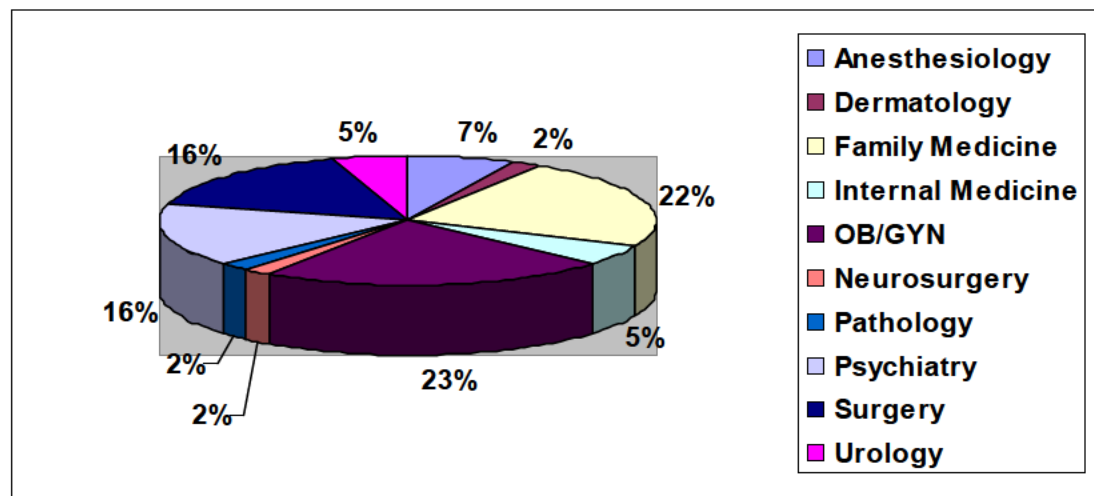
Following successful induction, meaning that the subject had reached a stable target dose of sublingual buprenorphine for a minimum of three consecutive days within 8 to 16 days of having started the induction period, subjects began double-blind treatment with four Probuphine or placebo implants or open-label treatment with sublingual buprenorphine at 12–16 mg/day.

24-week Treatment Period: Implant Insertion (Initial 4 Implants) and Removal

Implantation/Insertion of Implants

Within 12 to 36 hours after the last induction dose of SL buprenorphine, four Probuphine implants were inserted in the subject's inner upper arm in a brief, in-office procedure. All implant insertion and removal procedures were performed by trained health care providers at the clinical study sites. (The HCPs who performed implant insertion and removal procedures were licensed physicians who by his/her respective practice can be categorized as follows: approximately 7% Anesthesiology; 2% Dermatology; 23% Family Medicine; 5% Internal Medicine; 23% OB/GYN; 2% Neurosurgery; 2% Pathology; 16% Psychiatry; 16% Surgery; and 5% Urology. The breakdown is illustrated graphically below.)

Figure 2 **Implanting Physicians by Specialty**



Source: Reviewer-generated based on Response to Information Request

For Studies PRO-806, PRO-811, and PRO-810, modified surgical equipment (applicator and removal clamp), surgical techniques, and training were implemented. These modifications were intended to reduce implant procedure-related issues.

For the open-label extension studies, the opposite arm as that implanted in the preceding double-blind study was used in the majority of cases. There were 6

cases where this was not possible: 3 each for Studies PRO-807 and PRO-811, all of whom had been treated with Probuphine in the preceding double-blind study. In these instances, re-implantation occurred in a different area on the same arm.

Explantation/Removal of Implants

At the end-of-treatment visit or at early discontinuation, all implants were removed in a brief, in-office procedure.

24-week Treatment Period: Open-label Sublingual Buprenorphine Treatment

PRO-806 included an open-label sublingual buprenorphine treatment arm. Subjects' dose levels were to remain within a range of 12 to 16 mg/day SL buprenorphine throughout the 24-week treatment period.

Sublingual Buprenorphine Rescue and Additional Implant/Dose Increase

All subjects were allowed to receive limited supplemental rescue SL buprenorphine in increments of ≥ 2 mg. In the TTP-400-02-01 study, rescue medication was permissible, as clinically indicated. In the other studies, rescue medication was permissible based on the following pre-specified criteria, or at the investigator's discretion:

- Withdrawal symptoms with a score of >12 on the COWS
- Cravings with a score of >20 mm on the opioid-cravings VAS
- Subject request for supplemental SL buprenorphine deemed appropriate by the investigator

In PRO-805, PRO-807, and PRO-810, one or more of the criteria had to be met. In PRO-806 and PRO-811, all three criteria had to be met. As with the induction phase, supplemental SL buprenorphine was provided in the form of either SL Subutex tablets (Studies TTP-400-02-01 and part of PRO-805) or SL Suboxone tablets (all other studies).

Subjects requiring supplemental SL buprenorphine were required to obtain supplemental SL buprenorphine at their clinic/pharmacy for each dose. Supplemental Suboxone SL buprenorphine doses were to be administered under observation at the clinic/pharmacy to ensure compliance. A staff member served as witness that the SL tablet had completely dissolved under the subject's tongue. A maximum of 3 days of take-home dosing of Suboxone was provided for weekends/holidays or other circumstances at the discretion of the investigator, and a daily Suboxone take-home dosing log was given to the subject for drug accountability.

For all studies except the pharmacokinetics (PK) studies TTP-400-02-01 and PRO-810, subjects with the following SL buprenorphine requirements were to have received one additional implant:

- ≥ 3 days per week of supplemental SL buprenorphine for 2 consecutive weeks

- ≥8 days of supplemental SL buprenorphine over 4 consecutive weeks

Subjects were allowed to refuse the recommended additional implant, but were discontinued from the study in those circumstances. This occurred in 1 Probuphine and 2 placebo cases in Study PRO-806 only. The additional implant was not inserted within the first 2 weeks after initial implant insertion to allow for stabilization of blood levels.

In Study PRO-806, subjects in the open-label SL buprenorphine group were allowed to receive a dose increase of 2 to 4 mg arriving at a fixed dose not to exceed 16 mg/day as determined by the Investigator, if they met the above dose-increase criteria.

An investigator's decision to allow a subject to receive supplemental SL buprenorphine or a fifth implant was made on the basis of clinical signs and symptoms of opioid withdrawal symptoms or cravings, not on the basis of plasma buprenorphine levels or illicit drug use. (Investigators were blind to the results of urine toxicology tests.)

Subjects in the open-label sublingual arm were also allowed one dose reduction in response to an adverse event and if deemed clinically appropriate by the investigator. Subjects unable to tolerate 12 mg/day were discontinued from the study. Dose reductions were not permitted for subjects treated with Probuphine or placebo implants.

Psychosocial Counseling

Subjects were to receive an adequate amount of both pharmacologic and psychosocial treatment at all times while on study. For the double-blind studies PRO-805 and PRO-806, all subjects attended twice-weekly manual-guided drug counseling during study Weeks 1 through 12 and weekly drug counseling during Weeks 13 through 24. For Studies PRO-807 and 811, manual-guided individual drug counseling was provided as clinically indicated. Weekly manual-guided drug counseling was required of all subjects in Study PRO-810. Counseling was not provided for the first study, Study TTP-400-02-01.

Subject Early Withdrawal

Protocol specified criteria for early withdrawal from the study included:

- subject request
- subject non-compliance defined as refusal or inability to adhere to the study protocol:
 - if a subject missed 9 consecutive urine collections after the baseline visit, the subject was considered non-compliant and was withdrawn from the study;
 - if a subject missed 6 consecutive counseling sessions after the baseline visit, the subject was considered non-compliant and was withdrawn from the study;
 - any other instances of refusal or inability to adhere to the study protocol, as determined by the PI;

- treatment failure, defined as having either of the following supplemental buprenorphine needs any time after an implant or open-label sublingual buprenorphine dose increase:
 - ≥ 3 days/wk of supplemental SL buprenorphine for 2 consecutive wks
 - ≥ 8 days of supplemental SL buprenorphine over 4 consecutive wks
 - Subjects already at maximum dose in the OL SL buprenorphine group (16 mg) were considered treatment failures the first time the above SL buprenorphine requirements were met
- 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 >7 days”) that, in the judgment of the investigator, affected assessments of clinical status to a significant extent, required discontinuation of drug, or both;
- requirement for continual use of opioid analgesics >7 days or general anesthesia for surgery;
- at the request of Titan, regulatory agencies, or the Institutional Review Board (IRB);
- loss to follow-up.

Study Assessments

Similar safety measures were evaluated in each of the studies included in the pooled database and included extent of exposure, TEAEs, and vital signs (pupillary diameter and concomitant medications were collected in the individual study reports but were not evaluated in the pooled safety analyses). Information in regard to these outcomes was collected at each visit. Laboratory evaluations, physical examinations, and ECG were performed less frequently, per study protocol.

Study Visit Schedule

Subjects returned to the clinic numerous times during the study period for the collection of safety, efficacy, and PK data.

- Studies PRO-805 and PRO-806 had visits 3 times a week for intensive urine toxicology screening; the extension studies, PRO-807 and PRO-811, employed less frequent testing.
- Studies TTP-400-02-01 and PRO-810 were PK studies that required in-patient subject stays for approximately 3 days around the time of implantation, and also required a 24-hour post-removal inpatient period for elimination-phase blood sampling.
- In all studies except for PRO-811, subjects returned to the site for a follow-up visit 2 weeks post-removal. Study PRO-811 had the follow-up visit at 4 weeks post-removal.

Subjects were contacted by phone for a safety assessment within 1 to 5 weeks post-removal.

6 Review of Efficacy

Efficacy Summary

A 24-week, Phase 3 safety and efficacy trial, PRO-814, was completed to evaluate the efficacy of Probuphine for the maintenance of treatment of opioid dependence in a subpopulation of patients with opioid dependence. PRO-814 specifically enrolled patients who were deemed clinically stable by their treating healthcare provider, and had been maintained on a dose of no more than 8 mg/day of sublingual buprenorphine as a Subutex and Suboxone tablet equivalent. PRO-814 evaluated the efficacy of Probuphine for this subpopulation only. In this trial, subjects who were stably on 8 mg/day of Probuphine were transferred to 4 Probuphine implants or generic sublingual buprenorphine daily at their pretrial dose. This was a double-dummy trial, so those on Probuphine also received sublingual placebo, while those on daily sublingual buprenorphine also received placebo implants. Use of supplemental sublingual buprenorphine was permitted, although, use was anticipated to be rare. Study treatment was administered in conjunction with standardized, manual-based psychosocial support.

The protocol-specified primary endpoint 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. A total of 10 urine toxicology samples were collected throughout the 6 months of the study treatment period, with sample collection occurring during 6 scheduled visits (1 visit per month) and at 4 random urine toxicology visits. Self-report was collected at each of the scheduled, monthly visits. Evidence of illicit opioid use was defined as either a positive opioid urine toxicology result or self-reported illicit opioid use. For the primary efficacy endpoint, i.e., the rate of responders, a test of non-inferiority of Probuphine (active treatment) versus SL BPN (control treatment) was conducted using a 20% non-inferiority margin, as specified in the protocol. The Applicant proposed two definitions for the analysis population. The definition specified in the protocol was all subjects who have been randomized and have received an implant and/or received sublingual buprenorphine/placebo, while the Statistical Analysis Plan (SAP) definition was all randomized subjects who received study medication and provided some efficacy data. The Applicant's primary analysis used the SAP definition.

In their primary analysis, 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 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, as summarized in the table below.

Category	Probuphine n (%)	SL BPN n (%)	Proportion Difference (95% CI) Probuphine – SL BPN	P Value (2-Sided)
Applicant's Primary Analysis				
N	84	89		
Responder	81 (96%)	78 (88%)	0.088 (0.009, 0.167)	0.03
Non-responder	3 (4%)	11 (12%)		

Source: Statistical Reviewer's Replication of Applicant's Analysis

However, there were several issues identified over the course of the review that called into question, the appropriateness of the Applicant's analysis. The first is that in using the SAP definition for the analysis population, the Applicant omitted three patients in the Probuphine arm from the analysis, two of which were lost to follow-up and one who was incarcerated. These outcomes have implications for understanding treatment response with Probuphine, and should be included.

The second issue is the number of allowed months with evidence of illicit opioid use. In the above analysis, subjects were allowed two of six months with evidence of illicit opioid use, and by design, this permits submission of up to four opioid-positive samples in satisfying the responder definition. However, opioid-positive urines submitted in the three months prior to entry into the trial would render a patient ineligible for this trial. Accordingly, allowing two months with evidence of illicit opioid use does not seem justified in evaluating whether transfer to Probuphine could maintain clinical stability.

There were also a number of issues with the urine toxicology samples. Some urine toxicology samples were missing because subjects did not attend visits to provide urine samples. In other cases, the subject submitted the sample, but there were problems analyzing the samples. Although in previous addiction trials, opioid-positive samples were considered positive because they suggested that patients returned to opioid use, samples in this case were not considered positive because in a clinically stable population, the conjecture was that it is possible that not all missing samples would signify return to opioid use. However, observed data, and advisory committee member recommendation suggested otherwise. As such, it was considered more appropriate to consider urine samples in cases where patients did not present for visits to collect urine samples as positive. For improperly analyzed samples, it seemed plausible to employ a strategy where the sample is considered negative if the portions that were analyzed are negative, and vice versa.

Finally, with respect to supplemental buprenorphine use, sporadic use, if any, was anticipated. However, some patients were observed to have used supplemental buprenorphine for the entire treatment period. There is probably some minimal amount of rescue supplemental buprenorphine that could be attributed to extraordinary circumstances, but needing supplemental buprenorphine all along seems to indicate that Probuphine, which provides only a fixed dose, is not providing adequate treatment for that particular patient. Therefore, although it may seem to penalize Probuphine

unduly, the appropriate strategy for incorporating supplemental use in the definition appears to be the one that allows a finite amount of supplemental SL buprenorphine use for Probuphine, but allows all supplemental use for the SL BPN arm given that dose adjustments are a facet of management with sublingual buprenorphine, treatment as usual. In keeping with the recommendation of the Advisory Committee panel, use of sublingual buprenorphine was considered acceptable in the first and last months of Probuphine treatment (because of potential differences in the onset and duration of steady-state blood levels), while use at other points in the treatment cycle was taken to indicate inadequacy of Probuphine dose.

There are many approaches that would be considered reasonable for presenting the findings from this trial. In exploring the impact of the choice of analysis populations, the number of allowed positive months, the missing and incompletely analyzed urine toxicology samples, and the amount and pattern of supplemental use, the Agency preferred analysis is summarized below:

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			
Revised	0	Positive	Negative	Month 1 & 6	Yes	57 (66%)	57 (64%)	-0.13

Non-inferiority is established based on the protocol-specified non-inferiority margin, and also at a narrower margin, as has been recommended. Although, an NI margin of less than 13% may still be considered more appropriate, the responder rates for both are similar. This demonstrated that Probuphine is not unacceptably less effective than usual care with sublingual buprenorphine. While some patients may need some supplemental doses (labeling will emphasize that it should be minimal, and that ongoing use would indicate that the dose of Probuphine is inadequate for that patient), they can still be maintained and relapse can be prevented.

Probuphine provides an alternative treatment option for clinically stable patients, and again, clinical stability must be stressed, who may value the convenience that Probuphine offers in terms of not needing to travel with bottles, not needing to take medication on a daily basis for long-term and even lifelong use, reduced risk of accidental exposure for children who may be in the home, or the overall discreetness that Probuphine may offer. Additionally, Probuphine reduces the risk of misuse, abuse, and accidental pediatric exposure; however, these could occur if the implants come out accidentally or are removed, so it must be emphasized that it does not eliminate this risk.

6.1 Indication

The Applicant proposes the following language – taken from draft labeling – as the indication for Probuphine:

“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 proposed indication, however, does not fully define the patient population enrolled in PRO-814 and evaluated for Probuphine. This indication would indicate that all comers, including new entrants to treatment, would be appropriate for Probuphine. However, only a subpopulation of patients, specifically patients who are considered clinically stable by their treating health care provider, and meeting additional criteria based on buprenorphine treatment history and urine opioid toxicology status, were studied in the PRO-814 trial. The proposed indication should thus reflect the population that was eligible for the study intended to establish efficacy.

6.1.1 Methods

Efficacy data derive from the PRO-814 trial described above (Section 5.3). The Statistics Reviewer, Dr. James Travis, repeated the Applicant’s analyses to determine whether the Applicant’s findings could be reproduced if the same datasets and analytic procedures were employed. Given the novelty of many aspects of the study design, the primary analysis was subject to intense scrutiny and a number of sensitivity analyses were performed by the Statistics Reviewer to explore findings from the Probuphine and sublingual buprenorphine arms based on responder definitions that were considered to have more clinical relevance.

6.1.2 Demographics

Demographic and baseline characteristics for the PRO-814 trial are summarized below.

Table 5 Demographic Information – PRO-814

Category	Probuphine N=87	SL BPN N=89	Total N=176
Age (years)			
Mean (SD)	38 (11.2)	39 (10.8)	39 (11.0)
Min, max	21, 63.0	22, 64.0	21, 64.0
Gender, n (%)			
Male	52 (59.8)	52 (58.4)	104 (59.1)
Female	35 (40.2)	37 (41.6)	72 (40.9)

Category	Probuphine N=87	SL BPN N=89	Total N=176
Race, n (%)			
White	82 (94.3)	85 (95.5)	167 (94.9)
Black or African American	3 (3.4)	2 (2.2)	5 (2.8)
Asian	1 (1.1)	0	1 (0.6)
American Indian or Alaska native	0	1 (1.1)	1 (0.6)
Other	0	1 (1.1)	1 (0.6)
Ethnicity, n (%)			
Hispanic or Latino	3 (3.4)	3 (3.4)	6 (3.4)
Not Hispanic or Latino	84 (96.6)	86 (96.6)	170 (96.6)
BMI (kg/m²)			
Mean (SD)	28 (6.94)	27 (5.92)	28 (6.47)
Min, max	14, 46.4	19, 50.6	14, 50.6

Source: Adapted from PRO-814 Clinical Study Report, Table 7 Demographics (Safety Population), p. 57

The population studied in PRO-814 was a predominantly male, almost exclusively white, non-Hispanic/non-Latino group. Patients were about 40 years of age, on average, and all under 65 years of age.

Table 6 Opioid Abuse and Treatment History – PRO-814

Category	Probuphine N=87	SL BPN N=89
Primary Opioid of Abuse		
Prescription opioid pain reliever	66 (76)	65 (73)
Heroin	5 (5.7)	2 (2.2)
Other	--	1 (1.1)
Mean Buprenorphine Treatment Episode Duration Prior to Entry (Min, Max)	2.1 (0.05*, 14)	1.8 (0.2†, 7.7)
Buprenorphine Treatment Episode Prior to Entry < 24 weeks (6 months)	13 (15)	15 (17)
Mean Highest Lifetime Buprenorphine Dose (Min, Max)	14 (2,32)	14 (4,36)
Highest Lifetime Dose (mg/day)		
8 mg	31 (36)	26 (29)
16 mg	31 (36)	41 (46)
≥24 mg	11 (13)	11 (12)
Buprenorphine Dose at Study Entry (mg/day)		
2	6 (7)	3 (3)
4	12 (14)	15 (17)
6	8 (9)	4 (5)

Category	Probuphine N=87	SL BPN N=89
8	61 (70)	67 (75)

For Subject 012-006 (Probuphine), the substance abuse and substance abuse treatment histories were not completed at the screening visit

* 0.05 years $\approx$ 2.6 weeks / <1 month; $\pm$ 0.02 $\approx$ 8 weeks / 2 months

Source: Adapted from Table 7, PRO-814 CSR, p. 57, and Applicant response to Agency Information Request. Adapted from Table 9, PRO-814 CSR, pp. 59 – 60.

Subjects in PRO-814 reported prescription opioids as their primary opioid of abuse. In contrast, the population of new entrants to treatment studied in the earlier trials, PRO-805 and PRO-806, for the initial application submission, more commonly identified heroin as their primary opioid of abuse.

On average, subjects had been on buprenorphine for two years consecutively before entering the study. There were a total of 28 patients with a buprenorphine treatment episode prior to entry of less than 24 weeks, which would indicate that these subjects did not meet the clinical stability criteria as had been envisioned. It should be noted that these data may not fully represent the length of the treatment episode prior to entry. As mentioned earlier, patients were asked only how long they were on buprenorphine treatment in their lifetime. As such, these data are a rough approximation, indirectly estimated by the Applicant, from other sources of data available in the submission, e.g., from the concomitant medications history collected during Screening. The Applicant does not appear to have directly captured the specific length of the buprenorphine treatment episode prior to entry, by asking the question of either patients and/or providers. This was the intended criterion when the protocol was envisaged, and so this was a disappointing discovery unearthed during the review. However, for these patients, their reported lifetime buprenorphine history was on average 34 months, or nearly three years, and the shortest duration was six months for one patient, with the longest lifetime duration being almost 10 years. A potential break in lifetime treatment such that the treatment episode prior to randomization was in fact less than 24 weeks cannot be ruled out.

Lifetime buprenorphine history data for patients falling into the less than 24 week category were examined to determine if additional information could be garnered from these data. The lifetime buprenorphine treatment information was taken together with the data on the number of times that a patient entered buprenorphine treatment in their lifetime in further estimating the length of the treatment episode prior to entry. If the lifetime buprenorphine history was > 180 days (6 months), and the patient entered buprenorphine treatment only once, that patient would have been considered to have the intended minimum six months of continuous buprenorphine treatment prior to entry, because no interruption in treatment would have been reported. Of the 28 subjects identified above, the number was reduced, and there were 12 subjects who had a lifetime buprenorphine history less than 6 months and/or endorsed entry into buprenorphine treatment history more than once. These included four patients in the

Probuphine arm (5%), and 8 patients in the SL buprenorphine arm (9%). Although these numbers are not definitive, it is reassuring that aside from these 12 patients, enrolled subjects appear to have met the criterion of having a minimum of six months of buprenorphine treatment prior to entry.

The highest lifetime dose for the patients in the trial was 14 mg/day on average for both groups. The highest lifetime individual doses reported on average were 8 mg, 16 mg, and 24 or more daily. The daily dose endorsed by most of the sublingual buprenorphine group was 16 mg, with 46% of those subjects reporting 16 mg as their highest dose. At study entry, the majority of subjects were on the 8-mg dose.

The treating healthcare providers also completed a clinical stability checklist. A general summary of the results from the assessment is provided below:

Table 7 Stability Checklist Results – PRO-814

Stability Checklist Items – %	Probuphine N=87	SL BPN N=89*
Patient has not reported any illicit opioid drug use in the past 90 days	100	100
Patient has a stable living environment	98	100
Patient participates in a structured activity/job that contributes to the community	84	89
Patient has not reported significant withdrawal symptoms in the past 90 days	99	99
Patient has consistently participated in recommended cognitive behavioral therapy/peer support program	75	71
Patient has been consistently compliant with clinic visit requirements	97	98
Patient has reported low to no desire/need to use illicit opioids in the past 90 days	97	96
No episodes of hospitalizations (addiction or mental health issues), emergency room visits, or crisis interventions in the previous 90 days	74	82
Please describe any other indicators of clinical stability that you have observed		

On the clinical stability checklist, the health care providers were to check all the items that applied to their patients. The health care providers widely endorsed many of the items for their patients. Only participation in a structured activity or job; consistent participation in a recommended cognitive behavioral therapy program or support program; and having no episodes of hospitalizations, ER visits, or crisis intervention were not as widely endorsed, but still represent relatively high proportions of the patients. The Applicant noted that it is possible that the criterion of no hospitalizations, ER visits, or crisis intervention may have been underreported because of a form error

(specifically, that unlike each of the other items, there was no space provided to check off this item).

6.1.3 Subject Disposition

Subject disposition is presented in the following table.

Table 8 Subject Disposition – PRO-814

Category	SL BPN	Probuphine	Total
Randomized	90	87	177
Safety Population (N)	89	87	176
Completed, n (%)	84 (94.4)	81 (93.1)	165 (93.8)
Discontinued, n (%)	5 (5.6)	6 (6.9)	11 (6.3)
Reason for discontinuation, n (%)			
Adverse event	0	1 (1.1)	1 (0.6)
Request of sponsor or regulatory agency	1 (1.1)	0	1 (0.6)
Lost to follow-up	2 (2.2)	4 (4.6)	6 (3.4)
Other ^a	0	1 (1.1)	1 (0.6)
Subject request	2 (2.2)	0	2 (1.1)

Abbreviations: SL BPN, sublingual buprenorphine

^a Subject was incarcerated and not able to complete the study visits.

Source: PRO-814 Study Report

The vast majority of the subjects completed the study. For PRO-814, the subject disposition results for those included in the “completed” category above, and the treatment exposure data for those with 24 weeks of exposure as shown in the table below, appeared to be conflicting.

Table 9 Summary of Treatment Exposure (Safety Population) – PRO-814

Category	SL BPN N=89	Probuphine N=87	Total N=176
Subjects with at least, n (%)			
6 weeks of exposure	88 (98.9)	83 (95.4)	171 (97.2)
12 weeks of exposure	88 (98.9)	82 (94.3)	170 (96.6)
18 weeks of exposure	87 (97.8)	81 (93.1)	168 (95.5)
24 weeks of exposure	61 (68.5)	57 (65.5)	118 (67.0)
Exposure (days)			
Mean (SD)	167.5 (17.36)	159.6 (35.42)	163.6 (28.00)
Median	169.0	169.0	169.0
Min, Max	35, 190	1, 191	1, 191

Abbreviations: SD, standard deviation; SL BPN, sublingual buprenorphine

Source: PRO-814 Study Report

Based on the disposition summary, approximately 94% of subjects were in the completed category for the study. In contrast, for extent of exposure, on average, fewer than 70% of patients had 24 weeks of exposure. Because all patients received implants that were to remain in place for 24 weeks, the disposition data and extent of exposure data appeared contradictory.

In response to a request for clarification of this apparent discrepancy, the Applicant explained that it is correct that approximately 94% of subjects completed the study, as defined by completing the Week 24 EOT visit, including the implant removal procedure. For these subjects, exposure ended at the Week 24 EOT visit. Due to the 7-day visit window allowance, the Week 24 EOT visit could have occurred before or after Day 168 (=24weeks*7days), but not necessarily exactly on Day 168. Any subject that did not have the EOT visit at or after Day 168 was captured as having less than 24 weeks exposure (e.g., 23.7 weeks for 166 days). Based on the cutoff of 168 days, approximately 94% of the subjects completed the Week 24 EOT visit, with 93% of the subjects with at least 23 weeks of exposure and 67% of the subjects had exposure of at least 24 weeks.

6.1.4 Analysis of Primary Endpoint(s)

Primary Endpoint and Primary Efficacy Analysis

The protocol-specified primary endpoint 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. A total of 10 urine toxicology samples were collected throughout the 6 months of the study treatment period, with sample collection occurring during 6 scheduled visits (1 visit per month) and at 4 random urine

toxicology visits. Self-report was collected at each of the scheduled, monthly visits. Evidence of illicit opioid use was defined as either a positive opioid urine toxicology result or self-reported illicit opioid use.

For the primary efficacy variable, i.e., the rate of responders, a test of non-inferiority of Probuphine (active treatment) versus SL BPN (control treatment) was conducted using a 20% non-inferiority margin, as specified in the protocol. In defining the non-inferiority margin, the Applicant searched literature sources to find information about the historical effect of sublingual buprenorphine, and conducted a survey of addiction experts. The Applicant provided four publications and summarized the references as follows.

A meta-analysis of tapered discontinuation following long-term methadone or BPN treatment found an average abstinence rate of 33% (Korner & Waal, 2005)²⁶. However, because of the differences in methodology (single or double-blinding, naturalistic, etc.), definitions of abstinence, treatments administered during MAT and durations of follow-up, some studies are more relevant than others. In addition, this article didn't report on the baseline rates of percentage abstinence or urine toxicology results.

Breen et al., (2003)²⁷ reported on a study of stable methadone patients (for at least 6 months) to BPN and then gradual reduction to 0 mg BPN (i.e., blinded) over an average duration of 11 weeks showed that subjects at 1 month follow-up after complete BPN discontinuation had 31% negative opioid samples (relative to about 73% negative at baseline, 89% negative during BPN induction, and 91% negative during BPN taper).

One double-blind, double-dummy study in methadone users found 25% abstinence overall during 1 month follow-up after complete discontinuation following gradual taper regimens. Abstinence was 18% in the "rapid" withdrawal group (taper over 10 weeks) (versus 100% negative urine opioid results for 4 weeks preceding study entry and 92% negative for the 6 months prior to the study) (Senay, 1977)²⁸.

Most of the studies used tapered discontinuation, but in terms of abrupt discontinuation, one survey study in Australia reported that 15% of patients who abruptly discontinued opioid maintenance therapy (BPN or methadone) were abstinent for at least 3 months, while 26-27% were abstinent with either self- or physician-directed taper regimens (Winnstock et al., 2011)²⁹.

²⁶ Kornør H, Waal H. From opioid maintenance to abstinence: a literature review. *Drug Alcohol Rev.* 2005 May;24(3):267-74.

²⁷ Breen CL, Harris SJ, Lintzeris N, Mattick RP, Hawken L, Bell J, Ritter AJ, Lenne M, Mendoza E. Cessation of methadone maintenance treatment using buprenorphine: transfer from methadone to buprenorphine and subsequent buprenorphine reductions. *Drug Alcohol Depend.* 2003 Jul 20;71(1):49-55.

²⁸ Senay EC, Dorus W, Goldberg F, Thornton W. Withdrawal from methadone maintenance. Rate of withdrawal and expectation. *Arch Gen Psychiatry.* 1977 Mar;34(3):361-7.

²⁹ Winnstock AR, Lintzeris N, Lea T. "Should I stay or should I go?" Coming off methadone and buprenorphine treatment. *Int J Drug Policy.* 2011 Jan;22(1):77-81. doi: 10.1016/j.drugpo.2010.08.001. Epub 2010 Oct 16.

Based on these published sources, the Applicant summarized that previous studies with patients on longer term buprenorphine or methadone treatment found that 18 to 31% of patients remained abstinent following treatment discontinuation. In addition to the limited literature sources, the Applicant also conducted a survey of addiction experts (N=18). The results of the survey of addiction specialists are summarized in the table below.

The key questions in the physician survey that were used by the Applicant to inform the proposed non-inferiority analysis were:

- *In this same patient population [clinically stable patients on 8 mg/day or less of sublingual buprenorphine], how often do you expect the average stable patient in your practice to test positive for opioids over a 6-month period?*
 - Responses to this question were converted to opioid-negative urines and were reported as the proportion of negative urine drug screens anticipated over six months (% Negative UDS Over 6 mths). As seen in the table, on average, the specialists endorsed that their clinically stable patients would submit opioid-negative samples more than 90% of the time.
- *If these patients were to continue on the same dose, what would be the overall average percentage of opioid-negative urine toxicology result would you anticipate in 6 months?*
 - Responses to this question were reported as the amount of opioid-negative urines anticipated over the next 6 months. The respondents endorsed a proportion only slightly less than that for the first six months.
- *If their [clinically stable patients] buprenorphine treatment were to be stopped, what would be the average percentage of relapse in these patients over a 6-month period?*
 - This question was intended as a means of approximating the placebo response in these patients. On average, the respondents believed that approximately 70% of these patients would relapse if their buprenorphine treatment were to be stopped.
- *Assume urine toxicology is measured monthly for six months. What would you consider to be the maximum reasonable change in a stable patient's urine toxicology status, for the patient to continue to be considered stable?*
 - For this question, respondents were given four choices:
 - No change
 - 1 out of 6 urine-positive urine toxicology
 - 2 out of 6 urine-positive urine toxicology
 - 3 or more out of 6 urine-positive urine toxicology
 - These were converted to percentages to report the results. On average, the specialists thought that 14% was a reasonable change, which, as a percentage, is closest to 1 out of 6 positive urine toxicology

results over that period. Taken together with the earlier questions about expected urine toxicology status for one six-month period and a subsequent six-month period, this question was used to help define a responder. With buprenorphine, the specialists on average considered that their clinically stable patients would submit an opioid-positive urine sample one or fewer times in the first 6 months, and one or fewer times in the subsequent 6 months if they continued on buprenorphine. If they were to have one additional positive urine during a 6-month period, the respondents on average thought that those patients could still be considered stable in that setting. Given these survey outcomes, a responder was defined as a patient having no more than 2 months with evidence of illicit opioid use.

Table 10 Summary of Survey Results from Addiction Specialists

PI #	% Negative UDS Over 6 mths*	% Negative UDS Over Next 6 mths*	% Relapse upon BPN Discontinuation (Over 6 mths)	Maximum Reasonable Change in % UDS Positive	% of Patients
1	100	83	85	0	85
2	75	80	75	17	65
3	NNR	DNAQ	NNR	33	55
4	NNR	90	35	17	10
5	75	91.5	70	17	60
6	NNR	NNR	NNR	17	55
7	99	95	90	17	95
8	80	95	80	17	20
9	95	95	80	8.5	80
10	NNR	65	75	33	60
11	83	90	75	17	66
12	100	80	95	0	85
13	100	100	60	0	10
14	100	90	30	0	90
15	91.5	90	75	17	60
16	91.5	90	50	17	80
17	100	90	90	17	90
18	100	100	60	8.5	NNR
Mean					
(Median)	92 (97)	89 (90)	70 (75)	14 (17)	63 (65)
Range	75-100	65-100	30-95	0-33	10-95

Source: Adapted from PRO-814 Protocol, Amendment 3, Section 17, Summary of Survey Results from Addiction Specialists, p. 68.

The Applicant found that the addiction specialists reported that a median of 25% of subjects who were stabilized on 8 mg/day or less of sublingual buprenorphine would not relapse upon discontinuation of their buprenorphine dose. The Applicant estimated that the response rate for subjects receiving placebo would be 25% and the effect size for patients who continued buprenorphine treatment would be 75%. The effect size is the difference between the comparator (placebo) response rate and the treatment group response rate; therefore this effect size implies an assumption that all subjects who continue to receive their sublingual buprenorphine dose would remain stable, i.e. the

response rate would be 100%. Using this estimate, the Applicant selected a NI margin of 20% for this study. This margin was chosen to preserve at least 70% of their estimated effect size of the sublingual buprenorphine, which they considered to be clinically acceptable.

To determine if Probuphine was non-inferior to sublingual buprenorphine, the following procedure was followed: Let π_c and π_t represent the proportion of responders at 24-weeks for the active control arm (sublingual buprenorphine) and the experimental treatment arm (Probuphine), respectively. 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:

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

This hypothesis can then be tested by checking whether the lower bound of the 95% confidence interval for the difference between Probuphine and sublingual buprenorphine is larger than -0.20. If this is true, then the null hypothesis of inferiority can be rejected and non-inferiority can be concluded. The Applicant used the standard Wald confidence intervals for this test.

The typical conditions needed for a non-inferiority study were not present in this situation. What information could be gleaned from literature and the survey was used in designing this trial, again with the understanding that careful review of the findings would be undertaken because of the many uncertainties with a trial design such as this one.

Handling of missing data: For this analysis, the primary imputation utilized by the Applicant involved a 20% (non-inferiority margin) relative penalty. With this imputation scheme, missing urine values in the sublingual buprenorphine group were imputed based on the proportion of “opioid-positive” samples within the treatment group. This proportion was the average of the within-subject proportion of “opioid-positive” samples. The Applicant made the primary analysis 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 proportions of “opioid-positive” samples were to be 14% for the Probuphine group and 15% for the sublingual buprenorphine group, the imputation for the sublingual buprenorphine group would be based on 15% and the imputation for the Probuphine group would be based on 18%. The Applicant stated that because this was an active-controlled study, bias would be introduced if all missing values were replaced with extreme values (i.e., either all replaced with “negative” or all replaced with “positive”). The Applicant proposed the imputation scheme as above. Advisors and consultants participating in the January 12, 2016, Advisory Committee meeting disagreed, and felt if a patient failed to appear for visits or to provide requested urine samples, this was very likely to be a “red flag” for having resumed illicit opioid use, because patients in buprenorphine treatment typically have knowledge of the timing of detection of use by urine toxicology and are experienced in avoiding detection. The

Committee advised that it was appropriate to assume that a missing sample would be positive.

Analysis Populations: The Intent-to-Treat (ITT) Population was selected as the primary analysis population by the Applicant. There were two different definitions for this population, the definition as specified in the study protocol and the definition as specified in the statistical analysis plan (SAP):

Study Protocol Definition	All subjects who have been randomized and have received an implant and/or received sublingual buprenorphine/placebo.
Statistical Analysis Plan Definition	All randomized subjects who received study medication and provided some efficacy data.

Of the two definitions, the Applicant opted to use the SAP definition for the analysis population, and analyses based on this analysis population definition were included in the final study report. The review team considers the first definition, the study protocol definition, to be appropriate and more consistent with customary definitions for ITT or modified ITT (mITT) populations. Advisors and consultants participating in the January 12, 2016, Advisory Committee also endorsed the definition specified in the protocol as the more appropriate ITT definition, noting that if a previously-stable patient were completely lost to follow-up after receiving study medication and provided no efficacy assessments, that would most likely indicate a poor clinical outcome. Thus, such patients could not be excluded from the efficacy analysis.

Applicant’s Primary Efficacy Analysis

The Applicant’s primary analysis employed the SAP-defined ITT population, the responder definition of ≤ 2 of 6 months with evidence of illicit opioid use, the imputation strategy described above, and did not account for supplemental sublingual buprenorphine use in any way in the responder definition. 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 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 a number of issues with the primary analysis that were identified on review.

Category	Probuphine n (%)	SL BPN n (%)	Proportion Difference (95% CI) Probuphine – SL BPN	P Value (2-Sided)
Applicant’s Primary Analysis				
N	84	89		
Responder	81 (96%)	78 (88%)	0.088 (0.009, 0.167)	0.03
Non-responder	3 (4%)	11 (12%)		

Source: Statistical Reviewer’s Replication of Applicant’s Analysis

Reanalysis of PRO-814 Clinical Trial Efficacy Data

On review of the efficacy data, a number of the assumptions made by the Applicant did not appear justified.

- **Definition of ITT Population:** The first is the definition of the ITT population. Again, the Applicant defined the ITT, or intent-to-treat, population, as randomized subjects who were randomized *and* received study medication, *and* provided post-baseline efficacy data. Based on this definition, three patients in the Probuphine arm, who received study medication, but never returned again after receiving treatment, were omitted from the Applicant's analyses. These included two patients who were lost to follow-up, and one incarcerated patient. However, in a patient population deemed stable by their treating healthcare providers, discontinuations for these reasons in patients who just underwent procedures to insert Probuphine, would seem to have implications for judging treatment response. The incarceration, for example, may be considered a *direct* measure of the consequences of opioid addiction, as opposed to the *indirect* measure of drug-taking behavior, which is used as a surrogate marker for these physical and psychosocial consequences, the outcomes of interest. Additionally, for the two patients who were lost to follow-up, it is conceivable that they could have removed the rods or implants immediately after insertion for illicit purposes.
- **Urine samples:** Some urine toxicology samples were missing because subjects did not attend visits to provide urine samples. In other cases, the subject submitted the sample, but there were problems analyzing the samples. Of the total samples collected, samples that were missed or not properly analyzed occurred more frequently in the Probuphine arm than the sublingual buprenorphine arm. Of the samples submitted and analyzed, a higher proportion of positive samples were seen in the sublingual buprenorphine arm, as demonstrated in the table below.

Treatment Group	Negative n (%)	Positive n (%)	Incomplete Result n (%)	Missing Sample n (%)	Total
SL BPN (n=89)	765 (86.0%)	64 (7.2%)	34 (3.8%)	27 (3.0%)	890
Probuphine (n=87)	725 (83.3%)	31 (3.6%)	60 (6.9%)	54 (6.2%)	870

Source: Probuphine Statistical Review, Feb 2016, Table 6.

- **Supplemental buprenorphine use:** Although supplemental buprenorphine use was anticipated to be sporadic among stable patients, some patients required supplemental sublingual buprenorphine throughout the entire treatment period. None of the patients who required supplemental sublingual buprenorphine during the trial had received supplemental buprenorphine in the six months prior to entry to the study. Although the transmucosal forms of buprenorphine used to treat opioid addiction allow for dose titration, and so appears acceptable for examining the

treatment as usual arm, Probuphine is a non-titratable, fixed dose product that does not provide the same paradigm for dose adjustment.

Among the randomized subjects (who received study medication), approximately half completed the study and provided ten negative urine samples. These subjects are represented in the table as having no issues. For the remaining subjects, the issues identified for each subject are summarized. Note that the issues that were identified are not mutually exclusive.

Issue	Probuphine 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: Probuphine Statistical Review, Feb 2016, Table 7.

The Statistical Reviewer, Dr. Travis, conducted a number of sensitivity analyses to explore these concerns with the efficacy data. The analyses explored the effect of the chosen analysis population, the choice of responder definition, methods for handling missing data, and rescue use. The analyses are summarized in the table below.

Table 11 Summary of Analyses – PRO-814

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; SL BPN = sublingual buprenorphine

Source: Probuphine Statistical Review, Feb 2016, Table 13.

In the Agency's analyses, the analysis population, summarized in the first column of the table, includes the three patients omitted by the Applicant, and is referred to as the Revised analysis population. It is assumed that being completely lost to follow-up or being incarcerated are not positive outcomes in addiction treatment, and, therefore, these patients have been reinstated in the analysis population and included in the analyses as non-responders. The number of allowed positive months was also explored. The Applicant's responder definition allowed subjects to have up to two months of illicit opioid use. Said another way, a subject could submit as many as four opioid-positive urine samples – two monthly samples and two random samples in those same two months – and be considered a responder. However, allowing two months of opioid use does not appear to be justified clinically in a population that had not been using opioids before entering the trial. Recall that subjects were required to have had no positive urine toxicology results for at least the last 90 days prior to enrollment. Panel members at the January 12, 2016, Advisory Committee agreed that it was not warranted to allow two months of opioid use in defining a responder. As such, the analysis in which any positive sample (particularly when there are so few samples) indicates treatment failure might come closest to representing the true effect of the treatment.

The original assumptions made about missing urine samples when the protocol was being devised may need to be reconsidered. It was anticipated that the overwhelming majority of patients would submit opioid-negative samples and that an imputation strategy that doesn't assume missing samples are positive would be appropriate. However, it was observed that fully 20% of the patients actually provided a positive sample, which suggests that the original assumptions in that regard were incorrect. Accordingly, a missing = positive approach seems like the more appropriate strategy for handling missing urine toxicology data. There were a number of samples where the patient presented for the visit, submitted a sample, but because of issues with the specimen, those samples were not analyzed properly. In those cases where the samples were provided, but not analyzed correctly, it seems plausible to employ a strategy where the sample is considered negative if the portions that were analyzed are negative, and vice versa. This approach was endorsed by the experts at the January 12, 2016, PDAC meeting.

Finally, for the examination of the extent and pattern of rescue use, a few permutations were examined including all permitted, none permitted, up to 2 uses permitted, and use permitted during the first and last months of treatment. The latter strategy was employed based on the recommendation of the committee members at the January 12, 2016, Advisory Committee. There is probably some minimal amount of supplemental buprenorphine that could be attributed to extraordinary circumstances, but needing supplemental buprenorphine all along seems to indicate that Probuphine, which provides only a fixed dose, is not providing adequate treatment for that particular patient. This would further imply that Probuphine would probably not be appropriate for such a patient for any future treatment, if Probuphine failed the clinically stable patient on the initial treatment trial. Therefore, although it may seem to penalize Probuphine unduly, the appropriate strategy appears to be the one that allows a limited amount of supplemental SL buprenorphine for Probuphine, but allows all supplemental use for the SL BPN arm given that dose adjustments are part and parcel of management with sublingual buprenorphine, treatment as usual. In keeping with the recommendation of the Advisory Committee panel, use of sublingual buprenorphine was considered acceptable in the first and last months of Probuphine treatment (because of potential differences in the onset and duration of steady-state blood levels), while use at other points in the treatment cycle was taken to indicate inadequacy of Probuphine dose. At the same time, use of supplemental sublingual buprenorphine was considered appropriate at any point along the treatment cycle for those in the sublingual buprenorphine arm. The preferred analysis from a clinical perspective is that analysis summarized in the last row of the table. Using the protocol-specified NI margin, non-inferiority is established. It should also be noted that, in many cases, patients in both arms who received supplemental dosing successfully refrained from illicit opioid use (per self-report and toxicology results), indicating that even some "non-responders" can be adequately managed with appropriate clinical care. However, to provide a realistic expectation of the proportion of patients treated with Probuphine who can be expected

to have a relapse-free clinical course without need for supplemental dosing, the definition applied here seems appropriate.

Using the protocol-specified non-inferiority margin, non-inferiority was established for Probuphine in all but two of the cases. In the Statistical Review, Dr. Travis explores each of these issues individually and in greater detail. The reader is referred to the Statistical Review for a sequential discussion of each of these items. Upon review of the PRO-814 efficacy data, the Statistical Reviewer concluded that non-inferiority cannot be concluded for the more conservative margin that Dr. Travis considers more appropriate. Dr. Travis notes that although the Applicant's original non-inferiority margin is met, he does not believe that this margin is appropriate given the differences between the assumed and observed response rates for sublingual buprenorphine, when the non-inferiority was originally being selected.

On review of the summary of efficacy findings, non-inferiority would be established for most, although not all of the analyses at narrower margins than pre-specified, as has been recommended. Although, an NI margin of less than 13% may still be considered more appropriate, the responder rates for both treatment arms are similar. Therefore, overall, the efficacy data show that Probuphine is not unacceptably worse than treatment as usual with sublingual buprenorphine. While some patients may need some supplemental doses (labeling will emphasize that it should be minimal, and that ongoing use would indicate that the dose of Probuphine is inadequate for that patient), they can still be maintained and relapse can be prevented.

Probuphine provides another treatment option for clinically stable patients, who may value the convenience that Probuphine offers in terms of not needing to travel with bottles, not needing to take medication on a daily basis for long-term and even lifelong use, reduced risk of accidental exposure for children who may be in the home, or the overall discreetness that Probuphine may offer. Additionally, Probuphine reduces the risk of misuse, abuse, and accidental pediatric exposure; however, these could occur if the implants come out accidentally or are removed, so it must be emphasized that it does not eliminate this risk.

6.1.5 Analysis of Secondary Endpoints(s)

The Applicant specified several secondary endpoints that included the following:

- Percent of subjects with no urine illicit opioid use by month
- Time to first evidence of urine illicit opioid use
- Cumulative percentage of evidence of urine illicit opioid use by month
- Percent of subjects with no self-reported illicit drug use by month
- Measures of craving: desire to use visual analogue scale (VAS) and need to use VAS
- Measures of withdrawal: clinical opiate withdrawal scale (COWS) and subjective opioid withdrawal scale (SOWS).

No multiplicity adjustment was made for these endpoints. Hence, these secondary endpoints are exploratory, providing only supporting information for the primary endpoint. These data cannot support any efficacy claims, and will not be discussed further.

6.1.6 Other Endpoints

This section is not applicable to the review. There were no other additional endpoints analyzed.

6.1.7 Subpopulations

Results of the analysis by gender using the preferred responder analysis described above revealed that response rates were similar for females and males.

Gender	Category	Probuphine n (%)	SL BPN n (%)
Female	N	35	37
	Responder	23 (66%)	26 (70%)
	Non-Responder	12 (34%)	11 (30%)
Male	N	52	52
	Responder	34 (65%)	31 (60%)
	Non-Responder	18 (35%)	21 (40%)

Source: Probuphine Statistical Review, Feb 2016, Table 14.

Subgroup analyses based on BMI categories of obese/non-obese and overweight/not overweight were also conducted. No consistent effect was observed across BMI categories.

The Applicant did not conduct subgroup analyses based on race and age because most of the population was almost exclusively white, and all were below 65 years of age.

Subgroups based on pretrial buprenorphine treatment duration, transmucosal buprenorphine formulation used pretrial, and buprenorphine dose at study entry were also examined. A treatment effect based on buprenorphine treatment duration immediately before trial entry was not demonstrated. As described earlier in this review, these data, however, were a rough approximation, and although the eligibility criteria rest on this information, these data were not the most reliable.

The transmucosal form, to which Probuphine has been compared, is the sublingual buprenorphine tablet. However there are other transmucosal forms on the market, and some, like the SL film, offer higher levels of buprenorphine exposure at the same nominal dose of the tablet. As with pretrial treatment duration, a treatment effect was not demonstrated based on transmucosal formulation use, specifically film use, pre-trial. There was also no treatment effect observed by prior dose. However, it was observed

that subjects previously receiving 8 mg/day of sublingual buprenorphine had a lower response rate overall compared to those receiving a lower dose.

Prior Dose	Category	Probuphine n (%)	SL BPN n (%)
Received 8 mg	N	61	67
	Responder	38 (62%)	40 (60%)
	Non-Responder	23 (38%)	27 (40%)
Received less than 8 mg	N	26	22
	Responder	19 (73%)	17 (77%)
	Non-Responder	7 (27%)	5 (23%)

Source: Probuphine Statistical Review, Feb 2016, Table 14.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Additionally, “behavioral” stability was explored by evaluating use of other illicit substances while on treatment. No consistent effect was shown based on this parameter. However, this was again another piece of information that was not adequately captured by the Applicant.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Only a single, fixed-dose of Probuphine for six months was examined in this population. There were no explorations beyond this six-month period. When examining the submission of opioid-positive urines and sublingual buprenorphine, there was no clear pattern that suggests fluctuations in efficacy that are time based. This is illustrated in the figure below, which shows the points at which supplemental buprenorphine was dispensed, and when positive urine samples were submitted. (Missing urines are considered positive). For each occasion that supplemental buprenorphine was dispensed (in 2 mg tablets), the duration of the supply was calculated based on the patient using one 2 mg tablet per day and the length of the line illustrates the duration that supplemental medication could have been used based on the supply provided.

Figure 3 Summary of Supplemental Buprenorphine Use and Urine Toxicology Results

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SL BPN = sublingual buprenorphine

Source: Statistical Review. Figure 4: Missing or Incomplete Urine Tests imputed as Positive and Use of Supplemental Medication Considered to be Non-Response

6.1.10 Additional Efficacy Issues/Analyses

This section is not applicable to the review. There were no other additional efficacy issues and analyses for this review.

7 Review of Safety

Safety Summary

For this Review of Safety, safety data from the following sources were reviewed.

Phase 3 Safety and Efficacy Trials:	PRO-805, PRO-806, and PRO-814
Phase 3 Extension Trials:	PRO-807 & PRO-811
Clinical Pharmacology Studies:	TTP-400-02-01 & PRO-810

The Applicant's submission included pooled safety data from the Phase 3 safety and efficacy trials, PRO-805, PRO-806, and PRO-814, which were supplemented by data from two follow-on extension studies (PRO-807 and PRO-811) to each of the primary Phase 3 safety and efficacy trials (PRO-805 and PRO-806, respectively), that were submitted with the initial submission. Limited safety data were available from the clinical pharmacology studies, and were used to supplement and complement safety data provided by the major contributors to the safety database, namely the Phase 3 double-blind and extension studies.

As Probuphine is an implantable formulation of buprenorphine, the general framework used for the Review of Safety was one that centered broadly on (1) safety of Probuphine as it relates to the systemic effects of buprenorphine (buprenorphine drug substance), the active ingredient; and (2) safety of Probuphine as it relates to the implants themselves, indwelling foreign bodies, and the insertion and removal procedures necessary for Probuphine administration.

The safety profile for the transmucosal buprenorphine formulations has been fairly well-characterized. Probuphine provides much lower exposure to buprenorphine than target doses of the transmucosal formulations, from which our understanding of the buprenorphine safety profile derives, so, it is reasonable to presuppose that Probuphine could have a more favorable safety profile. As anticipated, review of the Probuphine safety data did not identify novel systemic safety concerns beyond those consistent with the established safety profile of buprenorphine. Although novel systemic safety concerns were not identified, there were still some minor imbalances in rates of reporting of some adverse events, like depression, for the pooled Probuphine arm when compared with a pooled combined placebo/sublingual buprenorphine comparator arm. These slight imbalances may stem from the continuous delivery of buprenorphine offered by Probuphine or the differences in exposure time for the Probuphine arms across some of the trials, with those on Probuphine having longer on-study times. No

matter the explanation for the slight imbalances, these will be important to monitor in postmarketing surveillance.

Regarding procedural safety, procedural complications were not common overall. There were few difficulties with insertion, but a greater number of removal difficulties. In short, the procedural complications associated with insertion and removal of the implants in the clinical trial database were not worrisome overall, although the rate of complications associated with removal, as well as bleeding and infection rates, in this small database is considered relatively high. Because the database is small, however, it should also be noted that it may not allow for full characterization of these safety issues. It is believed, however, that with appropriate training and if enough procedures are performed, the implanting clinician can become adept at the procedures and safely insert and remove the implants. Additionally, procedural safety will be under monitoring through required implementation of a program of enhanced pharmacovigilance. A REMS which ensures that clinicians performing the procedures are appropriately qualified will be aimed at mitigating the risks associated with improper insertion and removal of Probuphine.

7.1 Methods

For the evaluation of safety, an expanded safety database for Probuphine relative to the database available at the time of the initial NDA submission was examined. The Probuphine safety database has been augmented with safety data from subjects in the PRO-814 trial, the trial supporting this NDA Resubmission, and the most-recently completed trial.

PRO-814 safety data were pooled with data from PRO-805 and PRO-806 trials, the Phase 3, double-blind, placebo-controlled, safety and efficacy trials that were intended to support the application when initially submitted. Pooled safety data from these trials were presented in the Applicant's Integrated Summary of Safety (ISS) Addendum, which provides an update to the original ISS submitted as part of the initial NDA submission.

Data from the Phase 3, open-label, extension trials, PRO-807 and PRO-811 (PRO-805 and PRO-806 extension trials, respectively) were also appraised for this review of safety. Additionally, limited safety data were available from Probuphine clinical pharmacology studies, TTP-400-02-01 and PRO-810, and were used to supplement and complement safety data provided by the major contributors to the safety database, namely the Phase 3 double-blind trials, and extension studies. Review of the updated safety information from the ISS Addendum was emphasized over data from the original ISS. The original ISS submitted with the initial submission was reviewed at the time of the initial submission, and only key safety findings were revisited and summarized for this review. Safety information included in the individual study reports for PRO-814,

PRO-805, and PRO-806 was referenced when additional detail beyond that included in the ISS was needed.

Review Strategy for Examination of Current Probuphine Safety Database

For Probuphine, an implantable formulation of the drug substance buprenorphine, the framework used for the Review of Safety centered broadly on

- (1) safety of Probuphine as it relates to the systemic effects of the active ingredient, buprenorphine; and
- (2) safety of Probuphine as it relates to the implants, i.e., indwelling foreign bodies, and the insertion and removal procedures necessary for Probuphine administration.

The safety profile for buprenorphine is fairly well-characterized. At the same time, the Probuphine safety database affords an opportunity to observe additional buprenorphine exposures that may allow for ascertainment of further buprenorphine-specific safety findings. Accordingly, the Probuphine database was examined with an eye toward identifying new or unanticipated systemic effects of buprenorphine, if any, attributable to intrinsic properties of the buprenorphine drug substance, or to the drug substance when administered via this novel delivery system.

Given the established safety profile of buprenorphine, the primary focus of the safety evaluation ultimately was the safety experience related to the implants and insertion and removal procedures. First, this safety evaluation addressed the overall safety experience with Probuphine based on the clinical trial safety data available on Probuphine implant insertion and removal, and on local effects resulting from the indwelling implant. Secondly, because improvements were made to the device, techniques, and the training and certification program during the Probuphine clinical development program (changes made during the earlier development program), this resulting “natural experiment” was exploited in order to compare safety findings before and after these changes were introduced. Finally, a Human Factors evaluation was also conducted by the Applicant. Results from this evaluation were assessed to inform conclusions regarding the appropriateness of the proposed training program and the proposed Risk Evaluation and Mitigation Strategy (REMS).

Our Obstetrics and Gynecology physician colleagues in the Division of Bone, Reproductive, and Urologic Products (DBRUP) were consulted to assist with evaluation of the procedural safety data. Given the similarities between the outpatient procedures for insertion and removal of Probuphine, and the procedures for the implantable contraceptives, particularly, Norplant, our DBRUP colleagues who have specific experience with the implantable contraceptives, and with surgical procedures, in general, were asked to consultatively review the procedural safety data included in the submission, and to provide a clinical perspective based on their expertise in this area. The procedural-related safety discussion is based extensively on DBRUP’s consultative review. (Note that DBRUP was also consulted to review the procedural safety-related

data included in the initial submission. The reader is referred to the clinical review, dated April 7, 2013, for further details.)

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The entire Probuphine safety database includes 647 unique subjects that participated in the PRO-814 trial conducted to support this NDA Resubmission, as well as the previously completed trials that were intended to support the initial NDA submission. These included two Phase 3, six-month, placebo-controlled safety and efficacy trials (PRO-805 and PRO-806); two open-label extension studies (PRO-807 and PRO-811); a pharmacokinetic study (TTP-400-02-01); and a comparative bioavailability study (PRO-810).

Safety Database – Original NDA Submission

A total of 450 opioid-dependent patients were enrolled in the phase 3 studies for the initial NDA submission, of whom 222 received Probuphine implants and 109 received placebo implants; an additional 119 were treated with sublingual buprenorphine in an OL arm of Study PRO-806, and received no implants. A subset of these patients continued into open-label extensions providing data for longer-term exposure. Including patients receiving Probuphine in safety extension studies after completing the placebo arm in the controlled trials, 262 unique patients received Probuphine in these efficacy and safety studies, of whom 201 received one course of treatment (24 weeks) and 82 received a second course of treatment (a total of 48 weeks).

Expanded Safety Database – NDA Resubmission

With the completion of the PRO-814 trial, an additional 176 patients were added to the Probuphine safety database, of whom 87 received Probuphine and 89 received sublingual buprenorphine.

Key differences between PRO-805 and PRO-806, which were near identical in design, and the PRO-814 trial, are that PRO-805 and PRO-806 trials entailed the following trial design elements:

- enrolled new entrants to treatment who were required to reach a target dose of 12 to 16 mg/day of sublingual buprenorphine prior to insertion of implants
- had a placebo comparator arm and supplemental or rescue sublingual buprenorphine was permitted for these patients
- allowed for insertion of a fifth rod when certain protocol-specified criteria were met

PRO-806 also included an open-label (OL) sublingual buprenorphine arm. Subjects on sublingual buprenorphine in the PRO-806 OL arm were receiving 12–16 mg/day, approximately twice that of the patients in the PRO-814 arm who were receiving no more than 8 mg per day.

The following table summarizes the studies in the Probuphine clinical development program that were used to evaluate safety:

Phase 3 Safety and Efficacy Trials:	PRO-814, PRO-805 & PRO-806
Phase 3 Extension Trials:	PRO-807 & PRO-811
Clinical Pharmacology Studies:	TTP-400-02-01 & PRO-810

Safety data derive primarily from the Phase 3 safety and efficacy studies and extension trials, Studies PRO-814, PRO-805, PRO-806, PRO-807, and PRO-811. The clinical pharmacology studies, TTP-400-02-01 and PRO-810, contribute additional limited safety data and serve to supplement and complement safety data provided by the major contributors to the safety database, namely the Phase 3 double-blind and extension studies.

The clinical trials and studies used to evaluate safety are described above in Section 5.

7.1.2 Categorization of Adverse Events

The various procedures for categorizing adverse events were described in the ISS Addendum, the Statistical Analysis Plan (SAP) for the ISS Addendum, and the PRO-814 study report.

Adverse event terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Studies PRO-805 and PRO-807 used MedDRA Version 10, while the subsequent safety and efficacy trial, PRO-806, and its follow-on extension (PRO-811) used MedDRA Version 14. For PRO-814, the last clinical trial, MedDRA Version 17 was used for coding adverse event terms. MedDRA Version 17 was used for the Integrated Summary of Safety Addendum.

According to the Statistical Analysis Plan for the ISS, adverse events were to be coded by primary system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). Subjects were counted only once for each primary SOC and each preferred term. Adverse events were grouped in the following manner

- *implant site* adverse events
- *non-implant site* adverse events

For the ISS Addendum, a treatment-emergent AE (TEAE) was defined as any AE with an onset date on or after the date of the first dose of study drug, or any ongoing event on the date of the first dose that worsens in severity after the date of the first dose. All recorded TEAEs were to be displayed, even if the onset date fell after the follow-up periods that AEs would be recorded for each study following the implant removal or last dose of treatment regimen SL BPN, as shown below.

Protocol	Follow-up time (Days)
PRO-805	14
PRO-806	39
PRO-807	14
PRO-811	18
PRO-814	14

Starting at the time of enrollment in the open label studies, all adverse events were recorded in the study databases for the open label studies. Implant site AEs related to the implants in the double blind period occurring after open label enrollment were flagged and moved to the associated double blind studies, however, some non-implant site events occurred after open label enrollment, but within the follow-up period for their respective double blind studies and prior to the open label implantation. These were not considered to be treatment emergent by the Applicant; all adverse events that fell within this period were to be presented in a listing.

Categorization of implant site adverse events varied by study. In Study PRO-805 and Study PRO-807, the case report form (CRF) presented a check list of 6 possible preprinted implant site treatment-emergent adverse events (TEAEs), as well as “Other implant site TEAE” and “non-implant site TEAEs.” Only “Other implant site TEAEs” and “non-implant site TEAEs had free-text recorded. In the original Complete Study Reports, the implant TEAEs were not coded according to the Medical Dictionary for Regulatory Activities (MedDRA). For the ISS, all terms were coded using MedDRA; however, the Applicant chose to make the determination of whether or not an event was an implant site TEAE based solely on the designation from the individual study CRF check box.

In Study PRO-806, Study PRO-811, and Study PRO-814, all TEAEs (implant site or non-implant site TEAEs) were recorded in the adverse event (AE) CRF. The AE CRF had a check box to designate TEAEs as implant site-related. All TEAEs had free text descriptions that were coded; the Applicant noted that the determination of implant/non-implant status was based on the CRF check box. Studies PRO-806, PRO-811, and PRO-814 did not use a preprinted check list for implant site TEAEs.

The Applicant’s methods for categorizing the adverse events appear adequate overall. The differences in implant site adverse event data collection, coding, and categorization

across the studies could potentially make it difficult to correctly ascribe adverse events as being implant-related or non-implant-related. This is not anticipated to greatly impact the review of implant site adverse events because the implant site adverse events of interest in this case are generally those related to insertion and removal complications; these data were made available separately (in response to an Information Request). For the non-implant and implant site adverse events in general, it is possible that some of these events may be incorrectly classified as implant- or non-implant- related; however, because the local and systemic effects are fairly distinct, this is only likely to have an impact for certain adverse events that are commonly associated with buprenorphine exposure and procedures, e.g., pain.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The ISS Addendum presents integrated safety data from the three Phase 3, 24-week (6-month), controlled, double-blind studies: Study PRO-805, Study PRO-806, and Study PRO-814. Exposure data were provided for pooled data from both the double-blind and open-label studies.

The treatment groups used in the data summaries are as follows:

- Study PRO-805 included Probuphine and placebo groups.
- Study PRO-806 included Probuphine, placebo, and SL buprenorphine groups. In summaries for this study, SL buprenorphine denotes subjects assigned to open-label daily SL buprenorphine. This group of patients is the only group that did not undergo the insertion and removal procedures. All other comparator groups in all studies had either active or placebo rods inserted and removed.
- Study PRO-814 included Probuphine and SL buprenorphine groups.

A summary of the three Phase 3 trials pooled for the safety database for the NDA Resubmission, and the treatment groups used to estimate and compare incidence, is provided in the following table.

Table 12 Phase 3 Trials Included in the Pooled Safety Database for the ISS Addendum

Study	Design	Treatment Groups		
		Probuphine	Placebo	SL BPN
Phase 3 Randomized, Controlled Studies				
PRO-805	Placebo-controlled, double-blind	108	55	--
PRO-806	Placebo-controlled, double-blind; open-label active-comparator control	114	54	119
PRO-814	Double-blind, double-dummy, active-controlled	87	--	89
	Treatment Arm Totals	309	109	208
	Combined Placebo/SL BPN Total			317
	Phase 3 Safety Database Total			626

SL BPN = sublingual buprenorphine

Implant Site and Non-Implant Site TEAE Evaluation

Implant site treatment-emergent adverse events (TEAEs) and non-implant site TEAEs were evaluated using the pooled data.

In the evaluation of pooled data for implant site TEAEs, treatment groups included subjects in the Probuphine groups and subjects in the placebo implant groups, including subjects in the SL buprenorphine group of Study PRO-814, who received placebo implants. Subjects in the SL buprenorphine group of Study PRO-806 were excluded, as they received only open-label daily sublingual buprenorphine treatment and did not receive any implants.

With respect to the evaluation of pooled data for all TEAEs and non-implant site TEAEs, it is important to describe the conditions under which sublingual buprenorphine was administered across the trials. It should be noted that all subjects in Studies PRO-805 and PRO-806 took SL buprenorphine during induction and all subjects in all studies could have been offered SL buprenorphine by the principal investigator (PI) as rescue medication during treatment if they met certain protocol-specified criteria (also for Studies PRO-807 and PRO-811), or at the discretion of the investigator (for PRO-814).

In the evaluation of pooled data for all TEAEs and non-implant site TEAEs, the treatment groups included the Probuphine groups and a combined placebo/SL buprenorphine group. The Applicant's rationale for combining the placebo and SL buprenorphine groups in the statistical analysis was that such a high percentage of subjects in the placebo group received SL buprenorphine rescue medication, there ultimately was only a difference of degrees of exposure to buprenorphine between the SL buprenorphine group and the placebo group for safety issues.

The Applicant also notes that for the double-blind studies, there are instances where pooling of daily SL buprenorphine subjects with placebo subjects would not be appropriate, or a more thorough examination of these 2 groups in a separate manner would be warranted. The Applicant indicates that double-blind analyses where the daily SL buprenorphine subjects are presented separately from the placebo subjects include the following:

- Disposition
- Exposure
- Special Interest Adverse Events

Additionally, SL buprenorphine subjects in the open-label arm of PRO-806 were excluded from the following analyses because they did not have implants and were not at risk:

- Any analyses presenting the results by the number of implants
- Implant site TEAEs

The Applicant's procedures for pooling data across studies and presenting the findings are generally acceptable. Where appropriate for this safety review, the placebo and sublingual buprenorphine arms were analyzed separately when evaluating effects of systemic buprenorphine exposure. Procedure-related adverse events were primarily evaluated by aggregating data across the Probuphine and placebo treatment arms, as subjects in each arm were subjected to the same insertion and removal procedures. Implant site adverse events were evaluated separately to assess local toxicity given that both the Probuphine implants (buprenorphine + ethylene vinyl acetate [EVA]) and placebo implants (EVA only) have been demonstrated to produce local irritancy, with the buprenorphine in the Probuphine implants producing additional local irritant effects beyond that of the EVA alone.

In summary, the resulting pooled safety database used for the ISS Addendum for this submission includes information for 626 subjects who had Probuphine or placebo implants or received sublingual buprenorphine in the pooled double-blind studies. Again, as noted above, safety data from the PRO-814 trial were pooled only with the other two 24-week (six months) Phase 3 studies and were the focus of the integrated safety information for the NDA Resubmission. However, the complete safety database also includes safety data from two open-label trials and two clinical pharmacology trials.

The primary evaluation of safety is based on the pooled data from the three double-blind, placebo- and/or active comparator-controlled trials. However, for deaths, nonfatal SAEs, withdrawals due to TEAEs, safety information from the OL studies (PRO-807 and PRO-811) as well as the clinical pharmacology studies (TTP-400-02-01 and PRO-810) is also summarized.

Note that, for the purposes of safety comparisons, patients identified as treated with "placebo," in most cases, received sublingual buprenorphine. Therefore, some common

buprenorphine-associated adverse events may have occurred with similar frequency between the Probuphine arm and the placebo arm.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.1.1 Exposure

Overall Exposure to Probuphine

The following provides a summary of overall cumulative exposure to Probuphine across all studies with Probuphine (including the open-label studies and the clinical pharmacology studies).

Table 13 Cumulative Exposure to Probuphine across All Probuphine Clinical Studies

	TTP-400-02-01	PRO-805/ PRO-807 Continuing Probuphine	PRO-807/ Placebo-> Probuphine	PRO-806/ PRO-811 Continuing Probuphine	PRO-811/ Placebo-> Probuphine	PRO-811/ SL BPN-> Probuphine	PRO-810	PRO-814/ Probuphine	Total
Any Exposure	12	108	12	114	8	20	9	87	370
≥1 month	12	102	12	112	8	18	8	84	356
≥2 months	12	99	12	109	7	17	0	83	339
≥3 months	12	96	11	108	7	16	0	81	331
≥4 months	12	87	11	103	7	14	0	81	315
≥5 months	12	81	10	99	7	14	0	81	304
≥6 months	0	60	3	78	2	7	0	1	151
≥7 months	0	47	0	54	0	0	0	0	101
≥8 months	0	42	0	53	0	0	0	0	95
≥9 months	0	41	0	52	0	0	0	0	93
≥10 months	0	41	0	50	0	0	0	0	91
≥11 months	0	39	0	46	0	0	0	0	85
≥12 months	0	39	0	46	0	0	0	0	85

Abbreviations: CRF = case report form; SL BPN = sublingual buprenorphine

Note: Study drug exposure is calculated as the date of implant removal minus the date on implant insertion plus one. If the removal date is missing, the study discontinuation date from the CRF is used. For PRO-805, PRO-806, PRO-807, and PRO-811, subjects who completed their respective study are assigned 6 months of exposure in that study. Subjects with more than 28 weeks of exposure in a given study are recorded as 28 weeks.

Note: A month is defined as 365.25/12 days.

Source: ISS Addendum

Note that only one subject on Probuphine is considered to have had six months or more of exposure, although nearly all the subjects completed the study where they received implants that were intended to be indwelling for six months. This is likely the result of applying the exact removal date to adjudicate treatment exposure when summarizing the subject disposition results, as discussed above. Also, although the trials and extension studies are nominally six-month trials, the six-month timeframe was

operationalized as 24 weeks for the trials and studies, and therefore would represent shorter exposure times when treatment duration criteria are strictly applied as six months.

Supplemental buprenorphine use was permitted in all the studies. A fifth implant was an option when protocol-specified criteria were met in all the Phase 3 studies except for PRO-814. The following table summarizes the number of subjects who received supplemental buprenorphine across the trials and the number of subjects who received a fifth implant.

Table 14 Supplemental Buprenorphine Use - Double-Blind Studies

Study	Treatment Group	Number (%) of Subjects Requiring Supplemental SL Buprenorphine	Number (%) of Subjects Requiring Fifth Implant
PRO-805	Probuphine (N=108)	67 (62.0)	22 (20.4)
	Placebo (N=55)	50 (90.9)	32 (58.2)
PRO-806	Probuphine (N=114)	45 (39.5)	25 (21.9)
	Placebo (N=54)	36 (66.7)	21 (38.9)
	SL buprenorphine (N=119)	7 (5.9)	Not allowed
PRO-814	Probuphine (N=84)	15 (17.9%)	Not allowed
	SL buprenorphine (N=89)	13 (14.6%)	Not allowed

Abbreviations: SL = sublingual

Source: ISS Addendum, Table 6, p. 37 of 153

Table 15 Demographic and Baseline Characteristics - Pooled Double-Blind Studies

Demographic and Baseline Characteristics	Probuphine N=309 n (%)	Placebo/SL BPN ^a N=317 n (%)	Total N=626 n (%)
Sex			
Male	196 (63.4%)	195 (61.5%)	391 (62.5%)
Female	113 (36.6%)	122 (38.5%)	235 (37.5%)
Race			
White	259 (83.8%)	267 (84.2%)	526 (84.0%)
Black	31 (10.0%)	31 (9.8%)	62 (9.9%)
Asian	1 (0.3%)	3 (0.9%)	4 (0.6%)
American Indian or Alaskan Native	9 (2.9%)	1 (0.3%)	10 (1.6%)
Native Hawaiian or Other Pacific Islander	1 (0.3%)	0 (0.0%)	1 (0.2%)
Other	8 (2.6%)	15 (4.7%)	23 (3.7%)

Demographic and Baseline Characteristics	Probuphine N=309 n (%)	Placebo/SL BPN ^a N=317 n (%)	Total N=626 n (%)
Ethnicity			
Hispanic or Latino	39 (12.6%)	43 (13.6%)	82 (13.1%)
Not Hispanic or Latino	270 (87.4%)	274 (86.4%)	544 (86.9%)
Age (years)			
n	309	317	626
Mean (SD)	36.7 (11.06)	37.1 (11.04)	36.9 (11.04)
Median	35.0	35.0	35.0
Min, Max	19.0, 63.0	18.0, 64.0	18.0, 64.0
Age Groups			
18-35	156 (50.5%)	166 (52.4%)	322 (51.4%)
36-65	153 (49.5%)	151 (47.6%)	304 (48.6%)
Primary Opioid of Abuse			
Heroin	160 (51.8%)	159 (50.2%)	319 (51.0%)
Prescription opioid pain medication	143 (46.3%)	156 (49.2%)	299 (47.8%)
Other	5 (1.6%)	2 (0.6%)	7 (1.1%)
Opioid abuse treatment history			
Yes	230 (74.4%)	226 (71.3%)	456 (72.8%)
No	79 (25.6%)	88 (27.8%)	167 (26.7%)
Missing	0 (0.0%)	3 (0.9%)	3 (0.5%)
BMI (kg/m ²)			
n	305	313	618
Mean (SD)	26.5 (5.99)	25.9 (5.58)	26.2 (5.79)
Median	25.5	24.9	25.2
Min, Max	13.6, 67.0	17.4, 54.7	13.6, 67.0
BMI group			
≤25 (kg/m ²)	141 (45.6%)	162 (51.1%)	303 (48.4%)
>25 (kg/m ²)	168 (54.4%)	155 (48.9%)	323 (51.6%)

Abbreviations: BMI = body mass index; SL BPN = sublingual buprenorphine.

^a Denotes subjects assigned to daily SL BPN arm in Studies PRO-806 and PRO-814. All subjects in all studies took SL BPN during induction and had the option of taking SL BPN as rescue medication during treatment.

Source: ISS Addendum, Table 10, pp. 43 – 44.

Table 16 Demographic and Baseline Characteristics by Trial - Double-Blind Studies

	Study PRO-805 N=163		Study PRO-806 N=287			Study PRO-814 N=176	
	Probuphine N=108 n (%)	Placebo N=55 n (%)	Probuphine N=114 n (%)	Placebo N=54 n (%)	SL BPN N=119 n (%)	Probuphine N=87 n (%)	SL BPN N=89 n (%)
Sex							
Male	72 (66.7)	40 (72.7)	72 (63.2)	31 (57.4)	72 (60.5)	52 (59.8%)	52 (58.4%)
Female	36 (33.3)	15 (27.3)	42 (36.8)	23 (42.6)	47 (39.5)	35 (40.2%)	37 (41.6%)
Race							
White	82 (75.9)	40 (72.7)	95 (83.3)	45 (83.3)	97 (81.5)	82 (94.3%)	85 (95.5%)
Black	14 (13.0)	6 (10.9)	14 (12.3)	7 (13.0)	16 (13.4)	3 (3.4%)	2 (2.2%)
Asian	0 (0.0)	1 (1.8)	0 (0.0)	1 (1.9)	1 (0.8)	1 (1.1%)	0 (0.0%)
American Indian or Alaskan Native	5 (4.6)	0 (0.0)	3 (2.6)	0 (0.0)	0 (0.0)	1 (1.1%)	1 (1.1%)
Native Hawaiian or Other Pacific Islander	1 (0.9)	0 (0.0)	N/A	N/A	N/A	0 (0.0)	0 (0.0)
Other	6 (5.6)	8 (14.5)	2 (1.8)	1 (1.9)	5 (4.2)	0 (0.0%)	1 (1.1%)
Ethnicity							
Hispanic or Latino	12 (11.1)	12 (21.8)	24 (21.1)	11 (20.4)	17 (14.3)	3 (3.4%)	3 (3.4%)
Not Hispanic or Latino	96 (88.9)	43 (78.2)	90 (78.9)	43 (79.6)	102 (85.7)	84 (96.6%)	86 (96.6%)
Age (years)							
N	108	55	114	54	119	87	89
Median	33.0	39.0	36.0	33.0	32.0	36	37
Mean (SE)	35.8 (1.06)	39.3 (1.58)	36.4 (1.03)	35.2 (1.40)	35.3 (1.00)	38 (1.18)	39 (1.14)
Range	(19, 62)	(20, 61)	(19, 60)	(19, 59)	(18, 60)	(21, 63.0)	(22, 64.0)

Source: ISS Addendum

7.2.2 Explorations for Dose Response

There was an option for a 5th implant in the Phase 3 trials and extension studies that supported the initial submission and that preceded PRO-814. In these trials, the fifth implant was used only as a titration step in patients already demonstrating symptoms of craving and withdrawal on four implants, and the results suggested that this titration step was not helpful; no dose-response trial directly randomizing patients to treatment with five implants was performed to determine whether it might have yielded improved efficacy. After an action was taken for the initial submission, the Applicant decided to pursue development of Probuphine, forgoing the option for a 5th implant. Probuphine, in its present iteration, is a fixed-dose, non-titratable product. Rather than undertaking dose explorations, the Applicant has focused on matching the patient population to the dose provided by this product.

7.2.3 Special Animal and/or In Vitro Testing

Local tissue effects of Probuphine and Placebo (EVA only) implants were evaluated microscopically in dogs after subcutaneous exposures of 1 month and 10 months using

standard testing protocols for medical devices. These data were submitted with the initial application and evaluated during the initial review cycle.

Key findings from the Nonclinical Review Team's assessment of these data were as follows:

- Probuphine and Placebo were each moderately irritating after 1 month and slightly irritating after 10 months.
- Predominant histological observations observed were generally more severe in Probuphine treated animals compared to Placebo animals.
- Severity of local toxicity decreased over time but was substantial during the early phase after implant insertion with the presence of buprenorphine in Probuphine causing increased local toxicity compared to Placebo.

Refer to the Probuphine clinical review dated April 7, 2013 and pharmacology/toxicology review for further details.

7.2.4 Routine Clinical Testing

Routine clinical testing in the Probuphine clinical trials included evaluations of TEAEs, blood chemistry, hematology and urinalysis laboratory evaluations, urine toxicology screens, ECG evaluations, vital signs, and pupillary diameter; pupillary diameter was not assessed in PRO-814.

Refer to the description of the clinical trials in Section 5 and in the earlier reviews for the timetable of clinical testing in each of the studies.

The table below summarizes the adverse event collection timeframes for each of the studies.

7.2.5 Metabolic, Clearance, and Interaction Workup

The Applicant is relying on clinical pharmacology data for buprenorphine in the sublingual tablet formulation. No additional information related to metabolic, clearance, and interaction workup was provided or undertaken to support this submission.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Probuphine, buprenorphine hydrochloride; ethylene vinyl acetate is an implantable, extended release formulation of buprenorphine. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid. As a partial μ -receptor agonist with low intrinsic activity at the receptor site, buprenorphine exhibits a "ceiling effect" such that its opioid agonist effects plateau at higher doses. Potential adverse events then would be those anticipated for an opioid agonist, keeping in mind the ceiling effect on opioid agonist effects. In addition to the adverse events anticipated with the

active pharmaceutical ingredient, adverse events related to the insertion and removal procedures are also of importance. Thus, comprehensive evaluation involved review of adverse events observed in drugs using similar implantable formulations and insertion and removal procedures.

Expected adverse events include those relating to the systemic effects of opioid exposure, and those observed in the implantable contraceptives experience.

The Agency's previous experience with surgically-implanted 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 Probuphine 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, 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.

While implantable contraceptive methods are generally well-tolerated, procedure-related adverse events are notable for 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.

Notably, implantable contraceptive products are inserted and removed by obstetrician/gynecologists, who are surgically trained specialists. 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. Nonetheless, in the US, Nexplanon is distributed only to clinicians who have completed a specific manufacturer-provided training program on the insertion and removal procedures for the product. 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 implantation or removal procedures, or to manage complications.

7.3 Major Safety Results

Review of major safety results included a review of deaths, nonfatal serious adverse events, permanent treatment discontinuations, significant adverse events, and submission-specific primary safety concerns. Major safety results are reported for all clinical studies and trials in the Probuphine development program.

7.3.1 Deaths

There were no deaths reported during the PRO-814 trial. There were no deaths reported among subjects on Probuphine in any trial in the clinical development program.

There was a single death reported in the clinical development program for Probuphine. This occurred in a patient in the sublingual buprenorphine arm of Study PRO-806. PRO-806, the second Phase 3 safety and efficacy study had three arms, a Probuphine arm, a placebo implant arm, and an open-label sublingual buprenorphine arm.

Subject 619-036 was a 29-year-old female subject with opioid dependence, whose primary opioid of abuse was heroin. Following induction with sublingual buprenorphine from (b) (6) to (b) (6), the subject continued on buprenorphine until (b) (6), when treatment was discontinued at subject request. The subject had an accidental heroin overdose on (b) (6).

7.3.2 Nonfatal Serious Adverse Events

Nonfatal serious adverse events (SAEs) were reported in ten patients randomized to Probuphine (3%), seven of the patients randomized to placebo (6%), and nine of the patients randomized to sublingual buprenorphine (4%) in the pooled double-blind studies. Additionally, across the open-label extension studies, SAEs were reported for three patients continuing on Probuphine in the open-label extensions, and one patient who completed placebo treatment in the controlled studies and was newly exposed to Probuphine in the open-label extension. Across the two clinical pharmacology studies, one subject experienced nonfatal serious adverse events.

The table below briefly lists the types of events reported across the clinical studies and trials in the Probuphine clinical development program.

Serious Adverse Events, Probuphine Clinical Studies

Pooled DB Studies – PRO805,PRO-806, & PRO-814		
Probuphine (3%)	Placebo (6%)	SL BPN (4%)
1. Hypotension (sepsis, BP meds) (806)	1. Respiratory Failure (heroin withdrawal; agitation → intubation) (805)	1. Major depression (806)
2. COPD exacerbation & Pulmonary Embolism (805)	2. Suicidal Ideation((805)	2. Pyrexia (infxn) (806)
3. Pneumococcal pneumonia (806)	3. Tylenol overdose – non-suicidal (per pt., fifty 500-mg pills) (806)	3. Angina pectoris (806)
4. Pneumonia (806)	4. Pneumonia; Explant Site Cellulitis (805)	4. Pulmonary embolism (806)
5. Umbilical hernia, obstructive (806)	5. Limb abscess (not implant site) (806)	5. Rib fracture (806)
6. Tooth abscess (806)	6. Gastroenteritis (806)	6. Spontaneous abortion (806)
7. Second degree burns (805)	7. Relapse (805)	7. Biliary colic (814)
8. Breast cancer (806)	-	8. Chronic cholecystitis (814)
9. Convulsion (814)		9. Bronchitis (814)
10. Bipolar I disorder (814)		
Pooled OL Extension Studies – PRO-807 & PRO-811		
Probuphine → Probuphine	Placebo → Probuphine	
1. CAD, worsening	1. Pneumonia (pneumonia in primary study also)	
2. Cellulitis antecubital fossa (methamphetamine IV)		
3. Suicidal ideation		
Clinical Pharmacology Study PRO-810		
1. pancreatic cyst x 2, nausea		

Several of the serious adverse events among the patients in the studies were infectious disease events, including a limb cellulitis and a limb abscess potentially related to intravenous drug use. This was observed principally among the patients in the initial trials that enrolled new entrants to treatment (i.e., PRO-805 and PRO-806, and their extensions), who more commonly reported heroin as their primary opioid of abuse, in contrast to PRO-814 where prescription opioid pain relievers were reported as the primary opioid of abuse. Depression and suicidal ideation were also reported. Of interest is that biliary colic and chronic cholecystitis were reported as serious adverse events among patients in the sublingual buprenorphine arm in PRO-814. Labeling for the buprenorphine-containing transmucosal products warns that buprenorphine has been shown to increase intracholedochal pressure, as do other opioids, and thus should be administered with caution to patients with dysfunction of the biliary tract. Lastly, in some cases, because of an associated hospitalization, some events that are efficacy-related, e.g., relapse and hospitalization in a rehabilitation facility, are designated as having a serious outcome, although the underlying issue is not necessarily one of safety in the traditional sense.

Apart from the non-implant SAEs, there was one SAE related to the implant site 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. This implant site SAE occurred in Study PRO-805, which predates the surgical device and technique improvements, and training and certification program. No other implant site SAEs were reported subsequent to implementation of these procedural safety-related enhancements.

The following tables provide narrative information for the serious adverse events presented in the summary table above and examined in the above discussion. The SAE narratives for PRO-814 are presented first, representing the most recent safety information supplementing the Probuphine safety database, and summarizes the SAEs that occurred among patients deemed clinically stable. For the other studies in new entrants to treatment, the tables are presented by study type, controlled trial or extension, and by treatment arm within the study groupings. For all studies, except PRO-814, the induction/target dose of buprenorphine reached prior to insertion of the Probuphine or placebo rods is also provided, as well as the total number of rods, or implants received during the treatment cycle, i.e., four or five. For PRO-814 that evaluated a different treatment paradigm for Probuphine, and enrolled patients already on 8mg/day or less of a buprenorphine-containing transmucosal product, references to induction or target dosing are not applicable. As there are no longer plans for the optional fifth rod for the Probuphine product, only a single dose, four rods, was evaluated in PRO-814, so all patients in that trial received four rods.

PRO-814 Serious Adverse Event Narratives

Subject ID / Age/ # implants	Pre-enrollment dose	SAE(s)	Narrative
Probuphine (SL Placebo)			
(b) (6) 36 M	SL BPN/naloxone (8/2 mg QD) for ~ 7 months. Lifetime BPN tx 7 months, highest dose 16 mg	Worsening of bipolar I disorder, Day 90	Pt admitted himself to psych ward. Psychiatrist changed lithium Rx to lithium XR that pt. was not able to afford. Subsequently, pt. missed a few doses and had onset of manic episode
(b) (6) 47 M	SL BPN/naloxone (2/0.5 mg TID) since unknown date in 2013. Randomized (b) (6)	Day 88, found unresponsive by mother, who reported shaking and seizure-like grand mal activity at time, she denied fecal or urinary incontinence	EEG borderline abnormal Pt endorsed overuse of carisoprodol. The carisoprodol label includes a Warning regarding seizures.

Subject ID / Age/ # implants	Pre-enrollment dose	SAE(s)	Narrative
SL BPN (Placebo implants)			
(b) (6) 34 F	SL BPN/naloxone (8 mg/2 mg QD) for almost 2 years; No supplemental	Biliary colic Day 173, four days after implant removal	uneventful laparoscopic cholecystectomy, Day 185 received opioids (tramadol, hydromorphone) for pain control
(b) (6) 59 F	SL BPN (4 mg QD) for 45 days at randomization. On BPN treatment for 9 yrs, highest dose 8 mg	Hospitalization for bronchitis, Day 60	Considered resolved Day 64
(b) (6) 28 F	(8/2mg QD) x 9 months at randomization, On buprenorphine for 9 months, lifetime, entered treatment once, highest dose ever was 8 mg.	Chronic cholecystitis, lap cholecystectomy (CCY) Day 107	Onset of biliary colic Day 95 Except for CCY, no other corrective action

Probuphine Nonfatal Serious Adverse Events – Controlled Trials

Subject ID / Age/ # implants	Induction / Target dose	SAE(s)	Narrative
PRO-805			
(b) (6) 47 y/o M 4 implants	(b) (6) – (b) (6) 12mg	- SAE#1: COPD Exacerbation (b) (6) - SAE#2: COPD Exacerbation, Pulmonary Embolism (b) (6) - SAE#3: Pulmonary Embolism (b) (6)	- also c/o R calf pain x 2 mos - utox: (+) cocaine - utox (+) opiates & cocaine; also COPD exacerbation
(b) (6) 27 F 4 implants	(b) (6) 14 mg	2nd Degree Burns to Lower Bilateral Limbs (b) (6)	

Subject ID / Age / # implants	Induction / Target dose	SAE(s)	Narrative
PRO-806			
(b) (6) 21 F 4 implants	(b) (6) 12 mg	• Pneumonia pneumococcal ((b) (6))	Additional non-serious AEs of pleural effusions, empyema, pneumothorax, & dehydration
(b) (6) 39 F 4 implants	(b) (6) 12 mg	• breast cancer ((b) (6))	invasive ductal carcinoma of left breast
(b) (6) 60 M 4 implants	(b) (6) 16 mg	• Umbilical hernia, obstructive ((b) (6))	h/o ongoing diverticulum and umbilical hernia Implants removed (b) (6) for hernia surgery requiring general anesthesia.
(b) (6) 25 M 4 implants	(b) (6) 16 mg	• Tooth abscess ((b) (6))	Hospitalized; 8 teeth extracted.
(b) (6) 42 F 5 implants	(b) (6) 16 mg	• Pneumonia ((b) (6))	Hospitalization
(b) (6) 59 F 4 implants	(b) (6)	• Hypotension ((b) (6))	On lisinopril and atenolol (HTN before randomization, started on BP meds) Non-serious mild AE of sepsis

Placebo Nonfatal Serious Adverse Events – Controlled Studies

Subject ID / Age / # implants	Induction / Target dose	SAE(s)	Narrative
PRO-805			
(b) (6) 34 y/o M 5 implants	(b) (6) 16 mg	• Suicidal Thoughts ((b) (6))	• h/o depression
(b) (6) 51 M 5 implants	(b) (6) 16 mg	• Pneumonia ((b) (6)) • Left upper extremity cellulitis ((b) (6))	• Completed study (b) (6); • hospitalized (b) (6) after presenting to investigator's office with pneumonia; left arm abscess at explant site.
(b) (6) 58 M 4 implants	(b) (6) 16 mg	• Opiate dependency relapse ((b) (6))	• Inpatient rehabilitation facility hospitalization (efficacy vs. safety, but SAE because of hospitalization)
(b) (6) 40 M 4 implants	(b) (6) 16 g	• SOB, tremors, and diaphoresis. Assigned PT of "Respiratory failure" –by investigator ((b) (6))	• Transferred to hospital with SOB, tremors, and diaphoresis while incarcerated for heroin possession. Pt stated he was in heroin withdrawal. Because of delirium in

Subject ID / Age / # implants	Induction / Target dose	SAE(s)	Narrative
			the setting of fever, and possible drug withdrawal, patient was sent for an MRI. Patient became agitated and required sedation and intubation. Evidence of rhabdo was noted without renal failure.
PRO-806			
(b) (6) 26 F 4 implants	(b) (6) 14 mg	• Abscess limb ((b) (6))	• Not implant site
(b) (6) 46 M 4 implants	(b) (6) 16 mg	• Gastroenteritis ((b) (6))	• Hospitalized
(b) (6) 26 F 4 implants	(b) (6) 16 mg	• Tylenol Overdose ((b) (6))	• At a scheduled visit, reported swallowing fifty 500-mg tablets two days earlier, denied suicidal intent. No hospitalization. At a site visit ((b) (6)), Study staff instructed patient to go to hospital, but she refused. LFTs collected four days after ingestion were abnormal, demonstrating marked transaminitis, and patient did not comply with subsequent visits/evaluations until one month after ingestion, at which time LFTs were normal.

OL SL Buprenorphine Nonfatal Serious Adverse Events – Controlled Studies

Subject ID / Age / # implants	Induction / Target dose	SAE(s)	Narrative
PRO-806			
(b) (6) 46 M	(b) (6) 12 mg	• Angina pectoris ((b) (6))	• Hospitalization • Elevated BP prior to randomization and throughout study.
(b) (6) 24 M	(b) (6) 16 mg	• Pyrexia ((b) (6))	• Hospitalized with T 102.5. CT abd/pelvis findings suggestive of enterocolitis. Diphtheroids & gram(+) rods on blood culture. IV vanc/ceftriaxone. Pt. left AMA.
(b) (6) 24 M	(b) (6) 12 mg	• Rib fracture ((b) (6))	• Sustained in motorcycle accident.

Subject ID / Age / # implants	Induction / Target dose	SAE(s)	Narrative
(b) (6) 52 M	(b) (6) 16 mg	• Major depression (b) (6)	• h/o depression and suicide attempt (in 2004) • Voluntarily went to ER and hospitalized with complaints of auditory hallucinations and suicidal ideation. He reported hearing his own voice telling him to use heroin.
(b) (6) 26 F	(b) (6) 16 mg	• Abortion spontaneous (b) (6)	• hospitalized with severe vaginal bleeding
(b) (6) 46 M	(b) (6) 16 mg	• Pulmonary embolism (b) (6)	• No obvious predisposing factors.

Probuphine Nonfatal Serious Adverse Events – Uncontrolled Open-Label Extension Studies

Subject ID / Age / # implants	Induction / Target dose	SAE(s)	Narrative
PRO-807			
Placebo in Double-Blind Studies → OL Probuphine			
(b) (6) 51 M 4 implants	(b) (6) 16 mg	• Pneumonia (b) (6)	• See also above re: explant site infection
PRO-811			
Probuphine in Double-Blind Studies → OL Probuphine			
(b) (6) 54 M 4 implants	(b) (6) 16 mg	• Coronary artery disease • (b) (6)	• Completed PRO-806 on (b) (6). • Before study drug started, hospitalized for elective angiogram. Angiography revealed > 50% blockage of one right vessel.
(b) (6) 40 M 4 implants	(b) (6) 12 mg	• Right antecubital fossa cellulitis (b) (6)	• Completed PRO-806 on (b) (6). • IV methamphetamine use on (b) (6) and (b) (6). • On the CRF, it was mentioned that

Subject ID / Age/ # implants	Induction / Target dose	SAE(s)	Narrative
(b) (6)	(b) (6)		the location of the cellulitis was at the explant site.
51 F 4 implants	12 mg	• Suicide ideation (b) (6)	• Completed PRO-806 on (b) (6) • h/o bulimia nervosa (since (b) (6)), depression (since (b) (6)), panic disorder (since (b) (6)).

On review of the serious adverse events across the studies and trials, the pattern of SAEs did not identify novel systemic findings inconsistent with the known safety profile of buprenorphine. There were few SAEs overall, and the observed events were not of a pattern to suggest a new, unexpected safety signal related to buprenorphine systemic exposure. Additional safety labeling beyond current labeling for the sublingual formulations with respect to serious adverse events does not appear warranted. With respect to procedure-related safety, examination of serious adverse events, only a single event was reported, and it predated the enhancements. The serious adverse event findings do not specifically inform labeling pertaining to procedural safety.

7.3.3 Dropouts and/or Discontinuations

Analyses of adverse events leading to premature discontinuation of study drug identify the types of adverse events that subjects were unable to tolerate even in a clinical trial setting, and the frequency with which these types of events occurred. As there is perhaps more support for patients to persist on treatment while experiencing these adverse events in a clinical trial setting than would be the case in the clinical practice setting, review of these events helps characterize the tolerability profile anticipated for the drug when used outside of a controlled environment. Adverse dropouts may also provide a clue to unexpected, but important, adverse reactions that may be initially ascribed to intercurrent illness.

Across the Probuphine double-blind studies, adverse events leading to discontinuation of treatment and withdrawal from the trial occurred in seven subjects on Probuphine (2%), two subjects on placebo (2%), and five subjects on sublingual buprenorphine (4%) in the open-label arm of PRO-806. PRO-814, the last trial completed, contributed a single early discontinuation that was experienced by a patient in the Probuphine arm. In the pooled open-label extension studies, early discontinuations 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.

The following table provides an overall summary, by treatment arm, of the adverse events associated with study dropout. The numerical identifier for the study in which the

adverse event occurred is also included in parentheses next to each event, primarily for the appraisal of implant site adverse events. For Studies 806, 811, and 814, improvements to the applicator device, surgical technique and training and certification program were instituted for the insertion and removal procedures. Comparing across the studies may provide some insight into any shifts in the implant-related tolerability profile before and after these enhancements were implemented.

Additional details on the subjects who discontinued due to adverse events and the adverse events associated with the dropouts are provided in subsequent tables in this section of the review.

Pooled Double-Blind Studies – PRO-805, PRO-806, and PRO-814		
Probuphine (2%)	Placebo (2%)	SL BPN (2%)
1. Implant Site Pain/Infection (805) 2. Implant Site Pain/Infection (805) 3. Implant Site Pain (805) 4. Hepatic Enzyme increases (805) 5. LFT abnormal (806) 6. Breast Cancer (806) 7. Muscle Spasms [↑ CPK] (814)	1. Tylenol Overdose (806) 2. Hepatitis C (806)	1. ALT/AST increased (806) 2. Weight decreased (806) 3. Neck pain (806) 4. Sinus tachycardia (806) 5. Drug dependence (806)
Pooled OL Extension Studies – PRO-807 & PRO-811		
1. Implant Site Hemorrhage, Infection, Edema & Erythema (807) – Probuphine → Probuphine 2. Implant Site Infection (807) – Probuphine → Probuphine 3. ALT increased (811) Probuphine → Probuphine		
Clinical Pharmacology Study PRO-810		
1. Adverse dropout in BA Study (810) – pancreatic cyst		

Narrative information for the subjects who experienced adverse events that led to study discontinuation is provided in tables below. There was a single adverse event that led to discontinuation among the clinically stable patients evaluated in PRO-814, which occurred in a patient in the Probuphine arm, and this specific adverse event is discussed separately from those occurring in the earlier Phase 3 studies.

For the Phase 3 studies in new entrants to treatment, the tables are presented by study type, controlled trial or extension, and by treatment arm within the study groupings. For these studies, patients had to reach a target dose of 12 – 16 mg SL buprenorphine prior to insertion of implants, and the induction/target dose reached is also provided in the table, as well as the total number of rods, or implants, received during the treatment cycle, i.e., four or five, when this information has relevance to the case. There was formerly an option for a fifth rod. However, at this time, there are no longer plans for the optional fifth rod for the Probuphine product. In PRO-814, only a single, fixed dose, four rods, was evaluated.

PRO-814 – Probuphine Treatment Discontinuation

Subject (b) (6), a 29-year-old male was discontinued for the trial due to an adverse event of muscle spasm, described as continuous, starting from his toes, up to his head, and back down to his toes. At the time of randomization in the study, the subject had been receiving SL BPN/naloxone (8/2 mg QD) for 1 year and 2 months.

Onset of muscle spasms was on Day 34. He was discontinued on Day 38 and four implants were removed uneventfully. At that time, he was found to have an elevated creatinine phosphokinase CPK (1510 U/L; 7.3 × ULN, which had returned to normal by Day 44. All other Day 44 labs were unremarkable. Screening creatinine phosphokinase (CPK) was normal. The subject denied strenuous physical activity. The subject's urine toxicology tests throughout his participation (Screening, Days 29, 38, and 44) were negative except for benzodiazepine (on prescribed benzodiazepine) and/or cannabinoids (unspecified); urines tested positive for cannabinoids at each evaluation. Concomitant medications taken within 14 days prior to onset date of the event were clonazepam (0.5 mg prn, started (b) (6)), clonidine (0.1 mg QD, started in (b) (6)), and sertraline HCL (100 mg QD, started (b) (6)). He did not receive supplemental SL BPN (2 mg) during his participation in the study.

The etiology of the muscle spasms and CPK abnormalities is unclear, and may be the result of the combination of drugs with serotonergic effects in the setting of cannabis use. However, it does not appear to be a systemic effect of buprenorphine alone or solely related to the indwelling rods.

Probuphine Treatment Discontinuations – Controlled Studies

Subject ID / Age/ # implants	Induction / Target dose/ Supplemental SL BPN (where relevant)	AE(s) Leading to Discontinuation	Narrative
PRO-805			
(b) (6) 52 M 4 implants (no dose increase specified)	(b) (6) – (b) (6) Target dose reached not specified. Supplemental SL BPN at 8 mg started Dec 21; received doses of 4 to 8 mg from (b) (6) through (b) (6)	Hepatic enzyme increased (elevated liver enzymes) (b) (6) (b) (6))	- h/o hepatitis C - Pre-Induction ALT 75, AST 55 - high of 1304 U/L and 1048 U/L, respectively, on (b) (6). No addl laboratory testing reported. - Concomitant medications included ibuprofen, Vicodin, and lidocaine
(b) (6) 27 M 4 implants (no implant dose increase specified)	(b) (6) – (b) (6) Supplemental SL BPN, doses of 8 to 16 mg, (b) (6) – (b) (6)	- Implant site pain (b) (6)) - Implant site infection (b) (6))	- No meds given. (b) (6) – implants removed and subject discontinued from study. - Investigator reported the subject as recovered from the AEs of implant site pain and implant site infection on (b) (6).

Subject ID / Age/ # implants	Induction / Target dose/ Supplemental SL BPN (where relevant)	AE(s) Leading to Discontinuation	Narrative
(b) (6) 25 F 4 Probuphine implants (no implant dose increase specified)	(b) (6) – (b) (6) Target dose 16 mg Supplemental SL BPN 8 to 16 mg, (b) (6) to (b) (6)	- Implant site pain ((b) (6)) - Implant site infection ((b) (6))	- Paracetamol, PCN, and cephalexin. - Implant site pain and infection recovered ((b) (6)) and ((b) (6)), respectively. ((b) (6)) – implants removed and subject discontinued from study.
(b) (6) 32 F 4 implants	(b) (6) – (b) (6) 16 mg (b) (6) to (b) (6) supplemental at dose range of 2 – 8 mg.	implant site pain ((b) (6))	- recovered ((b) (6)). ((b) (6)) – implants removed and subject discontinued from study.
PRO-806			
(b) (6) 39 F 4 implants	(b) (6) – (b) (6) 12 mg No supplemental	breast cancer	((b) (6)) – SAE of breast cancer – invasive ductal carcinoma of the left breast
(b) (6) 40 M 4 implants	(b) (6) – (b) (6) 12 mg No supplemental BPN	Liver function test abnormal	((b) (6)) – AE of LFT abnormal. At baseline all values above ULN: ALT 73; AST 64; GGT 105; LDH 266; Peak values Jul 30 ALT 559; AST 634; GGT 280; LDH 478 ((b) (6)) – study drug d/ced, LFTs decreasing; Increasing again on ((b) (6)) after study drug withdrawn

Placebo Treatment Discontinuations – Controlled Studies

Subject ID / Age/ # implants	Induction / Target dose	AE(s) Leading to Discontinuation	Narrative
PRO-806			
(b) (6) 26 F 4 implants	(b) (6) – (b) (6) 16 mg Supplemental SL BPN started (b) (6) with 8 mg, and continued at this dose until (b) (6).	Tylenol Overdose ((b) (6)) See also SAEs	- Reported swallowing fifty 500-mg tablets. No hospitalization. - At a site visit ((b) (6)), instructed to go to hospital, but refused
(b) (6) 53 M 5 implants	(b) (6) – (b) (6) 16 mg	Worsening Hepatitis C ((b) (6))	1st diagnosis of hepatitis C in ((b) (6)) - At screening, AE of Hep C, condition didn't improve and AE of worsening Hep C on the ((b) (6)).

	Supplemental dosing 8 mg from (b) (6) to (b) (6)		• (b) (6) – Implants d/ced; subject withdrawn from study

OL SL Buprenorphine Treatment Discontinuations – Controlled Studies

Subject ID / Age/ # implants	Induction / Target dose	AE(s) Leading to Discontinuation	Narrative
PRO-806			
(b) (6) 46 M	(b) (6) – (b) (6) 12 mg No supplemental BPN.	- Alanine amino-transferase (ALT) increased (b) (6) - Aspartate amino-transferase (AST) increased (b) (6)	- Last SL BPN dose (b) (6) & AEs of ALT & AST increased. - ALT 38 AST 31 (b) (6) - ALT 559, AST 290 (b) (6) - Drug discontinued (b) (6) when ALT 717 & AST 382, also last day of contact
(b) (6) 39 M	(b) (6) – (b) (6) 16 mg No supplemental BPN.	Drug dependence (b) (6)	- AE of drug dependence; heroin and cocaine by self-report; urine tox (+) heroin metabolites. - Treatment for drug detoxification included diazepam and methadone, and he received dicycloverine hydrochloride for associated abdominal cramping. - Drug discontinued 21
(b) (6) 43 F	(b) (6) – (b) (6) 12 mg Supplemental SL BPN at a dose of 4 mg beginning on (b) (6); the dose was increased to 16 mg on (b) (6) and supplemental dosing continued at this dose until (b) (6). The subject's assigned SL BPN dose was increased to 16 mg on (b) (6).	Weight decreased (b) (6)	Baseline wgt 78.91 kg (b) (6) to 64.40 kg (b) (6) (Week 10) 31 lbs. Drug withdrawn and pt. discontinued on (b) (6)
(b) (6) 54 F	(b) (6) – (b) (6) 16 mg No supplemental BPN	neck pain (b) (6)	- Last SL BPN dose taken before event onset was on (b) (6). - No treatment was given for the event - Drug d/ced (b) (6)

			• Study withdrawal (b) (6) due to non-compliance; missed 9 consecutive urine samples. • investigator reported the event outcome as recovered on (b) (6)
(b) (6) 32 F	(b) (6) – (b) (6) 12 mg No supplemental BPN	• Sinus tachycardia (b) (6)	• Last SL BPN dose taken before event onset was on (b) (6). No treatment given for the event. • ECG: non-clinically significant sinus tachycardia with left atrial enlargement; Max HR = 109 bpm; QTcB & QTcF < 450 msec • On (b) (6), treatment with study drug was discontinued • investigator reported the event outcome recovered on (b) (6)

Probuphine Treatment Discontinuations – Uncontrolled Open-Label Extension Studies

Subject ID / Age/ # implants	Induction / Target dose	AE(s) Leading to Discontinuation	Narrative
Probuphine in Double-Blind Studies → OL Probuphine			
PRO-807			
(b) (6) 21 F 4 implants	(b) (6) – (b) (6) (completed PRO-805 (b) (6)) 12 mg No supplemental SL BPN	• Implant site bleeding (b) (6) • implant site infection (b) (6) • implant site erythema (b) (6) • implant site edema (b) (6)	• Implants Left arm PRO-805; Right arm PRO-807 on (b) (6) • (b) (6) – 1 of 4 implants removed intact that day • (b) (6) – subject d/ced treatment that day due to implant site AEs; remaining 3 implants removed.
(b) (6) 38 M 4 implants	(b) (6) – (b) (6) (completed PRO-805 (b) (6)) 12 mg No supplemental SL BPN	• Implant site infection (b) (6)	• Implants Left arm PRO-805 + Left arm dose increase; Right arm PRO-807 on (b) (6) • subject dced treatment (b) (6) due to event, and implants removed
PRO-811			
(b) (6) 33 F 4 implants	(b) (6) – (b) (6) (completed PRO-806 (b) (6)) 16 mg	• Elevated alanine aminotransferase (b) (6)	• History of hepatitis C • Met exclusionary ALT criteria prior to induction, but nevertheless received implants on (b) (6) • (b) (6) – elevated AST and

	Supplemental use not mentioned.		GGT. • (b) (6) – Discontinued because of elevated ALT and implants removed.

Adverse dropouts were infrequent across all the treatment arms in the studies, as reflected in the summary table and above narrative summaries. A number of these events were implant site related adverse events. Of note is that these occurred in Studies PRO-805 and PRO-807 which predate the improvements to the applicator, surgical technique, and training and certification program for the insertion and removal procedures. The drop in adverse events associated with discontinuation in the latter Phase 3 safety and efficacy trial may be a result of the improvements. Many of the sites participated in both studies; therefore, it may also be merely a result of the implanting physicians becoming more adept at the procedures over time, and with more opportunities for repeated procedures. Whatever the basis for the decrease, the adverse events have decreased considerably between the first and second sets of Phase 3 studies.

The other group of adverse events that occurred in more than one subject and may represent an important systemic effect of Probuphine and sublingual buprenorphine are the liver function test abnormalities. These were seen across all treatment arms, and in the double-blind and open-label studies. These patients typically had underlying diagnoses of hepatitis C and/or elevated hepatic enzymes at baseline. Some subjects were on concomitant medications that could cause hepatic enzyme elevations. One subject (b) (6) did not meet Hy’s Law criteria but had an elevated AST and ALT and a bilirubin approaching the total bilirubin threshold of > 2 x ULN. This patient saw a downward trend in the lab values while the Probuphine implants were still in place. Of note, this occurred in the extension study, and this patient had already been exposed to Probuphine in the primary safety and efficacy trial. It is conceivable that the higher buprenorphine exposures with Probuphine earlier in treatment may have played a contributory role.

Buprenorphine in combination with naloxone and in transmucosal form has been evaluated in patients with hepatic impairment. The labels for the transmucosal buprenorphine-containing products that also contain naloxone now include a Warning regarding use of the product in patients with impaired hepatic impairment. The Warning states:

Buprenorphine and naloxone products are not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. The doses of buprenorphine and naloxone in this fixed-dose combination product cannot be individually titrated, and hepatic impairment results in a reduced clearance of naloxone to a much greater extent than buprenorphine. Therefore, patients with severe hepatic impairment will be exposed to substantially higher levels of naloxone than patients with normal hepatic function. This may interfere with buprenorphine’s efficacy throughout treatment. In patients with moderate hepatic impairment, the

differential reduction of naloxone clearance compared to buprenorphine clearance is not as great as in subjects with severe hepatic impairment. Therefore, buprenorphine/naloxone products may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine product without naloxone. However, patients should be carefully monitored and consideration given to the possibility of naloxone interfering with buprenorphine's efficacy.

The label for Probuphine will include a Warning regarding use of the product in patients with hepatic impairment, and will be adapted in order to be consistent with the properties of Probuphine's properties relative to transmucosal buprenorphine/naloxone products, namely that Probuphine does not contain naloxone, and is a fixed-dose product containing a single-entity drug substance as compared with a product containing two drug substances.

Other adverse events associated with discontinuation were solitary events, and are not critical events that would seem to significantly alter the recognized buprenorphine safety profile. One of these single occurrences was an event of relapse in a patient on sublingual buprenorphine that pertains to efficacy of sublingual buprenorphine rather than a safety concern.

7.3.4 Significant Adverse Events

Specific adverse events have been designated significant adverse events for the purposes of this review because they are known safety concerns for the buprenorphine drug substance, for which there are warnings and precautions, or because they are safety concerns that are currently undergoing evaluation.

Of the special interest AEs, unanticipated systemic findings were observed for the hepatic injury data and QT interval data for the Probuphine initial new drug application submission, and the current NDA Resubmission.

Hepatic Injury

Buprenorphine has been associated with hepatitis and other hepatic events. The *Warnings and Precautions* section of current labeling for sublingual buprenorphine (as Suboxone) includes safety labeling regarding hepatitis and hepatic events as follows:

5.6 Hepatitis, Hepatic Events

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through post-marketing adverse event reports. The spectrum of abnormalities ranges 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. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Liver function tests, prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, SUBOXONE sublingual tablet may need to be carefully discontinued to prevent withdrawal signs and symptoms and a return by the patient to illicit drug use, and strict monitoring of the patient should be initiated.

Hepatitis and hepatic events are considered part of the known safety profile of buprenorphine. In evaluating the hepatic safety of Probuphine, the objective was to establish whether the hepatic safety findings from the Probuphine clinical trial database were consistent with the known safety profile of buprenorphine, and to identify new safety information, if any, for buprenorphine exposure intrinsically or as a result of buprenorphine exposure in the setting of this novel delivery system. To facilitate this effort, the Applicant has been advised to search the pooled safety database for hepatic adverse events with emphasis on “Hy’s Law”³⁰ cases. These cases are indicative of hepatocellular injury sufficient to impair bilirubin excretion, and are used to identify drugs likely to be capable of causing severe liver injury.

The laboratory convention used most commonly for identifying Hy’s Law cases are aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations > 3xULN along with total bilirubin elevations $\geq$ 2xULN. However, the Applicant used the following liver function test criteria to identify possible Hy’s Law cases:

- ALT >3X ULN (upper limit of normal) or AST >3X ULN, and
- Total bilirubin >2X ULN or >1.5 X baseline.

The Applicant applied a different definition and initially reported that Hy’s Law cases were identified; however, when applying the usual case definition, it was determined that there were no Hy’s Law cases in the overall database, although LFT changes consistent with the labeled effects of buprenorphine were observed.

³⁰ Hy’s Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

Excerpt from Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation available at: <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf>

In addition to an evaluation of abnormal liver function tests, the Applicant performed a search for adverse events using hepatic injury-related SMQs. The Applicant explained that the adverse event terms included in the SMQs were used as a starting point to identify AE terms of interest, and the lists of AEs affiliated with each category were augmented or terms were removed to ensure all events were identified correctly. In searching for possible adverse events that may signify hepatic injury, the Applicant found that, apart from two placebo-treated patients with AEs coded to the term "Hepatitis C," all events were in the SOC Investigations. The findings from the search of possible hepatic injury treatment-emergent adverse events are consistent with the LFT findings.

The LFT abnormalities observed in the Probuphine clinical trial database for patients exposed to Probuphine in addition to sublingual buprenorphine or sublingual buprenorphine alone, were primarily marked transaminase elevations that occurred in patients with baseline LFT abnormalities, underlying viral hepatitis diagnoses, and/or use of concomitant licit or illicit substances that may have had a causal or contributory role. Buprenorphine exposure, alone, or in combination with these other potential etiologies, could be causal as well. In the end, however, the Probuphine safety database reveals no new hepatic safety concerns beyond those previously identified in the clinical trial and postmarketing setting for the marketed buprenorphine-containing transmucosal products.

QT prolongation

Prolongation of the QT/QTc interval is associated with increased susceptibility to arrhythmias, in particular, Torsades de Pointes.

A signal for QT prolongation has been identified in a study of transdermal buprenorphine used for analgesia. The extent of prolongation noted was considered to meet the threshold for regulatory concern, a value which is used to determine whether or not the effect of a drug on the QT/QTc interval in target patient populations should be studied intensively during later stages of drug development. 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 (tQT) studies. Given the design of the traditional tQT studies, which evaluates suprathreshold doses of the drug product, buprenorphine when used for treatment of addiction may not lend itself to study using the traditional designs, and a modified design may be required.

Electrocardiogram (ECG) data from the Probuphine clinical trials were evaluated for the pooled double-blind and open-label studies. An analysis of QT interval data based on Probuphine clinical trial data was performed and summaries are provided for QT interval data using Bazett's corrections and Fridericia's corrections, based on QT/QTc interval and changes from baseline.

While there is no consensus concerning the choice of upper limit values for absolute QT/QTc interval and changes from baseline, categories have been offered as guideline thresholds. These categories have been used for analysis here, and were also explored more thoroughly in the clinical review for the initial submission, where the Probuphine, placebo, and sublingual buprenorphine arms are evaluated separately. (The reader is referred to the primary clinical review for the initial submission for the previous discussion).

Table 17 QTcB and QTcF Summary – Pooled Double-Blind Studies

Parameter and Visit	Result (msec)	Probuphine N=309 n (%)	Placebo/SL BPN N=317 n (%)
	QTcB		
QTcB at Baseline	<450	291 (94.2)	294 (93.6)
	450 - <480	12 (3.9)	15 (4.8)
	480 - <500	1 (0.3)	3 (1.0)
	≥500	2 (0.6)	2 (0.6)
QTcB across all visits based on maximal value	<450	276 (87.6)	274 (83.8)
	450 - <480	21 (6.7)	34 (10.4)
	480 - <500	2 (0.6)	2 (0.6)
	≥500	2 (0.6)	5 (1.5)
Change from Baseline in QTcB based on maximal value	<30	230 (80.1)	254 (84.9)
	30 - <60	38 (13.2)	32 (10.7)
	≥60	19 (6.6)	13 (4.3)
QTcB at Week 24/EOT	<450	252 (94.0)	247 (89.8)
	450 - <480	14 (5.2)	23 (8.4)
	480 - <500	1 (0.4)	2 (0.7)
	≥500	1 (0.4)	3 (1.1)
Change from Baseline in QTcB at Week 24/EOT	<30	223 (83.8)	242 (89.0)
	30 - <60	32 (12.0)	20 (7.4)
	≥60	11 (4.1)	10 (3.7)

	QTcF		
QTcF at Baseline	<450	293 (94.8%)	303 (96.5%)
	450 - <480	10 (3.2%)	10 (3.2)
	480 - <500	1 (0.3%)	0 (0.0)
	≥500	2 (0.6%)	1 (0.3)
QTcF across all visits based on maximal value	<450	287 (92.0)	293 (91.0)
	450 - <480	8 (2.6)	15 (4.7)
	480 - <500	1 (0.3)	1 (0.3)
	≥500	2 (0.6)	1 (0.3)
Change from Baseline in QTcF based on maximal value	<30	246 (85.7)	270 (90.3)
	30 - <60	30 (10.5)	20 (6.7)
	≥60	11 (3.8)	9 (3.0)
QTcF at Week 24/EOT	<450	264 (98.5)	267 (97.1)
	450 - <480	2 (0.7)	7 (2.5)
	480 - <500	1 (0.4)	0 (0.0)
	≥500	1 (0.4)	1 (0.4)
Change from Baseline in QTcF at Week 24/EOT	<30	235 (88.3)	255 (93.8)
	30 - <60	25 (9.4)	10 (3.7)
	≥60	6 (2.3)	7 (2.6)

Source: Integrated Summary of Safety Addendum, Table 40, pp. 120–121.

Prolongation of QTc > 500 ms during therapy has been a threshold of particular concern in clinical trials. However, there were subjects with baseline QTcB values above 500 in the Probuphine arm and the combined Placebo/SL BPN arm. The observed cases of QTcB > 500 remained about the same post baseline.

Because Bazett's correction overcorrects at elevated heart rates and under corrects at heart rates below 60 beats per minute (bpm), Fridericia's correction is considered more accurate than Bazett's correction in subjects with such altered heart rates. QTcF findings across the treatment arms were similar to that seen with the QTcB data. With the more accurate QTcF correction, there were fewer cases overall meeting these thresholds.

QT interval prolongation was observed across all treatment arms in the clinical trial database, suggesting that this is not a phenomenon specific to Probuphine. The larger shifts, i.e., changes relative to baseline > 60, were observed with more frequency in

certain instances in the Probuphine arm to a small degree. This may reflect the continuous exposure with Probuphine, where passive compliance is offered. However, these differences are small, and definitive conclusions cannot be made from these data.

The potential for doses of buprenorphine used for the treatment of opioid dependence to prolong the QT interval is to be evaluated in dedicated QT studies. Because the signal was identified when several formulations of buprenorphine were already on the market, sponsors of new buprenorphine products have been informed that they will be permitted to complete the QT evaluations as post-marketing requirements.

Other Events – Pregnancy

There were a total of six pregnancies. Three were carried to term, only one of which was on Probuphine. There was no information about NAS/NOWS after delivery. There were two spontaneous abortions, both in patients on sublingual buprenorphine. One patient had an elective abortion.

7.3.5 Submission Specific Primary Safety Concerns

Because Probuphine is a novel implantable formulation of buprenorphine, the review of safety data specific to the implants and insertion and removal procedures was emphasized.

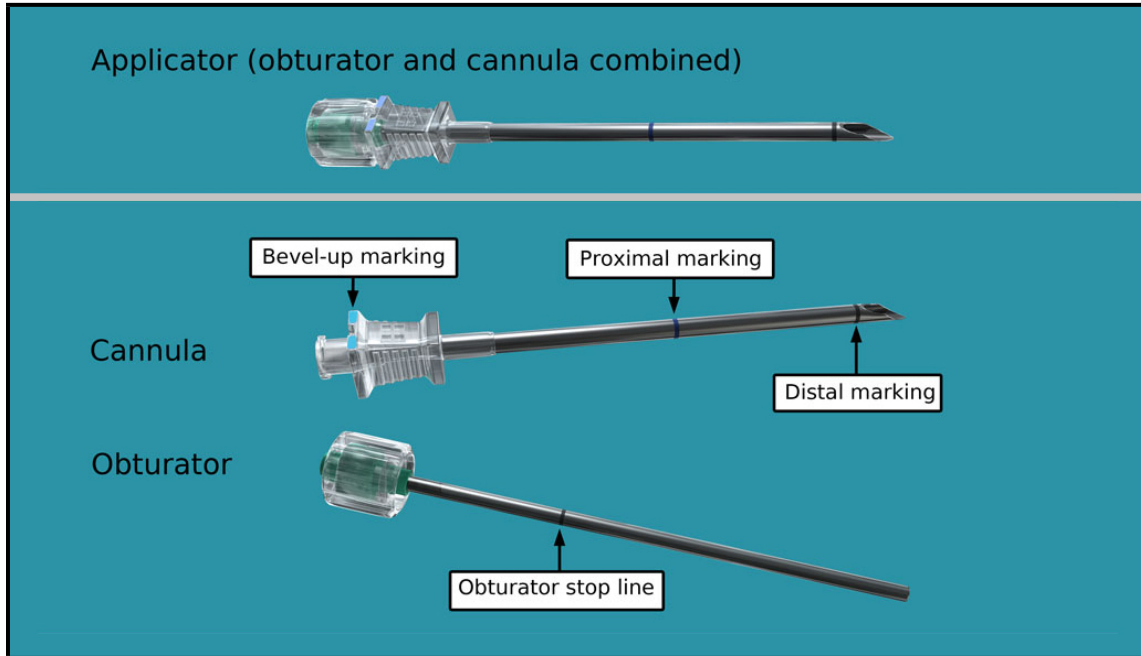
Probuphine requires an in-office surgical procedure for insertion of the implants at the beginning of a treatment cycle, and a second procedure to remove the implants six months later at the end of the treatment cycle. When the NDA was originally submitted, Probuphine was envisioned as a product where initially, four implants would be inserted, and an additional procedure would be performed if a dose increase was needed, to insertion one additional implant. At present, there are no longer plans for an option for a fifth rod. Probuphine is now to be used as a fixed, single dose product with no means of titration. As such, in a best case scenario, if there are no complications, it requires one procedure for insertion and another for removal at the end of six months for one treatment cycle. Additional procedures, e.g., removal and reinsertion into another site, have been required for some patients in the Probuphine development program. This has occurred, for example, in the context of an implant site reaction where early removal and reinsertion into another unused site became necessary to manage the event, but meanwhile continuing treatment for that cycle.

As mentioned earlier in this review, our Obstetrics and Gynecology physician colleagues in the Division of Bone, Reproductive, and Urologic Products (DBRUP) were consulted to assist with evaluation of the procedural safety data. This procedural-related safety discussion is based extensively on DBRUP's consultative review.

The following figures are illustrations of the device used for insertion, the target location for the implants, and aspects of the insertion and removal processes.

7.3.5.1 Insertion and Removal Procedures

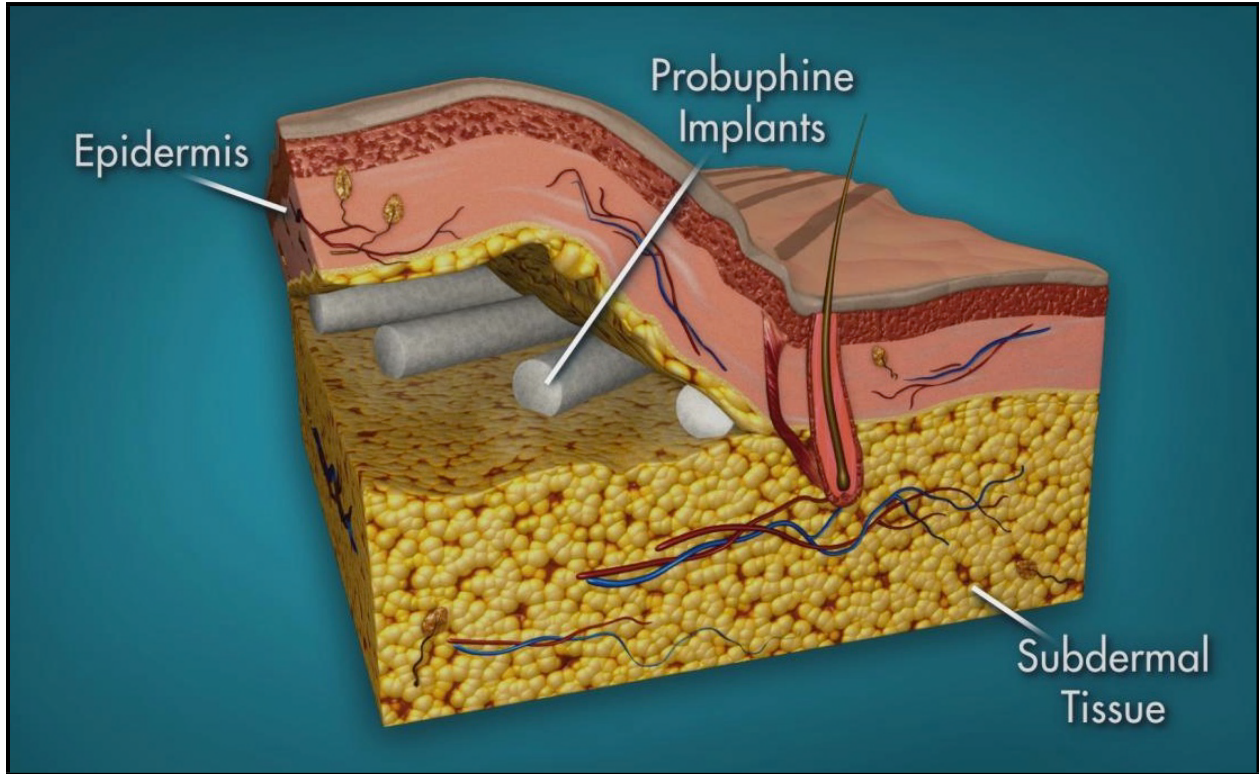
Figure 4 Insertion - Applicator (Obturator and Cannula)



Source: PRO-814 Manual of Procedures

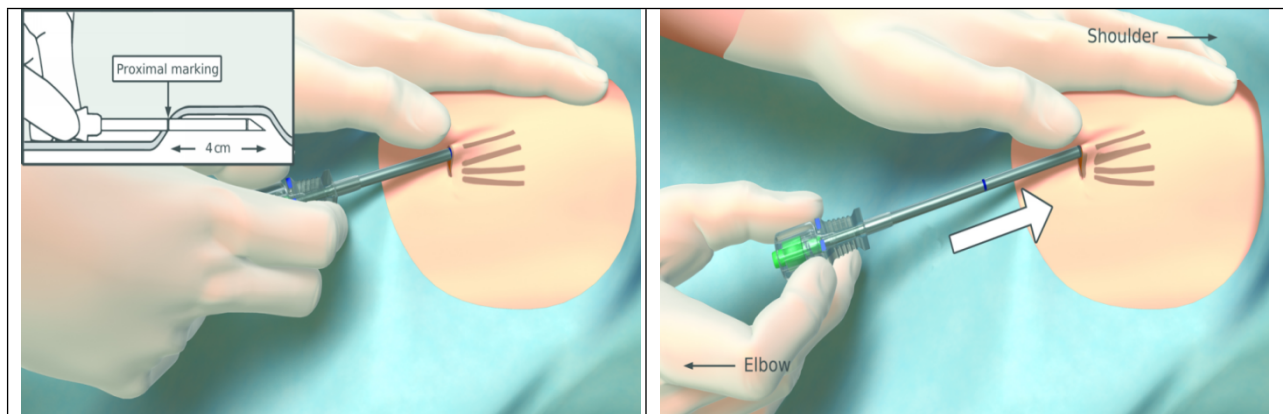
Insertion of Four Probuphine Implants

Figure 5 Implant Insertion



Source: PRO-814 Manual of Procedures

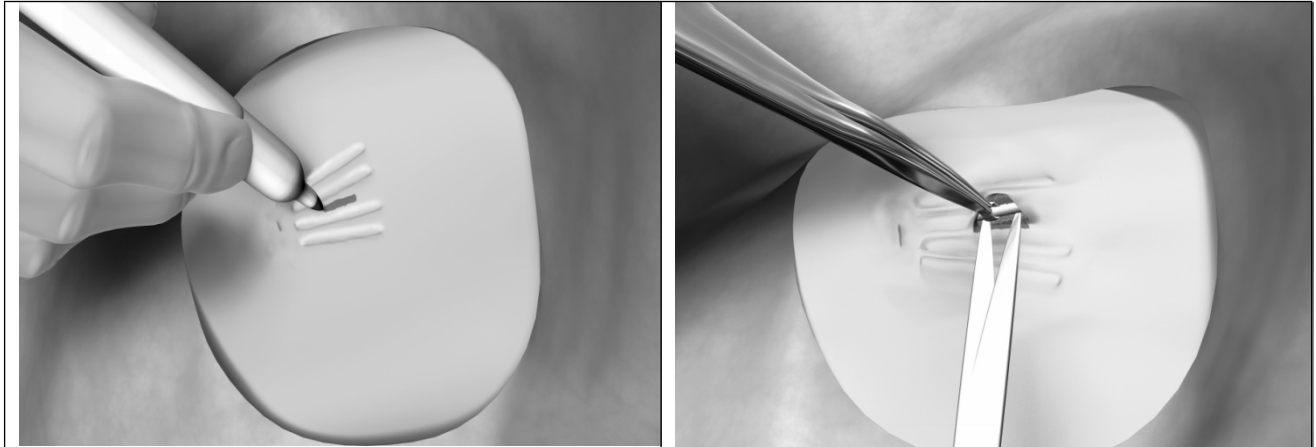
Figure 6 Implant Insertion



Source: PRO-814 Manual of Procedures

Removal

Figure 7 Implant Removal



Source: Proposed (draft) label

The Applicant documented the following with respect to the insertion and removal procedures for Probuphine and Placebo implants across the clinical development program. (The text below is an excerpt from the ISS Addendum).

Clinicians were instructed to follow the procedures described below for implant insertion and removal. A copy of the written Implant Insertion and Removal Instructions was provided during training.

All Probuphine and placebo implants were implanted and removed by trained clinicians. The sponsor provided an Implant Insertion/Removal Training Video as well as written instructions for the proper, aseptic subdermal insertion and removal of Probuphine and placebo implants. For Studies PRO-806, PRO-811, and PRO-814, the sponsor also instituted the Probuphine Clinical Training and Certification program to ensure that clinicians who performed the implant insertion and removal procedures met competency standards. All health care providers documented their implant training in signed statements.

- Prior to insertion of implants, study staff confirmed that the subject had no allergies to buprenorphine, EVA, or the antiseptic and local anesthetic that were used. Aseptic techniques, sterile gloves, and sterile drapes were used, with efforts to avoid contamination in the sterile field.
- For the insertion procedure, a site on the inner side of the upper, non-dominant arm was identified and cleaned with an antiseptic solution. Four channel tracks, where the implants were to be inserted, were marked with a skin marker, in a fan-shaped distribution 4 to 6 mm apart. A local anesthetic was injected at the incision area and just under the skin along the planned insertion channels. A 2-mm incision was made through the dermis (all 4 implants were inserted through the same skin incision). An applicator (consisting of a cannula and obturator combined) was then advanced under the channel

markings on the skin. Using the applicator, 4 implants were inserted, 1 at a time, in a fan-shaped distribution, all on the same plane just below the dermis. There should have been at least 5 mm between the incision and the end of the implant when the implant was properly positioned. The incision site was then cleaned, and liquid adhesive and Steri Strips™ were placed over the incision and then covered with an adhesive bandage. Complete details for implant insertion are found in the Implant Insertion and Removal Instructions (included in the proposed label). For studies conducted prior to PRO-814, fifth implant titration was allowed, and the procedure used for inserting the fifth implant (Implant Dose Increase), when clinically warranted, was identical to that used for insertion of the initial 4 implants. The fifth implant was inserted immediately adjacent to the initial implants, with the exact location being subject to the discretion of the implant physician.

- Prior to removal of implants, study staff confirmed that the subject had no allergies to the anesthetic and local anesthetic that were used. Aseptic techniques, sterile gloves, and sterile drapes were used, with efforts to avoid contamination in the sterile field.
- For the implant removal procedure, the location of all implants was confirmed by palpation prior to removal (clinicians were instructed to locate nonpalpable implants using ultrasound prior to removal). The location of implants was marked with a skin marker, and the removal site was cleaned with an antiseptic solution. The incision site and subdermal space containing the implants were anesthetized. Once anesthesia was determined to be adequate, a 10-mm incision was made parallel to the axis of the arm, between the second and third implants. Fibrous tissue surrounding or adhering to the implant was adequately separated from the implant prior to removal. The center of the implant was gently grasped using a specially designed clamp and removed from the subdermal space. These steps were repeated until all implants were removed. If any implants were broken, clinicians were instructed to remove all pieces of the broken implant and ensure the broken pieces approximated 26 mm in length (the length of each implant). Once all implants were removed, the incision site was cleaned, closed with sutures, and covered with an adhesive bandage. Complete details for implant removal are found in the Implant Insertion and Removal Instructions (included in the proposed label).

In addition to counseling the subject on proper wound care, the study staff provided each subject with written wound care instructions after the insertion and removal of the implants.

Over the course of the Probuphine Phase 3 clinical development program, the surgical equipment needed to perform the procedures underwent modifications, so too the surgical technique. The images above reflect the new equipment and procedures that were instituted approximately midway through the Phase 3 development program. For Study PRO-805, the first Phase 3 double-blind trial, and Study PRO-807, the follow-on extension, a blunt applicator was used for insertion. The Applicant explained that the original applicator in the PRO-805 and PRO-807 studies was blunt-tipped and was associated with more tissue adhesions to the implants, resulting in more implant fractures. The modified sharp applicator, according to the Applicant, mitigated tissue damage and allowed closer placement of implants, thus facilitating easier removals.

For these earlier studies, PRO-805 and PRO-807, the standard removal technique used for removals of Norplant³¹, (the first implantable contraceptive, and the one that Probuphine most closely resembles in design and procedures for administration) and a straight removal clamp were utilized for the removal process. For Studies PRO-806, PRO-811, and more recently, PRO-814, a beveled applicator was used for the insertion, and the “U” technique and a modified vasectomy clamp were used for implant removal.

During the previous review cycle, there had been concerns about use of this so-called U-technique for removal, which is not commonly used in the US. This issue was raised during the March 21, 2013, Advisory Committee, by the Obstetrics and Gynecology physician experts on the panel. DBRUP addressed this issue in their review of the procedural-related safety data for the NDA Resubmission, and they documented evidence supporting the use of this method for Norplant removal. DBRUP highlighted that for Probuphine, an additional modification to the U-technique was introduced. For Probuphine removal, a longer incision is used, i.e., 7 – 10 mm in length vs. 4 mm, as described for the U-technique, making suturing necessary for closure in the case of Probuphine. Additionally, it should be noted that compared with procedures for continuation of treatment for the implantable contraceptives in general, Probuphine requires a new incision to continue treatment. In contrast, for the contraceptive implants, a single incision can be used for the rods that are to be removed, and for the insertion of new rods. When rods are removed at the end of a treatment cycle, the new rods are commonly inserted through the same incision, in the opposite direction from the rod³² being removed.

7.3.5.2 Probuphine Procedural Safety Database

Extent of Experience with Implant Insertion and/or Removal Procedures – Probuphine Safety Database from Phase 3 Studies

The primary source of safety data available on the Probuphine insertion and removal procedures, and the indwelling implants, are the Phase 3 safety and efficacy trials and the follow-on extension trials. Because patients in the placebo arm were subjected to the same insertion and removal procedures, procedural safety data from this arm are examined along with that of the Probuphine data to provide a more complete picture of the safety experience with insertion and removal of these implants.

Throughout the Phase 3 safety and efficacy trials and the extension studies, at least 654 insertion procedures were performed to insert the initial four implants into the inner

³¹ Norplant is a six-capsule (or 6 implants/rods) levonorgestrel contraceptive implant system that was approved for an up to 5-year treatment cycle in 1990. Although adopted readily, and with high penetration, its use declined dramatically upon media coverage of the removal difficulties. This product is no longer marketed in the US, as of 2002, but continues to be marketed in developing countries.

³² Currently marketed contraceptive implants consist of a single implant, or rod.

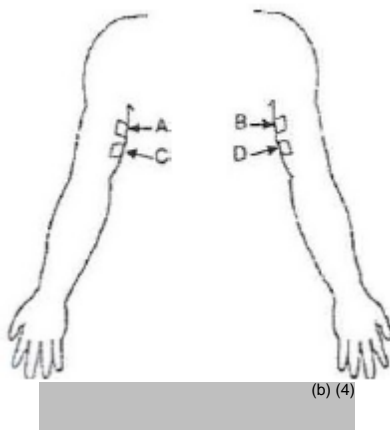
surface of the upper arm of the participants in each of these trials and extension studies.

Pooled Extent of Exposure to Procedures

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

Source: DBRUP Consult Review

The table summarizes the number of subjects who underwent at least one insertion procedure during a particular trial. Some subjects may have additional insertion procedures beyond the initial procedure. Some required more than one insertion procedure when there were complications requiring removal of the initial set of rods, and insertion of new rods to continue a treatment cycle. Still others had a fifth rod placed in the studies prior to the most recent trial, and underwent another insertion procedure for the dose increase. The cumulative exposure across the trials was 654, that is, 654 patients underwent an initial insertion procedure. At this stage in Probuphine’s development, there has only been experience with insertion of Probuphine into two sites, one on each arm. The Applicant has identified and proposes four possible sites for Probuphine administration, 2 sites each on the inner upper surface of the left and right arms.



There are a maximum of four sites that are available for Probuphine administration which is intended to be used for a chronic, relapsing condition that may require long-term, and even lifelong treatment. So, at best, this product can currently be used for a maximum of four, six-month treatment cycles, or a maximum of 2 years. In cases where early removal and reinsertion is necessary, Probuphine treatment would be possible for an even shorter period.

Of those patients who underwent one or more insertion procedures, the vast majority, though not all, also had removal procedures performed at the end of the treatment cycle to have the implants removed. Loss to follow-up in this case, thus, is identified here as a safety consideration. Those lost to follow-up, with no removal procedure documented, may still have the implants in place and the consequences, if any, and the fate of Probuphine (or placebo) implants that have remained in place indefinitely, is unknown.

Of the 654 patients who underwent the implant insertion procedure over the Probuphine development program, 456 had Probuphine implants inserted. Of the Probuphine insertions, 309 took place in the controlled studies and 147 took place during the open-label studies. Of the 147 patients who underwent insertion procedures during the open-label extensions, 107 were repeat Probuphine exposures and 40 were new Probuphine exposures who had been in the placebo or open-label sublingual buprenorphine arms during the controlled studies, PRO-805 and PRO-806. There were 198 patients who underwent insertion procedures to have placebo implants inserted during the controlled studies.

To place the size of the Probuphine procedural safety database in context, DBRUP summarized pre-approval exposure for contraceptive implants. Prior to approval, Norplant and Jadelle clinical programs, and the Implanon and Nexplanon development programs, combined, included larger numbers of removals than for the Probuphine development programs. The number of removal procedures across these contraceptive implant development programs was as follows:

Contraceptive implant development program and brief description	Number of pre-approval removal procedures
Norplant (6 levonorgestrel capsules or implants)	849
Jadelle (aka Norplant-2; 2 levonorgestrel implants)	>1100
Implanon (1 etonogestrel implant)	942
Nexplanon (radiopaque version of Implanon)	296
Combined Implanon and Nexplanon programs	942 + 296 = 1238

By comparison, the Probuphine development program represents a relatively small database, and includes a considerable number that were performed using equipment and procedures that are now obsolete for Probuphine. As such, there may not have been a sufficient number of procedures – particularly removals, the more challenging of the procedures – performed to fully characterize the safety profile associated with the insertion and removal procedures.

Extent of Experience with Implant Insertion and/or Removal – Proceduralists

In Studies 805 and 806, the clinicians who inserted and removed Probuphine rods were members of a variety of specialty practices. The table below provides a summary of the number of physicians performing insertion and removal procedures in each of the studies by specialty. The numbers of physicians in a particular specialty who performed

the procedures are represented in the yellow columns. The table also provides the numbers and proportions of patients who underwent removal and insertion procedures by the physicians in a particular specialty practice. These patients are represented in the columns with no shading or color-coding.

	PRO-805						PRO-806					
	Insertions			Removals			Insertions			Removals		
	# MDs	N=163 patients n (%) of patients		# MDs	N=148 patients n (%) of patients		# MDs	N=168 patients n (%) of patients		# MDs	N=147 patients n (%) of patients	
Specialty		n	%		n	%		n	%		n	%
Anesthesiology	2	12	7	2	12	8	3	8	5	3	7	5
Family Medicine	7	36	22	6	36	24	7	62	37	7	54	37
Internal Medicine	1	2	1	1	1	1	1	5	3	1	4	3
Neurosurgery	1	2	1	1	1	1	-	-	-	-	-	-
OB/GYN	6	43	26	6	35	24	5	45	27	5	35	24
Occupational Medicine	1	4	2	1	2	1	-	-	-	-	-	-
Orthopedic Surgery	-	-	-	1	3	2	-	-	-	-	-	-
Psychiatry	4	40	25	3	29	20	1	7	4	1	7	5
Surgery	3	24	15	2	29	20	3	24	14	3	23	16
Urology	-	-	-	-	-	-	2	17	10	2	17	12
Surgical Subspecialties		69	42		68	46		86	51		75	51

Most of the proceduralists were family medicine physicians or obstetrics and gynecology physicians, followed by psychiatrists, and surgeons. Physicians in these specialties and subspecialties also performed the majority of the procedures.

The provider mix and the number of procedures performed by the various specialties generally remained stable across the studies. However, in 806 compared to 805, a much smaller number of psychiatrists were performing the procedures, and the amount of procedures performed by psychiatrists was substantially less. Titan also commented at the March 21, 2013, Advisory Committee meeting that took place during the first

review cycle that the psychiatrists who volunteered to be trained as proceduralists had prior experience in another specialty (such as OB/GYN) before entering the field of psychiatry or were residents or early career practitioners whose medical school experience with procedures was relatively recent. At the same time, while the number of family medicine physicians stayed the same across the studies, more procedures were performed by family medicine physicians, members of a procedurally-oriented specialty. Again, in 806, modified surgical equipment, techniques, and training were implemented. Blue font was used in the table to highlight surgery and surgical subspecialties. A number of procedures were performed by surgically-trained physicians, and the proportion of procedures they performed increased in Study PRO-806 compared to Study PRO-805 with the new modifications to the equipment, techniques, and training.

In PRO-814, the provider mix included only a single clinician belonging to specialties that do not traditionally perform procedures, which still does not obviate familiarity with procedures. The remaining clinicians all belonged to surgical specialties or procedurally-oriented specialties. The proceduralists for PRO-814 included 8 Family Medicine, 6 Obstetrics & Gynecology, 3 General Surgery, 3 Anesthesiology, 1 Neurology and Psychiatry, and 1 Radiation Oncology physicians, and 1 Family Practice Nurse Practitioner. The clinical practice model proposed for Probuphine is one where clinicians with recent experience with an invasive procedure performed under sterile conditions will be eligible to perform the insertion and removal procedures, and all clinicians who will insert or remove Probuphine will need to demonstrate procedural competency in a model of the procedure.

7.3.5.3 Implant Site Adverse Events and Key Procedural-Related Events

Summaries of implant site adverse events are presented by study. Modifications to the surgical equipment and procedures were made during the clinical development program, and occurred approximately after Studies PRO-805 and PRO-807 completed and before studies PRO-806, PRO-81, and PRO-814 commenced. The training program also evolved. In Studies PRO-805 and PRO-807, the training comprised an instructional DVD, self-guided written instructions, and on-site training by the implant medical monitor, if needed. For Studies 806, 811, and 814, the competency-based training components included a training manual, a training video, a half-day training class, and a hands-on training using a “meat model” – pork tenderloin.

Examining the implant site adverse events by study may provide some insight as to whether implementation of the device and procedure modifications, and revised training program was met with differences in the numbers and types of implant adverse events before and after implementation of the device and procedure modifications. It should be noted that these are all the implant site adverse events that occurred, and this encompasses a spectrum of events from non-serious adverse events, like erythema and pain that are not unexpected, to the more important procedural complications.

Nonetheless, exploiting this “natural experiment” resulting from the introduction of the equipment and procedure modifications during Phase 3 development, still provides some indication of potential improvements in, or worsening of, the safety experience following introduction of the modifications.

Table 18 Implant Site Treatment-Emergent Adverse Events by Classification in Study PRO-805

Implant Site TEAE from CRF or Pre-Specified List	Probuphine N = 108 n (%)	Placebo N=55 n (%)
Any Implant Site TEAE per CRF	62 (57.4)	25 (45.5)
Implant site erythema	27 (25.0)	12 (21.8)
Implant site itching	27 (25.0)	8 (14.5)
Implant site pain	24 (22.2)	6 (10.9)
Implant site edema	14 (13.0)	5 (9.1)
Implant site bleeding	13 (12.0)	7 (12.7)
Implant site infection	4 (3.7)	1 (1.8)
Other Implant Site TEAE	27 (25.0)	15 (27.3)
Implant site scar	10 (9.3)	7 (12.7)
Implant site bruising	6 (5.6)	8 (14.5)
Implant site reaction	6 (5.6)	0 (0.0)
Implant site hemorrhage	4 (3.7)	1 (1.8)
Implant site pain	4 (3.7)	2 (3.6)
Impaired healing	3 (2.8)	0 (0.0)
Implant site erythema	3 (2.8)	0 (0.0)
Implant site hematoma	2 (1.9)	1 (1.8)
Implant site irritation	2 (1.9)	0 (0.0)
Complication of device removal	1 (0.9)	0 (0.0)
Implant expulsion	1 (0.9)	0 (0.0)
Implant site edema	1 (0.9)	0 (0.0)
Implant site pruritus	1 (0.9)	1 (1.8)
Implant site rash	1 (0.9)	1 (1.8)
Incision site complication	1 (0.9)	0 (0.0)
Incision site hemorrhage	1 (0.9)	0 (0.0)
Cellulitis	0 (0.0)	1 (1.8)

Source: Integrated Summary of Safety (Summary of Clinical Safety), p. 112

Table 19 Implant Site Treatment-Emergent Adverse Events in $\geq$ 5% of Subjects in Study PRO-807

	Probuphine N=62 n (%)
Any Implant Site TEAE	28 (45.2)
Implant site erythema	16 (25.8)
Implant site itching	12 (19.4)
Implant site pain	12 (19.4)
Implant site bleeding	10 (16.1)
Implant site edema	8 (12.9)
Other implant site TEAEs ^a	
General Disorders and Administrative Site Conditions	13 (21.0)
Implant site bruising	6 (9.7)
Implant site hemorrhage	4 (6.5)

Source: Integrated Summary of Safety (Summary of Clinical Safety), p. 121

As noted earlier, in Study PRO-805 and Study PRO-807, the case report form (CRF) presented a check list of 6 possible implant site TEAEs, as well as “Other implant site TEAE” and “non-implant site TEAEs.” Only “Other implant site TEAEs” and “non-implant site TEAEs” had free-text recorded. The determination of whether or not an event was an implant site TEAE was based solely on the designation from the individual study CRF check box.

In Study PRO-805, more than half of the subjects (n=87 subjects, 53%) experienced an implant site adverse event. In Study PRO-807, a little less than half (45%) of the subjects experienced an implant site adverse event. These numbers may, in fact, underestimate the total number of subjects who experienced an implant site adverse event, because the subjects represented in the “Other implant site TEAEs” categories may include subjects who were not already captured by the check list of 6 possible implant site TEAEs.

Studies PRO-806, PRO-811, and PRO-814 occurred after the equipment and procedure modifications were implemented. In Study PRO-806 and Study PRO-811, there was a CRF check box to designate TEAEs as implant site related. All TEAEs had free text descriptions that were coded; again, the determination of implant/non-implant status was based on the CRF check box.

Table 20 Implant Site Treatment-Emergent Adverse Events in >1 Subject by Preferred Term in Study PRO-806

System Organ Class Preferred Term	Probuphine N=114 n (%)	Placebo N=54 n (%)
Any Implant Site TEAEs	31 (27.2)	14 (25.9)
General Disorders and Administration Site Conditions	21 (18.4)	11 (20.4)
Implant site erythema	4 (3.5)	0.0
Implant site hematoma	8 (7.0)	6 (11.1)
Implant site hemorrhage	2 (1.8)	2 (3.7)
Implant site edema	2 (1.8)	0.0
Implant site pain	6 (5.3)	5 (9.3)
Implant site pruritus	5 (4.4)	2 (3.7)
Implant site swelling	2 (1.8)	0.0
Injury, Poisoning and Procedural Complications	8 (7.0)	3 (5.6)
Procedural pain	4 (3.5)	0.0
Procedural site reaction	3 (2.6)	2 (3.7)
Skin and Subcutaneous Tissue Disorders	3 (2.6)	1 (1.9)
Ecchymosis	2 (1.8)	0.0

Source: Summary of Clinical Safety, p. 117

Table 21 Implant Site Treatment-Emergent Adverse Events in >1 Subject by Preferred Term in Study PRO-811

	Probuphine N = 85 n (%)
Any Implant Site TEAE	12 (14)
Implant site erythema	1 (1)
Implant site haematoma	2 (2)
Implant site haemorrhage	3 (4)
Implant site pruritus	1 (1)
Implant site rash	2 (2)
Implant site reaction	1 (1)
Cellulitis	1 (1)
Implant site abscess	1 (1)
Implant site infection	1 (1)
Subcutaneous abscess	1 (1)

Source: Table generated from PRO-811 Study Report

Table 22 Summary of All Implant Site Treatment-Emergent Adverse Events in Study PRO-814

System Organ Class/Preferred Term	SL BPN N=89 n (%)	Probuphine N=87 n (%)	Total N=176 n (%)
General Disorders and Administration Site Conditions	7 (7.9)	12 (13.8)	19 (10.8)
Implant site pain	4 (4.5)	4 (4.6)	8 (4.5)
Implant site pruritus	1 (1.1)	4 (4.6)	5 (2.8)
Implant site bruising	1 (1.1)	1 (1.1)	2 (1.1)
Implant site erythema	1 (1.1)	1 (1.1)	2 (1.1)
Device expulsion ^a	1 (1.1)	0	1 (0.6)
Implant site discolouration	1 (1.1)	0	1 (0.6)
Implant site haemorrhage	0	1 (1.1)	1 (0.6)
Oedema peripheral	0	1 (1.1)	1 (0.6)
Infections and Infestations	3 (3.4)	3 (3.4)	6 (3.4)
Cellulitis	1 (1.1)	1 (1.1)	2 (1.1)
Wound infection	1 (1.1)	1 (1.1)	2 (1.1)
Incision site infection	1 (1.1)	0	1 (0.6)
Purulent discharge	0	1 (1.1)	1 (0.6)
Injury, Poisoning and Procedural Complications	1 (1.1)	2 (2.3)	3 (1.7)
Contusion	1 (1.1)	0	1 (0.6)
Incision site complication	0	1 (1.1)	1 (0.6)
Postoperative wound complication	0	1 (1.1)	1 (0.6)
Nervous System Disorders	1 (1.1)	1 (1.1)	2 (1.1)
Paraesthesia	0	1 (1.1)	1 (0.6)
Peripheral sensory neuropathy	1 (1.1)	0	1 (0.6)
Skin and Subcutaneous Tissue Disorders	3 (3.4)	2 (2.3)	5 (2.8)
Dermatitis contact	2 (2.2)	1 (1.1)	3 (1.7)
Rash	0	1 (1.1)	1 (0.6)
Skin irritation	1 (1.1)	0	1 (0.6)
Abbreviations: SL BPN, sublingual buprenorphine; SOC, system organ class; TEAE, treatment-emergent adverse event			
^a Implant expulsion			
Notes: SOC's are presented in order of decreasing incidence in the Total column. Within each SOC, TEAEs are ordered by decreasing incidence in the Total column and then alphabetically for terms with like incidence.			
Denominators for percentages were N, the total number of subjects overall. At each level of subject summarization, a subject was counted only once if the subject reported 1 or more events.			
Only events that started on or after first dose date and within 30 days of last dose date were summarized.			

Source: PRO-814 Clinical Study Report, Table 30, p. 90 of 395.

In Study PRO-806, approximately one quarter (n=45, 27%) of all the patients in the study experienced an implant site adverse event. In PRO-811, the PRO-806 extension study, the proportion continued to decline, and by this time there were 14% of patients experiencing implant site adverse events. In PRO-814, the last trial completed, 32 patients (18%) had at least one implant site TEAE. This represents an increase, albeit minimal, in the proportion of patients reporting at least 1 implant site TEAE compared to PRO-811, the last study before PRO-814.

Nevertheless, across all these studies, this represents a dramatic decrease in events compared to that observed for studies PRO-805 and PRO-807 where about half the patients experienced an implant site adverse event (53% and 45% respectively.) The decline in adverse events may be attributable to the modifications to the device and the procedures, and the revised training and certification program.

The summary of implant site adverse events provided above was a summary of all implant site adverse events that occurred, including mild and self-limiting events. DBRUP evaluated the procedural safety database, and identified and summarized key procedure-related adverse events. The following table summarizes events that are regarded as key procedure-related events in DBRUP's estimation. PRO-805 and PRO-807, the clinical trial and extension study, respectively that predated the modifications made to enhance procedural-related safety are shaded tan to distinguish them from the other trials.

	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 α	5 (3.1%)	2 (1.2%)	1 (0.6%)	2 (4.8%)	0	8	1.5%
Implant site infection*	9 (5.5%)	3 (1.8%)	6 (3.4%)	4 (6.4%)	4 (4.7%)	26	4.0%
Wound complications ∞	4 (2.5%)	2 (1.2%)	2 (1.1%)	1 (1.6%)	1 (1.1%)	10	1.5%
Complication of removal or requiring multiple attempts	15 (9.2%)	0	7 (4.0%)	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%

α 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

∞ 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

Source: DBRUP Consult Review, dated December 11, 2015

When comparing the earlier and later studies, fewer key procedure-related adverse events were reported following the enhancements. For example, removal complications were reported in about 9% of patients in Study 805, and in no subjects in 806, the subsequent controlled trial after 805.

Despite these improvements, it must be noted that in the Probuphine development program, events of bleeding (10.9%), complicated removals (3.2%), and implant site infection (4.0%), were observed

Procedural Complications – Narrative Description.

Procedural complications associated with removal have been noted above. This section of the review provides additional details about the insertion and removal procedural complications, which include information on implant protrusions and full expulsions of the implants from the skin.

Procedural Complications – Insertions

All insertion procedures were successful on the first attempt. There was a single case in which one of the implants was dropped, and not inserted because it was contaminated and not suitable for insertion. This case is noted solely for completeness, but does not represent an insertion difficulty for this product.

There were seven cases that required manipulation of the rods after they were inserted.

Study	Pt Info	Physician Specialty	Case Summary
805	(b) (6) 32 F Probuphine	Occupational Medicine	- In course of inserting a 5th implant, initial implant #3 found to be exposed. - Implant removed and new implant inserted.
805 & 807	(b) (6) 51 F Probuphine	Psychiatrist	Implant protrusion or expulsions replaced on 4 occasions (1 in PRO-805 and 3 in PRO-807)
805	(b) (6) 27 M Probuphine	Family Medicine	2 implants “extruding from incision site” 3 weeks after insertion; 2 new implants placed.
805	(b) (6) 46 F Probuphine	Family Medicine	“Skin infection” 2 wks after initial 4 implants inserted. - Implants removed, 4 replacement implants inserted into contralateral arm.
805	(b) (6) 37 M Probuphine	Family Medicine (same for Pt 030-010)	“Implant site erythema” 3 wks after insertion of initial 4 implants. 1 wk later returned for 5th implant. 4 initial implants removed, 4 replacement implants + 5th in contralateral arm.
806	(b) (6) 35 M Placebo	Obstetrics and Gynecology	Mild protrusion of 1 of initial implants noted when pt returned for 5th implant. Protruding implant removed and replaced.
814	(b) (6)	General	Day 5 moderate [purulent] cellulitis. Received cephalexin

Study	Pt Info	Physician Specialty	Case Summary
	57 M Placebo implants	Surgery	then Bactrim with resolution on Day 18. - On Day 30, protrusion of one rod without complete expulsion. - Day 31, 4 rods removed from left arm and 4 inserted into right arm.

These occurred most often in patients in Study 805, which again predates the surgical equipment, procedure, and training modifications, usually occurred with Probuphine implants, and with an even sex distribution overall. Except for occupational medicine, these cases occurred among the specialties that performed most of the procedures, which appears consistent with procedure volume rather than a procedure operator matter.

There were no cases in which there were difficulties obtaining adequate anesthesia.

Procedural Complications – Removals

There were more difficulties with the removals than with the insertions. In 20 cases (4.7%) across the earlier Phase 3 studies, a second attempt was required to remove the implants. The nearly 5% of cases in which this occurred represents a relatively high rate given the small numbers of procedures performed.

As illustrated in the table below showing the number of cases by study, Study PRO-805 had the greatest number of cases, followed by study PRO-807. There were no cases in 806 but still a notable proportion in 811, the last of these studies performed.

Study Identifier	Cases Requiring a Second Attempt at Removal
PRO-805	15 (10)
PRO-807 (PRO-805 Extension)	3 (5)
PRO-806	0
PRO-811 (PRO-806 Extension)	2 (3)

Ultrasound was used in 13 cases where a second attempt at removal was required, amounting to 65% of the cases requiring multiple attempts, and 3% of the total cases. Of these 13 cases in which ultrasound was used, eleven cases were in Studies PRO-805 and PRO-806. General anesthesia was required in one case where a second attempt at removal was required. This was for “uncooperative nature” of the patient. At the March 21, 2013, Advisory Committee meeting, it was noted that this patient also had experienced a deep insertion into the brachial muscle.

At the time of removal, fragmentation of the implant into two to three fragments was common. This, however, is not considered a major safety concern, as the health care

practitioner performing the procedure can be able to determine with fair certainty that all pieces were removed.

In Study PRO-814, there were 7 subjects (4.0%) of the total (N=176) who did not get all four implants removed in the first attempt. These included 2 subjects on Probuphine and 5 with Placebo implants:

- Probuphine – (b) (6)
 - Subject, (b) (6) needed a 3rd attempt for removal of all 4 implants and also needed referral to a specialist, a surgeon, to remove the 4th implant. In this case, the Implant physician (Family Medicine) was unable to remove 1 of the 4 implants from the patient after performing an ultrasound, thus the patient had to go to a private surgeon (referred by the Principal Investigator) to set up an appointment for Implant removal. The 4th implant was successfully removed by the surgeon.
- Placebo – (b) (6)

All seven subjects required ultrasound to locate the implants. In two of these cases, an ultrasound was performed to remove the 4th implant; however the 4th implant in each case was ultimately not located by ultrasound. The following are details of these 2 cases:

- Subject (b) (6), a 31-year-old white male in the SL BPN group, completed 24 weeks of treatment and underwent his Week 24 EOT Visit on Day 175. The Investigator reported palpating only 3 implants prior to the removal procedure, as well as visualizing only 3 implants during the procedure. An ultrasound was performed the same day, but the fourth implant could not be located. All implant site examinations prior to removal were unremarkable. The subject had only one AE during the study, explant site infection (onset Day 190), assessed, by the investigator, as mild in severity and not related to study treatment. (Anesthesiology)
- Subject (b) (6), a 45-year-old white male in the SL BPN group, completed 24 weeks of study treatment and underwent his Week 24 EOT Visit on Day 170. Ultrasound was not needed prior to removal, since the implants were palpable. The Investigator reported palpating 4 implants prior to the removal procedure. However, only 3 implants were accounted for after removal. On Day 197, the subject underwent an ultrasound of the region of the scar, but the missing implant could not be located. All implant site examinations prior to removal were unremarkable. No AEs were reported. (OB/GYN)

In PRO-814, there were a total of 22 subjects with at least one fragmented rod.

There were also cases in which the implants were not recovered in the earlier Phase 3 trials and extension studies. This was the result of loss to follow up and failure to return for removal, rather than a procedural complication. The following table summarizes implants that were not recovered in PRO-805, PRO-806, PRO-807, and PRO-811.

Probuphine		Placebo	
Lost/Total Inserted Implants (% Unaccounted For)	Affected Subjects	Lost/Total Inserted Implants (% Unaccounted For)	Affected Subjects
146 / 1610 (9.1%)	36	37 / 489 (7.6%)	9

In PRO-814, three subjects were lost to follow up in the Probuphine arm after the implants were removed, and these patients would not have had their implants removed. The Applicant reported that one of these subjects, the subject who was incarcerated shortly after the implants were inserted, later returned to have the implants removed. Similarly, the Applicant reported that a removal procedure was recently performed on a subject with rods indwelling for seven years. Specifically, the Applicant had been informed about a “lost to follow up patient” from study 807 who returned to have his implants removed (approximately 7 years after insertion). All 4 implants were successfully removed. Ultrasound was used prior to attempting the removal to be certain of the location of the implants, given the length of time since insertion.

The procedural complications associated with insertion and removal of the implants in the clinical trial database are not worrisome overall, although the rate of complications associated with removal in this small database is considered relatively high. Because the database is relatively small, however, it may not allow for full characterization of these safety issues.

7.3.5.4 Human Factors Evaluation

In the April 30, 2013, Complete Response Letter, the Applicant was informed that one of the deficiencies for the application was that the training program has not been validated. Again, as noted previously, a new technique for removal not commonly used in the US has since been adopted for Probuphine removal, and in turn, the training program. In order to address this deficiency, the Applicant was advised to conduct a Human Factors Evaluation to validate the training program, specifically to demonstrate proficiency in the hands of non-proceduralists, who are among the provider mix prescribing buprenorphine and who may be performing the procedures to administer Probuphine.

The Human Factors Evaluation was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA). A complete description of the Human Factors Evaluation is provided in the DMEPA consult review. (The reader is referred to the DMEPA review for details of the Human Factors Evaluation and DMEPA’s assessment). Based on the Human Factors Evaluation the Applicant conducted, the Applicant concluded that clinicians without recent experience performing a procedure with some similarities to the insertion and removal procedures for Probuphine, would have difficulty with the training and with performing procedures to insert and remove Probuphine. The Applicant proposes that candidates for Probuphine training should be those who are proceduralists.

DBRUP also reviewed the Human Factors Evaluation to lend a proceduralist perspective to interpretation of the findings. DBRUP identified several important limitations of the evaluation related to the live practicum, which are summarized in this review.

For the proposed training, a live practicum of procedures used a pork tenderloin as a simulated human arm. For training purposes, DBRUP noted that although the pork tenderloin may be a suitable model for demonstrating technical proficiency for the insertion procedures, it is not suitable for predicting whether certain events like infection and bleeding can be mitigated by training. The only pertinent task that could be assessed was “depth of implant placement,” which on its own has limited clinical relevance.

The removal procedures and potential complications do not lend themselves to modeling. Although the scenarios designed to mimic complicated removals (from either breakage or densely adhered implants) appeared reasonable, the pork tenderloin is not adequate as a substitute for the removal procedure. The pork tenderloin, or an artificial arm, for that matter, cannot provide an adequate representation of the scarring that would develop after a foreign body has been indwelling for 6 months. Additionally, situations that may arise when performing the procedures on a patient, such as a patient moving, or having pain that may require more anesthesia, or have bleeding cannot be simulated in this fashion.

For this evaluation, only clinicians from specialties that involve performing procedures or surgery participated in the simulation/validation component of the human factors study. Therefore, the results are not generalizable to clinicians from non-surgical specialties.

DBRUP found that overall, the subtasks and critical subtasks for the live practicum appeared appropriate. Most of the 15 proceduralists, which included 8 physicians and 7 mid-level practitioners, could adequately perform the tasks required to mitigate the risks of infection, bleeding and fibrous scar formation around implants. Notwithstanding this overall finding, review of the narratives of task failures revealed important issues related to procedural safety. One such issue is that the Applicant appeared to equate receipt of knowledge with ability to perform a task. There was an assumption that once a provider recognizes a task failure, they would be able to perform the task the next time around. However, the study provides no data to support this notion. There were three task failures related to mitigating infection. This is noteworthy as infection-related AEs in the Probuphine clinical development program have already been seen at higher rates than those for the implantable contraceptives. Not all participants could remove all the implants, even in the practice session. Postmarketing data for implantable contraceptives have revealed that some implants are never localized or removed. DBRUP advised that the Applicant should address how these situations are to be managed in a real-world setting. The Applicant will be asked to collect more information

about this is in a postmarketing study. Finally, fully 10% of the clinicians inserted the rods beyond desired depth, that is, more than 5 to 7 mm but less than 10 mm. Although an insertion depth that is still less than 10 mm is unlikely to result in injury, DBRUP noted that the finding suggests that the training program tasks related to insertion depth may need to be reinforced. [REDACTED] (b) (4)

The human factors evaluation was discussed at the January 12, 2016, Advisory Committee, and advisory committee consultation was sought in forming an assessment of the steps the Applicant should take to ensure that removals, including complicated removals, are performed appropriately. The committee members did not consider the pork tenderloin to be the most suitable model for ensuring that the procedures are performed correctly. They generally thought that a system that involved observed procedures would be more fitting, essentially in keeping with the so-called, see one, do one, teach one model. They also suggested that a master trainer program should be instituted, and that ideally there would be training hubs. These would be centers where the procedures were performed frequently, and a novice could train there or a previously trained clinician could visit when a refresher was needed. The Committee also noted that a key determinant that would afford dexterity with the procedures was volume, and that proficiency would be gained with repeated procedures. [REDACTED] (b) (4)

[REDACTED]

At the time of this writing, findings from the procedural safety database, the human factors evaluation, and the Committee's recommendations are still under deliberation in the review of the REMS. Based on these various pieces of evidence and information, a number of aspects of the REMS are considered to be unresolved. Efforts are underway to address these outstanding issues and formalize the REMS to promote adequacy in addressing the potential risks associated with the insertion and removal procedures, and abuse, misuse, and accidental overdose.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events are displayed in the table below. The Applicant summarized adverse events reported in at least 2% of the Probuphine group and more commonly than in the Placebo/SL BPN group. For labeling, the Applicant proposes [REDACTED] (b) (4)

[REDACTED]

However, for the purposes of labeling, the Applicant will be asked to include a common adverse events table by System Organ Class (SOC) that includes any Higher Level Group Term (HLGT) reported by 5% or more in Probuphine and more commonly

placebo, and any Preferred Term (PT) under the HLGTT that is 1% in any arm from the pooled dataset.

Because the Applicant provided a preferred term analysis and there are myriad adverse event terms at the PT level, an adverse event analysis at a higher MedDRA level, namely the HLGTT, was requested, and provided by the Applicant. The analysis of AEs grouped at the MedDRA HLGTT is intended to cluster similar adverse events to evaluate whether a pattern of events might emerge when these similar AEs are assessed together. Results from the adverse event analysis at the HLGTT level are shown below.

Clinical Review
 Rachel Skeete, MD, MHS
 NDA 204442 (Class 2 Resubmission)
 Probuphine (buprenorphine) implant

System Organ Class High Level Group Term MedDRA Preferred Term	Probuphine (N=309) n (%) [b]	Placebo/ SL BPN[a] (N=317) n (%) [b]	TOTAL (N=626) n (%) [b]
GASTROINTESTINAL DISORDERS	78 (25.2)	61 (19.2)	139 (22.2)
DENTAL AND GINGIVAL CONDITIONS	16 (5.2)	12 (3.8)	28 (4.5)
Toothache	14 (4.5)	10 (3.2)	24 (3.8)
GASTROINTESTINAL MOTILITY AND DEFAECATION CONDITIONS	27 (8.7)	23 (7.3)	50 (8.0)
Constipation	20 (6.5)	9 (2.8)	29 (4.6)
Diarrhoea	10 (3.2)	13 (4.1)	23 (3.7)
GASTROINTESTINAL SIGNS AND SYMPTOMS	42 (13.6)	39 (12.3)	81 (12.9)
Abdominal discomfort	6 (1.9)	6 (1.9)	12 (1.9)
Abdominal pain upper	10 (3.2)	7 (2.2)	17 (2.7)
Nausea	20 (6.5)	15 (4.7)	35 (5.6)
Vomiting	17 (5.5)	11 (3.5)	28 (4.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	120 (38.8)	66 (20.8)	186 (29.7)
ADMINISTRATION SITE REACTIONS	89 (28.8)	41 (12.9)	130 (20.8)
Implant site erythema	5 (1.6)	1 (0.3)	6 (1.0)
Implant site haematoma	14 (4.5)	11 (3.5)	25 (4.0)
Implant site haemorrhage	23 (7.4)	10 (3.2)	33 (5.3)
Implant site oedema	16 (5.2)	5 (1.6)	21 (3.4)
Implant site pain	39 (12.6)	18 (5.7)	57 (9.1)
Implant site pruritus	38 (12.3)	14 (4.4)	52 (8.3)
Implant site reaction	7 (2.3)	3 (0.9)	10 (1.6)
Implant site scar	11 (3.6)	8 (2.5)	19 (3.0)
EPIDERMAL AND DERMAL CONDITIONS	27 (8.7)	12 (3.8)	39 (6.2)
Implant site erythema	27 (8.7)	12 (3.8)	39 (6.2)
GENERAL SYSTEM DISORDERS NEC	40 (12.9)	25 (7.9)	65 (10.4)
Asthenia	5 (1.6)	1 (0.3)	6 (1.0)
Fatigue	9 (2.9)	4 (1.3)	13 (2.1)
Influenza like illness	1 (0.3)	4 (1.3)	5 (0.8)
Oedema peripheral	6 (1.9)	5 (1.6)	11 (1.8)
Pain	12 (3.9)	9 (2.8)	21 (3.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	43 (13.9)	39 (12.3)	82 (13.1)
INJURIES NEC	26 (8.4)	24 (7.6)	50 (8.0)
Contusion	6 (1.9)	9 (2.8)	15 (2.4)
Excoriation	7 (2.3)	3 (0.9)	10 (1.6)
Laceration	8 (2.6)	4 (1.3)	12 (1.9)
Muscle strain	1 (0.3)	4 (1.3)	5 (0.8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	42 (13.6)	39 (12.3)	81 (12.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS NEC	27 (8.7)	23 (7.3)	50 (8.0)
Back pain	18 (5.8)	15 (4.7)	33 (5.3)
Neck pain	4 (1.3)	3 (0.9)	7 (1.1)
Pain in extremity	9 (2.9)	3 (0.9)	12 (1.9)
NERVOUS SYSTEM DISORDERS	63 (20.4)	54 (17.0)	117 (18.7)
HEADACHES	42 (13.6)	35 (11.0)	77 (12.3)
Headache	39 (12.6)	32 (10.1)	71 (11.3)
Migraine	5 (1.6)	3 (0.9)	8 (1.3)

Clinical Review
 Rachel Skeete, MD, MHS
 NDA 204442 (Class 2 Resubmission)
 Probuphine (buprenorphine) implant

NEUROLOGICAL DISORDERS NEC	26 (8.4)	16 (5.0)	42 (6.7)
Dizziness	11 (3.6)	7 (2.2)	18 (2.9)
Somnolence	9 (2.9)	1 (0.3)	10 (1.6)
PSYCHIATRIC DISORDERS	64 (20.7)	68 (21.5)	132 (21.1)
DEPRESSED MOOD DISORDERS AND DISTURBANCES	20 (6.5)	13 (4.1)	33 (5.3)
Depression	20 (6.5)	10 (3.2)	30 (4.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	39 (12.6)	23 (7.3)	62 (9.9)
RESPIRATORY DISORDERS NEC	31 (10.0)	19 (6.0)	50 (8.0)
Cough	10 (3.2)	4 (1.3)	14 (2.2)
Oropharyngeal pain	14 (4.5)	10 (3.2)	24 (3.8)
Rhinorrhoea	4 (1.3)	4 (1.3)	8 (1.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	32 (10.4)	22 (6.9)	54 (8.6)
EPIDERMAL AND DERMAL CONDITIONS	19 (6.1)	10 (3.2)	29 (4.6)
Rash	6 (1.9)	2 (0.6)	8 (1.3)

 [a] 'SL BPN'=Denotes subjects assigned to Daily Sublingual Buprenorphine Arm in PRO-806 and PRO-814 studies. All subjects in all studies took SL BPN during induction and had the option of taking SL BPN as rescue medication during treatment.

[b] A subject reporting more than one adverse event for a particular MedDRA Preferred Term or System Organ Class is counted only once for that MedDRA Preferred Term or System Organ Class.

Source: Submitted by Applicant in Response to IR

The common adverse events pertaining to the systemic effects of buprenorphine are overall consistent with the common adverse events seen in current labeling for the sublingual formulations. A number of events were reported more commonly in the Probuphine arm, e.g., depression, somnolence, fatigue, and constipation. These slight imbalances may stem from the continuous delivery of buprenorphine offered by Probuphine or from differences in exposure time for the Probuphine arms across some of the trials, with those on Probuphine having longer on-study times. There were a number of contusions reported. Review of the verbatim terms revealed that these represented limb bruises, including some that appeared implant site related based on the described location, as well as bruises on other areas of the body.

7.4.2 Laboratory Findings

Summaries of laboratory data were reviewed. Overall, there were few changes from baseline in laboratory results. There were elevations in liver function tests seen in the Probuphine and comparator arms. (See also Section 7.3.4. above for a discussion of hepatic laboratory abnormalities).

Table 23 Normal-to-High Shifts in Liver Enzymes in Pooled Double-Blind Studies

	Maximal Value		End of Study	
	Probuphine N=309 n	Placebo/SL BPN N=317 n	Probuphine N=309 n	Placebo/SL BPN N=317 n
ALT	31	48	12	30
AST	43	31	22	20
Bilirubin	5	5	3	1
Gamma-glutamyltransferase	27	20	18	14

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; SL BPN = sublingual buprenorphine

Source: ISS Addendum, Table 16, p. 54.

Liver enzyme shifts occurred across all subjects on buprenorphine either as Probuphine or as the transmucosal product. For ALT, fewer subjects in the Probuphine arm experienced shifts. This may be the result of lower plasma exposures among patients on Probuphine, as, for example, patients in the open-label SL buprenorphine arm were receiving 12 – 16 mg/day of buprenorphine.

Because this is an implantable drug product, basophil and eosinophil laboratory data were examined to assess for potential allergic phenomenon associated with the indwelling implant. There were few differences observed with respect to basophils. However, there were a greater number of categorical shifts from normal to above the upper limit of normal in subjects on Probuphine compared to subjects on the combined

placebo and sublingual buprenorphine arms. Relevant information about laboratory results is discussed in sections above on allergic reactions and hepatic effects.

7.4.3 Vital Signs

No consistent effects on vital signs were observed across treatment groups in the pooled double-blind studies.

7.4.4 Electrocardiograms (ECGs)

See Section 7.3.4 Significant Adverse Events for a discussion of ECG findings, specifically related to QT effects.

7.4.5 Special Safety Studies/Clinical Trials

There were no special studies/clinical trials designed to evaluate a specific safety concern or concerns associated with Probuphine.

7.4.6 Immunogenicity

There are no specific data on the effect of immunogenicity on safety, efficacy, and/or clinical pharmacology and pharmacokinetics for Probuphine.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Probuphine is a fixed-dose, non-titratable product. Dose dependency thus is no longer applicable. (Previously, there was an option for a fifth implant or dose increase. There are no longer plans for this option).

7.5.2 Time Dependency for Adverse Events

Time dependency for adverse events was not explored by the Applicant.

7.5.3 Drug-Demographic Interactions

Subgroup analyses of subjects who reported implant site and non-implant site TEAEs in the pooled double-blind studies (PRO-805, PRO 806, and PRO-814) were performed for the following subgroups:

- Sex (male and female)
- Age (18 to 35 years and 36 to 65 years)
- Race (White, Black, and other)

There were few differences overall across the subgroups, and no clear patterns emerged. Female subjects on Probuphine were more likely to report an implant site AE than those on placebo. Among those in the black and other categories for race, there was more reporting of adverse events, implant and non-implant site adverse events. These patients represented a considerably smaller population than their white counterparts.

7.5.4 Drug-Disease Interactions

Adverse events were examined by primary opioid dependence, heroin vs. prescription opioid pain medication/other. For both implant site and non-implant site adverse events, patients on heroin had higher rates of reporting. Patients on prescription opioid pain medication/other reported depression more commonly.

7.5.5 Drug-Drug Interactions

No formal clinical studies with Probuphine have been performed to evaluate drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity data have not been provided in this new drug application.

7.6.2 Human Reproduction and Pregnancy Data

No formal clinical studies on the use in pregnancy and lactation have been conducted with Probuphine.

7.6.3 Pediatrics and Assessment of Effects on Growth

For the initial submission, the Applicant, in its pediatric plan, sought a partial waiver of pediatric studies, (1) requesting a waiver of studies in pediatric subjects (b) (4) years of age, and (2) entering a deferral request for studies in pediatric (b) (4) patients, ages (b) (4) years (b) (4)

The Division agreed with Titan's proposal to seek a waiver for studies in pediatric subjects (b) (4) years of age. A fixed dose delivery system that requires a minor surgical procedure for insertion and removal was not considered an appropriate treatment paradigm for neonatal abstinence syndrome/ neonatal opioid withdrawal

syndrome (NAS/NOWS). Additionally, for the other pediatric populations, the prevalence of treatment-seeking children and adolescents with opioid addiction, (b) (4) is small, and renders the studies impossible or highly impractical. For this reason, the Division considered a full waiver of pediatric studies more appropriate. The Pediatric Review Committee (PeRC) concurred with the Division, and a full waiver was granted.

With the NDA Resubmission, the pediatric plan again included: (1) a partial waiver for the development of Probuphine in pediatric subjects with opioid dependence (b) (4) years of age, and (2) a deferral for the development of Probuphine in pediatric (b) (4) patients who are (b) (4) years of age. A full waiver is once again being granted based on the same considerations used to make the determination during the original submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose, drug abuse potential, withdrawal and rebound for Probuphine are under evaluation by the Controlled Substance Staff (CSS) particularly for labeling guidance.

7.7 Additional Submissions / Safety Issues

No additional safety submissions beyond revisions to REMS were made by the Applicant. No additional safety issues beyond those associated with the REMS and training program and the safety issues described throughout this review of safety are under evaluation.

8 Postmarket Experience

At the time of this application, Probuphine is not marketed in any country.

9 Appendices

9.1 Literature Review/References

The cited literature for this review and submission is discussed above in Section 4 and Section 6.

9.2 Labeling Recommendations

The submitted proposed labeling is in Physician's Labeling Rule (PLR) format. The approved labeling for Suboxone/Subutex tablets forms the foundation for Probuphine labeling, with new information related to the novel delivery system and the clinical trials, included throughout in relevant sections.

The following are key issues in labeling:

- The proposed indication for Probuphine is: "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 proposed Dosage and Administration section instructs providers that "PROBUPHINE implants should be used only in patients who are opioid tolerant and are currently on a maintenance dose of 8 mg/day or less of sublingual Subutex or Suboxone equivalent." The proposed wording of the indication is problematic because it implies that Probuphine may be used for a broader population than studied. The proposed indication and Dosage and Administration instructions regarding dose do not fully convey the characteristics of the limited population for whom Probuphine may be appropriate. Study PRO-814 enrolled subjects who were considered clinically stable by their treating healthcare provider, and on no more than 8 mg/day of sublingual buprenorphine (as a Subutex/Suboxone equivalent). As written, the proposed indication would imply that Probuphine is appropriate for all patients with opioid dependence, including new entrants to treatment. However, there is no evidence that Probuphine is appropriate for patients with opioid dependence other than the well-circumscribed population studied. Similarly, the Dosage and Administration instructions require revision to reflect the appropriate population. Labeling should include information about the population studied, and criteria that should be considered in making judgments regarding clinical stability.
- Clinical supervision recommendations should be included that provide revised guidelines about use of supplemental buprenorphine in transmucosal forms in the setting of Probuphine treatment. In proposed labeling, clinicians are instructed as follows: (b) (4)

Although only sporadic use of supplemental buprenorphine was

anticipated in the clinically stable population studied, in some instances, some patients in the trial received supplemental buprenorphine throughout the entire treatment period, and some patients were provided as needed dosing of sublingual buprenorphine. Healthcare providers should be advised that patients should not be provided with prescriptions for buprenorphine-containing transmucosal products for as-needed use. Clinicians should also be advised that if patients express the need for supplemental dosing, they should be seen and evaluated promptly. Clinicians should also be informed that patients who require supplemental dosing on an ongoing basis are unlikely to be candidates for continuing treatment with Probuphine. Instead, this suggests that Probuphine may not be providing an adequate dose or adequate plasma exposures, of Probuphine for that patient. These guidelines, in particular, were made on the advisement of the Advisors and Consultants who participated in the January 12, 2016, Advisory Committee meeting.

- In studies of Probuphine, there has only been experience with insertion of Probuphine implants into two sites, one on each arm, and removal of the implants from these sites.

(b) (4)

Labeling should inform providers of the limited number of anatomic sites for which there is experience in the clinical trials and the limitations this places on use, given the limited number of anatomic sites available for treatment of a chronic, relapsing disorder.

- The Adverse Reactions section currently lists implant and non-implant site adverse events that were reported to occur by at least 5% of patients in the pooled double-blind, Probuphine Phase 3 studies. The tables should be revised and provide an analysis based on the Higher Level Group Term (HLGT).
- Under the Clinical Studies section, the PRO-814 trial design should be summarized. The trial results based on the more clinically relevant responder definition should be reported. The PRO-805 and PRO-806, the earlier trials in which efficacy was not established, should not be described in this section, beyond informing providers that the two trials have occurred.
- Clinical pharmacology information related to special populations and drug interactions should be updated and tailored to unique delivery system. Nonclinical data should be updated based on the bridging studies submitted.

9.3 Advisory Committee Meeting

On January 12, 2016, a Psychopharmacologic Drugs Advisory Committee (PDAC) meeting was held to discuss NDA 204442, Probuphine (buprenorphine hydrochloride) subdermal implant, and its safety and efficacy for the proposed indication of maintenance treatment of opioid dependence. The following specific discussion topics and voting questions were posed to the committee for deliberation, and embodied the unresolved issues about which advisory committee consultation was sought:

1. Probuphine is a non-titratable product that provides a fixed plasma level of buprenorphine. The original studies raised concerns about the appropriateness of the dose for a broad population. The Applicant has specified a population, namely stable patients on a relatively low dose of sublingual buprenorphine, for whom they believe the dose provided by Probuphine is adequate.

DISCUSSION:

- a. Discuss whether there is a population that would benefit from the use of Probuphine and how to define this population.
 - b. If there is a population that would benefit from Probuphine, discuss whether the study entry criteria adequately define this patient population.
 - c. Discuss whether the population studied reflected this population.
2. In general, occasional dose adjustments for patients on sublingual buprenorphine can be expected over time. The sponsor chose not to include rescue medication as an element of the responder definition because there was an expectation that patients would require little to no rescue medication. However, that was not the case, as rescue medication was used by a number of patients, some throughout the 6-month treatment period.

DISCUSSION: Discuss whether use of rescue should be considered in defining a responder for a long-acting formulation of buprenorphine such as Probuphine, where the dose cannot be adjusted over time. If rescue should be part of the responder definition, should the use of rescue buprenorphine be differentiated based on the pattern or the frequency of rescue use over the 6-month treatment? Consider the following patterns of use:

- a. Use primarily after first initiating Probuphine
 - b. Use throughout the 6-month period
 - c. Use only at the end of the 6-month treatment period
3. Customarily in opioid addiction treatment trials, there are many missing urine samples due to relapse and dropout from treatment. Because relapse is the most common reason for dropout, missing urine samples are assumed to be positive. However, in this study, the patients were stably abstinent from illicit drugs, and they were asked to provide only 10 samples over six months. Therefore, it was expected that there would be few missing samples, and that these could be missing for reasons other than relapse. Therefore, the strategy for imputation of missing data did not assume that all missing samples were positive. However, some situations arose in which it might be appropriate to assume that missed samples are indicators of illicit use.

DISCUSSION: Discuss how missing or incomplete urine toxicology results should be considered when defining a responder. Consider the following:

- a. Patients who were completely lost to follow-up immediately after receiving the Probuphine implant
 - b. Samples that were not collected due to:
 1. Missed scheduled visit
 2. Missed random sample visit
 3. Refused by patient
 - c. Samples that were collected on schedule but were not analyzed in a timely fashion (out of stability window for the test)
4. The protocol-specified responder definition did not take rescue use into account, and employed an optimistic imputation strategy for missing urine toxicology results, yielding a responder rate of 96% vs 88% for Probuphine and sublingual buprenorphine, respectively. As you have seen, there are many different possible responder rates once these factors are taken into account.

DISCUSSION: Discuss which of the various approaches to expressing a responder rate you think is most appropriate.

5. Patients managed with buprenorphine may require dose adjustment over time. However, in clinical practice, unlike patients on sublingual buprenorphine, Probuphine-treated patients would not necessarily be seen for regular visits with buprenorphine dose adjustments.

DISCUSSION:

- a. Discuss how the need for occasional supplemental doses will translate to clinical practice for patients treated with Probuphine. If patients need to have sublingual buprenorphine on hand in addition to Probuphine, discuss how these prescriptions will impact the product's ability to mitigate misuse, abuse, and accidental pediatric exposure.
- b. Some patients on Probuphine required supplemental sublingual buprenorphine only briefly after insertion of the implant, while others required it only at the end of the dosing period when plasma levels could have been falling. In contrast, some patients required ongoing supplemental dosing throughout the 6-month treatment period.

Discuss whether the pattern of supplemental sublingual buprenorphine should be taken into consideration when deciding if Probuphine is effective and should be continued for a given patient **in clinical practice**. Discuss whether there is a pattern of sublingual buprenorphine use that should result in the discontinuation of Probuphine.

6. The Sponsor has provided information on a training and certification program to ensure that practitioners can safely insert Probuphine. However, the procedure of removing

Probuphine after six months of implantation is not readily modeled for the purposes of training because there is development of fibrotic tissue around the implants.

DISCUSSION: Discuss the steps the Sponsor should take to ensure that removals, including complicated removals, are performed appropriately.

7. The Sponsor has proposed a Risk Evaluation and Mitigation Strategy (REMS) which consists of restricted distribution and a training/certification program for healthcare professionals who will insert and remove the product.

DISCUSSION: Discuss whether the REMS is adequate to address the risks of potential complications associated with the insertion and removal procedures, and abuse, misuse, and accidental overdose.

8. **VOTE:** Based on the data presented and discussed today, do the efficacy, safety, and risk-benefit profile of Probuphine support the approval of this application for a population of patients previously stable on a regimen of sublingual buprenorphine (as defined during prior discussion)?

YES: 12 NO: 5 Abstain: 0

9. **DISCUSSION:** Comment on any further development or explorations, e.g. higher doses, the Sponsor should undertake.

The Advisory Committee panel members recommended approval as a majority, although not unanimously.

With respect to the patient population, the Committee stressed the importance of clearly articulating the population for whom Probuphine is intended. There were concerns about the length of continuous buprenorphine treatment prior to enrollment of the trial, given there were patients who may have had less than 6 months of treatment consecutively. The Committee also noted that the six-month timeframe may even be too brief a duration to declare a patient stable. They also highlighted the importance of demonstrating that “behavioral stability” has been achieved, for example, that the subject is not simultaneously using other illicit substances.

The Committee communicated that in the management of opioid addiction, appropriate dose adjustments with supplemental sublingual buprenorphine should be viewed in the same manner as dose adjustments made to manage any other chronic disease, when not well controlled. That being said, for Probuphine, the non-titratable product, they considered that need for supplemental use in the first month and six month might be viewed as acceptable. However, if the patient requires ongoing and excessive supplemental use throughout the entire treatment cycle, Probuphine would not be meeting that patient’s buprenorphine needs, would not be suitable for that patient, and

the AC members would not continue Probuphine beyond that treatment cycle. The committee members also discussed the implications of ongoing supplemental sublingual buprenorphine use when considering whether the touted public health benefits of this implantable formulation would be realized.

In defining a responder, the panel suggested that certain patterns of supplemental buprenorphine use may be considered acceptable, as described above. The panel expressed that missed urine samples as a result of missed scheduled or random visits, or patient refusal, are not tolerated in practice, are presumed to represent that the patient may have relapsed, and are viewed as an indicator that treatment may need to be intensified. For the responder definition, the panel advised that missing urine samples, when the patient missed a scheduled or random visit or refused to submit a sample, be considered opioid-positive. Furthermore, they collectively judged that the ITT population should include the three patients who the Applicant omitted from their (SAP vs. protocol-specified) ITT definition. With respect to establishing non-inferiority, committee members voiced concerns about the non-inferiority margin which they considered too wide, and voiced a preference for a much smaller margin, in the range of 5–15%, as compared to the protocol-specified margin of 20%.

The training program and REMS were discussed. Some panel members were concerned that the training program that used a pork tenderloin to simulate a human arm might not be sufficient for training purposes. Instead, they advocated for a training program to give clinicians the opportunity to be observed during initial procedures, and an opportunity to visit high volume centers to be reoriented to the training procedures, or to reinforce the training when desired. The panel emphasized the importance of maintaining training, and ensuring that proceduralists have an adequate volume of procedures to remain current, or they should retrain. It was also noted that the training program may be burdensome for some practitioners, and may prove a barrier for some.

Despite the misgivings expressed by some committee members about the limitations of the trial, the majority of the committee believed the application should be approved. They considered the conservative and thorough analysis of the clinical trial data was appropriate and they were satisfied that non-inferiority was established. Missing efficacy data, limitations on the duration of use, i.e., a maximum of 4 treatment cycles or 2 years, and the role of supplemental buprenorphine were all concerns that induced other panel members to veto.

Committee members had several recommendations for further development or explorations. Panelists recommended enhanced postmarketing surveillance to examine use of supplemental dosing, frequency of monitoring visits and urine toxicology, and for tracking of improper implant removal, and attempts at abuse. The committee also submitted that additional studies in more diverse populations are needed, and higher doses and treatment beyond two years should be studied. It was also posited that this product may have a role in slow, auto-taper, and this potential role should be evaluated.

Additional Appendices

Clinical Investigator Financial Disclosure Review Template

Application Number: 204442

Submission Date(s): August 27, 2015

Applicant: Titan Pharmaceuticals

Product: Probuphine (buprenorphine implant)

Reviewer: Rachel Skeete, MD, MHS

Date of Review: January 25, 2016

Covered Clinical Study (Name and/or Number): PRO-814

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: <u>149</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: <u>2</u> Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		

Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.³³ Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

The Applicant provided financial interests/arrangements for the clinical investigators and sub-investigators in the trial. All, except for two of the investigators, are certified as having no Financial Arrangement as defined in 21 CFR 54.2. Two sub-investigators, (b) (6) received payments in excess of \$25,000. (b) (6) received payment for services rendered (b) (4)

As such, these significant payments are not anticipated to materially impact interpretation of the efficacy finding, although it could conceivably have an impact on procedural safety reporting. (b) (6)

(b) (6) Procedural complications appear to have been documented for the procedures performed.

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

As discussed above, the disclosed financial interests/arrangements are not anticipated to adversely impact data integrity, and are not considered to affect the approvability of the application.

³³ See <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf>.

Clinician Survey
Feb 24, 2014

1. How would you describe the general clinical presentation of a clinically stable patient on low-dose (≤ 8 mg/day) maintenance treatment with buprenorphine, and what data could you provide to substantiate that assessment?
2. What patient factors influence their ability to achieve and maintain clinical stability?
3. How does the duration of treatment impact your definition of clinical stability (Early clinical stability versus established clinical stability)?
4. In your practice, what types of events are most likely to destabilize patients who were designated as stable?
5. What would you do to identify and prevent loss of stability?
6. In your clinically stable patients how often do you perform urine testing for opioids and/or other substances?
7. In this same patient population, how often do you expect the average stable patient in your practice to test positive for opioids over a 6-month period?
8. If these patients were to continue on the same dose, what would be the overall average percentage of opioid-negative urine toxicology result would you anticipate in 6 months?
9. If their buprenorphine treatment were to be stopped, what would be the average percentage of relapse in these patients over a 6-month period?
10. Assume urine toxicology is measured monthly for six months. What would you consider to be the maximum reasonable change in a stable patient's urine toxicology status, for the patient to continue to be considered stable?
 - a. No change
 - b. 1 out of 6 urine-positive urine toxicology
 - c. 2 out of 6 urine-positive urine toxicology
 - d. 3 or more out of 6 urine-positive urine toxicology
11. What percentage of stable patients do you expect would fall into the above category? (i.e., to have the maximum reasonable change in urine toxicology status over six months)

Summary of Survey Results from Addiction Specialists

PI #	% Negative UDS Over 6 mths*	% Negative UDS Over Next 6 mths*	% Relapse upon BPN Discontinuation (Over 6 mths)	Maximum Reasonable Change in % UDS positive	% of Patients
1	100	83	85	0	85
2	75	80	75	17	65
3	NNR	DNAQ	NNR	33	55
4	NNR	90	35	17	10
5	75	91.5	70	17	60
6	NNR	NNR	NNR	17	55
7	99	95	90	17	95
8	80	95	80	17	20
9	95	95	80	8.5	80
10	NNR	65	75	33	60
11	83	90	75	17	66
12	100	80	95	0	85
13	100	100	60	0	10
14	100	90	30	0	90
15	91.5	90	75	17	60
16	91.5	90	50	17	80
17	100	90	90	17	90
18	100	100	60	8.5	NNR
Mean (Median):	92 (97)	89 (90)	70 (75)	14 (17)	63 (65)
Range:	75-100	65-100	30-95	0-33	10-95

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

Source: PR0-814, Amendment 3, Section 17.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RACHEL SKEETE
02/08/2016

CELIA J WINCHELL
02/08/2016



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

Summary Review for Regulatory Action

Date	April 30, 2013
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Addiction Products
Subject	Division Director Summary Review
NDA #	204442
Applicant Name	Titan Pharmaceuticals, Inc.
Date of Submission	October 31, 2012
PDUFA Goal Date	April 30, 2013
Proprietary Name / Established (USAN) Name	Probuphine Buprenorphine HCl implant for subdermal use
Dosage Forms / Strength	80 mg/implant
Proposed Indication	Maintenance treatment of opioid dependence
Action:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
CDTL	Celia Winchell, M.D.
Clinical Review	Rachel Skeete, M.D., M.H.S.
Biostatistics Review	David Petullo, M.S.; Dionne Price, Ph.D.
Pharmacology Toxicology Review	Gary P. Bond, Ph.D.; Adam M. Wasserman, Ph.D.
ONDQA-CMC/Quality Review	Edwin Jao, Ph.D.; Prasad Peri, Ph.D.
OPS/NDMS-Microbiology Review	Vinayak B. Pawar, Ph.D.; Bryan S. Riley, Ph.D.
Biopharmaceutics	Elsbeth Chikhale, Ph.D.; Angelica Dorantes, Ph.D.
Clinical Pharmacology Review	David J. Lee, Ph.D.; Yun Xu, Ph.D.
OSI-Clinical	Cynthia F. Kleppinger, M.D.; Janice Pohlman, M.D., M.P.H.; Susan D. Thompson, M.D.
OSI-GLP	Zhou Chen, M.D.; Charles R. Bonapace, Pharm.D.; William H. Taylor, Ph.D.
Project Management	Lisa Basham, M.S.; Parinda Jani
OSE/DMEPA	Vicky Borders-Hemphill, Pharm.D.; Jamie Wilkins Parker, Pharm.D.; Carol Holquist, R.Ph.
OSE/DRISK	Jason Bunting, Pharm.D.; Reema Mehta, Pharm.D., M.P.H.; Claudia Manzo, Pharm.D.
Controlled Substances Staff	Stephen Sun, M.D.; Michael Klein, Ph.D.
CDRH	Jacqueline Ryan, M.D.
DRUP	Barbara Wesley, M.D., M.P.H.; Christina Chang, M.D.

OND=Office of New Drugs
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error and Prevention Analysis
 DRISK= Division of Risk Management
 OSI=Office of Scientific Investigations
 CDTL=Cross Discipline Team Leader
 ONDQA=Office of New Drug Quality Assessment
 OPS/NDMS=Office of Pharmaceutical Sciences/New Drug Microbiology Staff
 CDRH =Center for Devices and Radiological Health
 DRUP=Division of Reproductive and Urological Products

1. Introduction

Titan Pharmaceuticals, Inc. (the Applicant) has submitted an NDA for their buprenorphine-containing, rod-shaped implant designed to provide sustained delivery of a therapeutic level of buprenorphine over a six-month period. Four to five rods are implanted subdermally in the patient's anterior proximal upper extremity. Probuphine was developed with the intention of providing not only a buprenorphine formulation that would address one of the major problems found in treating opioid addiction, i.e., non-compliance with the medical regimen, but also to provide some degree of abuse deterrence compared to the already approved formulations.

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2. Background

Based on the Applicant's contention that this implantable formulation of buprenorphine would provide better compliance and reduced diversion for abuse compared to the currently marketed buprenorphine products, the NDA was given a priority review. While early evidence of efficacy had been established during the development program, the clinical relevance of the treatment effect could only be assessed by reviewing the full set of clinical studies once the application had been submitted. As noted by the clinical review team, any change in use patterns for opioid dependent subjects in a clinical trial, even complete abstinence, is really only a surrogate for the critical clinical outcomes one would expect from successful treatment of these patients. While complete abstinence might logically be extrapolated to result in successful clinical outcomes, exactly what amount of reduction of use might result in clinical benefits such as improved morbidity and mortality, or improvements in social functioning that would allow a patient to establish and maintain family relationships, hold a job or attend school, etc., has not been established. Therefore, the agreement reached between the Division and the Applicant was that Titan would analyze the data for the primary efficacy outcome measure, percentage of clean urines for Weeks 1 through 24 on toxicological testing, as a cumulative distribution function (CDF). This CDF could then be analyzed by the Applicant and the Division to assess the overall patterns of use during treatment between the Probuphine-treated and the placebo-treated subjects. Unfortunately, the overall treatment effect seemed to be at best described as small, with a large majority of the subjects in the Probuphine arm having either positive urine tests or acknowledged opioid use, or both, at most of the study visits. In addition, most of the study-drug subjects still required rescue treatment with sublingual buprenorphine throughout the study period.

This finding of limited effectiveness is also consistent with the pharmacokinetic evaluation of Probuphine which demonstrated that the systemic exposure for Probuphine was approximately 30% compared to an equivalent dose of sublingual buprenorphine at steady state. It is also important to note that Probuphine was formulated such that it should only be adequate for patients requiring a dose in the 12 to 16 mg range of buprenorphine. This limited dose range raises questions as to the product's safety if it were to be used in patients requiring lower doses, and efficacy concerns regarding the large proportion of the patient population that requires doses of buprenorphine that are higher than 16 mg. While the Probuphine arm did show a statistically significant treatment effect compared to placebo, the review team did not find the effect to be of a magnitude that would address the dosing concerns, or weigh in favor of efficacy compared to the risks associated with the use of the product.

In addition to the concerns raised by the review team regarding the efficacy of Probuphine, the review team found that the proposed model of care for the implantation and removal of the rods had been inadequately evaluated and appeared to be associated with potentially serious adverse events. The REMS that was submitted with the NDA was not acceptable as it did not fully address these concerns, and

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because it did not adequately address the potential conflicts between the REMS elements and the legal and regulatory requirements of the Controlled Substances Act (CSA) and the Drug Addiction Treatment Act of 2000 (DATA 2000), under which buprenorphine products for the treatment of opioid dependence are dispensed and prescribed.

The NDA was presented to the members of the Psychopharmacologic Drugs Advisory Committee on March 21, 2013. As that committee consists primarily of psychiatrists without specific training or clinical experience in addiction medicine, additional Special Government Employees (SGEs) with addiction treatment expertise were seated for this particular meeting. SGE OB/GYNs with experience in implantation and removal of birth control treatments formulated similarly to Probuphine were also seated for the meeting, as were SGEs with expertise in risk management and mitigation. In general, the committee members expressed their hope that this product would benefit the patient population, but also noted their concerns that the efficacy and dosing had not been adequately evaluated. In addition, they were clearly troubled that the proposed REMS (even the modified, more restrictive version presented by the Applicant at the meeting that had not been submitted to or reviewed by the Agency) was less than adequate to address their concerns regarding training and oversight of the implantation and removal procedures required for Probuphine treatment. While there clearly was -a mix of opinions, and the members did ultimately vote in favor of approval of the application (10 for approval, 4 against approval, 1 abstention), the concerns noted above were heard from nearly all of the members whether they voted in favor of or against approval of the application as presented to them.

Based on the concerns regarding the efficacy and dosing, the implantation and removal procedures, and the adequacy of the REMS, the clinical review team has recommended that the application not be approved.

3. CMC

The following summary of the CMC and Device reviews has been reproduced from pages 8 through 11 of Dr. Winchell's review:

Probuphine is a combination product comprising drug and device constituent components. The drug constituent component is the individual implant or rod that contains buprenorphine and ethylene vinyl acetate (EVA). The device constituent component is the applicator which consists of an obturator and cannula. The CMC review of the drug component 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.

Text below is primarily excerpted from Dr. Jao's review.

- General product quality considerations

The **drug substance** is buprenorphine hydrochloride. 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.

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 buprenorphine. The quality and stability of the registration batches of the drug substance are adequately demonstrated by release and stability data.

The drug product, Probuphine® (buprenorphine HCl implant) is a subdermal implant containing 80 mg buprenorphine hydrochloride USP (BPN) in a (b) (4) mg of ethylene vinyl acetate copolymer (EVA, the only excipient) matrix. 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.

Each implant measures 26 mm in length and 2.5 mm in diameter. Implants are individually packaged into laminated foil pouches. The pouches are terminally sterilized using gamma irradiation.

The manufacturing process of the drug product involves (b) (4)

(b) (4)
packaging, and terminal sterilization. Various experiments were conducted during pharmaceutical development stage to better understand and optimize the manufacturing process. Adequate in-process and material controls are in place.

The proposed drug product specification is acceptable from 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. The requested shelf life of 36 months is supported by stability data.

Probuphine implants are packaged in a laminated foil pouch (b) (4). No safety issues associated with the container/closure system were identified.

- 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 pending.

The device for delivery of the implants was reviewed by Jacqueline Ryan, CDRH. The text below is primarily from her review.

The Applicator is comprised of three main components:

1. Cannula Needle: Thin walled piercing needle, 10 gauge internal diameter and 60 mm length

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2. Insertable Stylet Rod: Obturator used to advance the Probuphine implants to the proper subdermal position; diameter of 0.110 in (2.79 mm), and length of 3.5 mm ± 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.

3. Cover (Needle Guard): 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 Probuphine.

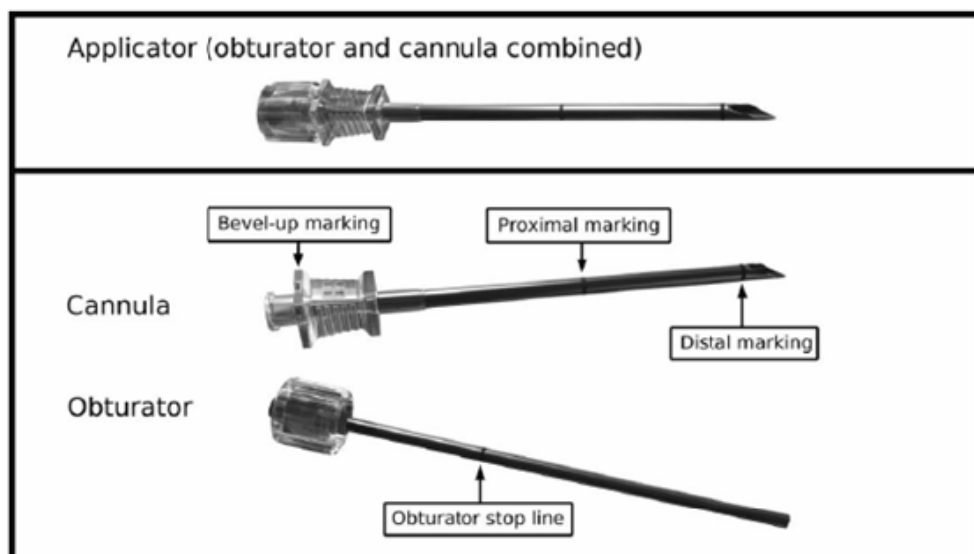


Figure 1: Probuphine Applicator Components

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 Probuphine 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 Probuphine 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 concluded that all aspects of the device were acceptable.

According to page 12 of his review, Dr. Pawar found that “The Probuphine product implant meets the regulatory requirements for a terminally sterilized product.”

As of April 29, 2013, the manufacturing sites have all been inspected and found to be acceptable. I agree with the review team that there are no CMC or device concerns that preclude approval of this application.

4. Nonclinical Pharmacology/Toxicology

The following summary of the pharmacology/toxicology review has been reproduced from pages 11 and 12 of Dr. Winchell’s review:

The non-clinical pharmacology/toxicology portion of the application was reviewed by Gary Bond, Ph.D., supervised by Adam Wasserman, Ph.D. Text below is taken primarily from Dr. Wasserman’s memo. 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.

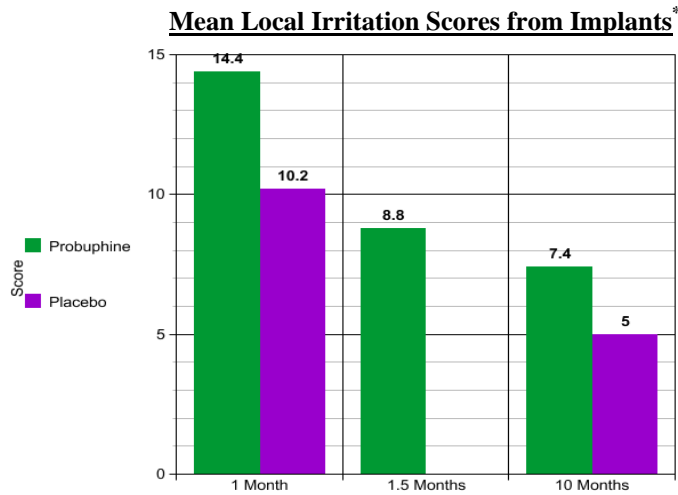
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* - Nonirritant (0.0-2.9), Slight Irritant (3.0-8.9),
 Moderate Irritant (9.0-15.0), Severe Irritant (≥ 15.1)
 - Figure from Dr. Bond's review

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.

I concur with the review team that there are no outstanding nonclinical pharmacology or toxicology concerns that would preclude approval of this application.

5. Clinical Pharmacology/Biopharmaceutics

The following summary of the clinical pharmacology and biopharmaceutics reviews has been reproduced from page 14 of Dr. Winchell's review:

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.

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 approximately half the trough concentrations observed with 16 mg/day SL buprenorphine at steady state (1.6 ± 0.6 ng/mL). 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%.

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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 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 ^a n=6
C _{max} (ng/mL)	8.61 (6.900)	10.40 (13.400)	4.89 (1.110)	0.91 (0.157)	0.78 (0.128)
T _{max} ^b (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 _{0-t} ^c (ng•hr/mL)	66.25 (35.878)	62.67 (36.397)	113.13 (27.737)	19.60 (3.372)	10.23 (2.264)
AUC ₀₋₂₄ (ng•hr/mL)	66.25 (35.878)	62.67 (36.397)	75.191 (24.443)	19.60 (3.372)	10.23 (2.264)
t _{1/2} ^b (hr)	11.42 (11.04, 12.09)	7.63	--	--	--
λ _z (hr ⁻¹)	0.0604 (0.00231)	0.0908	--	--	--

λ_z = apparent elimination rate constant; AUC₀₋₂₄ = area under the plasma concentration-time curve from time 0 to 24 hours; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to t, where t is the last measurable plasma concentration; C_{max} = maximum observed plasma concentration; t_{1/2} = apparent terminal elimination half-life; T_{max} = 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).

^a Day 57 represents parameters after removal of the Probuphine implants.

^b Median (minimum, maximum) reported for T_{max} and t_{1/2}.

^c On Days -1 and -2, AUC_{0-t} represents the AUC from Day -1 or Day -2 Hour 0 through Day 1 or Day -2 Hour 12. On Day 1, AUC_{0-t} 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.

The following information was reproduced from pages 15 and 16 of Dr. Winchell's review:

The effect of hepatic impairment on the pharmacokinetics of buprenorphine is unknown. Since the drug is extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine.

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.

The following conclusions and recommendations regarding the biopharmaceutics data submitted in this application have been reproduced from page 16 of Dr. Chikhale's review:

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Reviewer's Final Assessment on the revised dissolution acceptance criteria: Acceptable

All clinical batches passed the revised dissolution acceptance criteria at release (stability time point of zero months). Therefore, the revised dissolution criteria reflect the dissolution properties of the clinical batches, assuming that the batches were used in the clinical trials shortly after release. Evaluation of the dissolution data obtained during the drug product stability do not indicate a trend, upwards or downwards, when the drug product is stored at room temperature for up to 48 months. It should be noted that the dissolution-stability data showed a few points outside the dissolution acceptance criteria limits. However, since upward or downward trends were not observed, Biopharmaceutics does not recommend a change in the requested 36 months shelf-life.

RECOMMENDATION:

- The applicant's dissolution methodology, as summarized below is acceptable by the Agency:
USP Apparatus II (paddle)
Temperature: 37 °C
Rotation speed: 50 rpm
Medium: 900 mL water
- Dissolution acceptance criteria:
Based on the dissolution data provided, the following dissolution acceptance criteria are acceptable:
24 hrs: (b) (4) %
48 hrs: (b) (4) %
144 hrs: NLT (b) (4) %

From the Biopharmaceutics perspective, NDA 204442 for Probuphine Implants containing 80 mg bupronorphine HCl per implant is recommended for **APPROVAL**.

I concur with the review team that there are no outstanding clinical pharmacology or biopharmaceutics concerns that would preclude approval of this application.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

The following summary of the efficacy data for this application has been reproduced from pages 16 through 18 of Dr. Winchell's review:

The efficacy data were reviewed by Rachel Skeete, M.D., M.H.S., medical officer, and David Petullo, M.S., biostatistics reviewer. Mr. Petullo was supervised by Dionne Price, Ph.D. Both reviewers concluded that efficacy was demonstrated, although Dr. Skeete expressed concern about the clinical benefit associated with minor changes in drug-taking behavior. My own conclusions are similar, and are explained in detail below.

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Evidence of efficacy is provided from 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 implantation 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.

6.1 Study Design and Endpoints

Both studies were randomized, double-blind, placebo-controlled, parallel group design. Eligible participants included patients 18 to 65 years of age who met DSM-IV criteria for current opioid dependence.

Patients were ineligible to participate if they had received treatment for opioid dependence in the previous 90 days, required opioid treatment of a current chronic pain condition, were considered candidates for short-term detoxification only, met criteria for dependence on other psychoactive substances (nicotine dependence permitted), or used illicit benzodiazepines. Medical reasons for exclusion included elevated hepatic enzymes, bilirubin, or creatinine; anticoagulant treatment; use of CYP3A4 inhibitors; a current AIDS diagnosis; or other medical or psychiatric conditions at investigator discretion.

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 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])

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.

Implantation 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. Visits included assessments of safety (extent of exposure, adverse events [AEs], laboratory evaluations, vital signs, physical examination, electrocardiography [ECG]), concomitant medications) and efficacy (urine toxicology screening, quality of life, withdrawal symptoms and cravings, clinical global impressions [CGI]).

The protocols allowed for administration of supplemental sublingual buprenorphine during the study. 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

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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.

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

Investigators were blind to the urine toxicology results; therefore, supplemental buprenorphine was not provided on the basis of ongoing illicit drug use.

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

After the first two weeks, if a subject required 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.

The following summary of additional information regarding the design, conduct, analysis and results of the efficacy studies has been reproduced from pages 18 through 26 of Dr. Winchell's review:

The implantation procedure was performed by a health care provider who had received training from the sponsor 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 implantation incision. New pieces of equipment were provided to facilitate removal via this alternate method. Implantation 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 implantation and removal procedures.

As discussed above, because of lack of consensus on what pattern of drug use short of abstinence should be deemed a successful outcome, but recognizing concern that patients might have occasional lapses, a primary endpoint capturing the full range of responses was used. The primary efficacy outcome for both studies was the cumulative distribution function (CDF) of the percent of urine samples negative for opioids.¹ 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

¹ 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 Titan entered Phase 3 of the development program, the Applicant still had some uncertainty about the full duration of therapy with the implant. While Titan 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.

week during the studies, and tested for opioids with the exception of buprenorphine, as well as other illicit drugs.

6.2 Population

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.

Baseline characteristics were fairly well balanced across the treatment arms, except for a slightly higher proportion of subjects in the Probuphine arm reporting heroin use as their primary opioid of abuse in PRO-806. This is not, however, anticipated to bias results in favor of Probuphine.

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.

6.3 Statistical Methodologies

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.

It is noted that analyses which describe the percent of visits, samples, or weeks that are opioid-free cannot distinguish between patients who require some time to engage in treatment but ultimately attain and sustain abstinence, and patients who have an initial

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period of abstinence but relapse to regular drug use while still on-treatment. The former patient would be regarded as more successful than the latter. Moreover, if there were a number of patients in the latter category, this might suggest that the duration of effect of the implant had been over-estimated. Therefore, the data were examined using various “grace periods.” In these analyses, drug use during the initial grace period is not included in the calculations. Patients who attained and sustained abstinence by the end of the grace period would be represented as fully abstinent. The data presented below show the results using no grace period, or using a grace period of four months (i.e., only drug use in the final two months “counts”).

6.4 Results

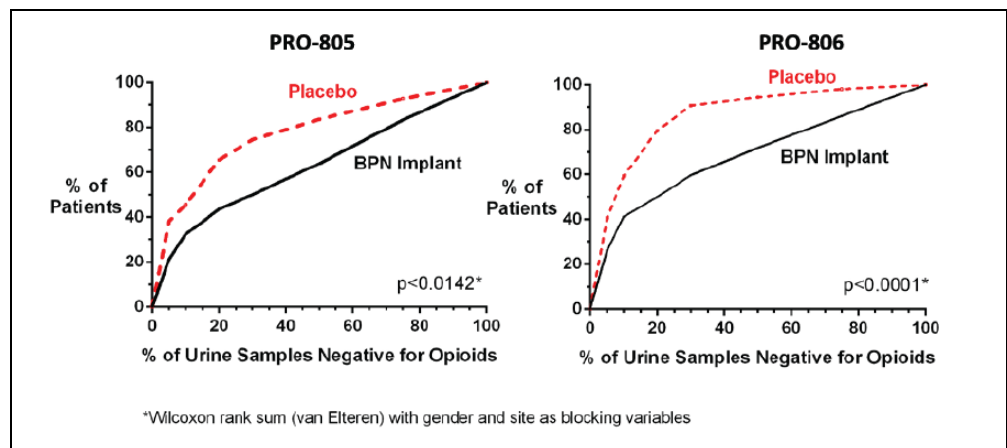
All results presented were obtained by incorporating self-reported use.

6.4.1 Analysis of Urine Samples, Weeks 1-24

6.4.1.2 Applicant’s results

Titan’s graphs 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 Titan’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 Titan’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.

6.4.1.3 Reviewer Analysis

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

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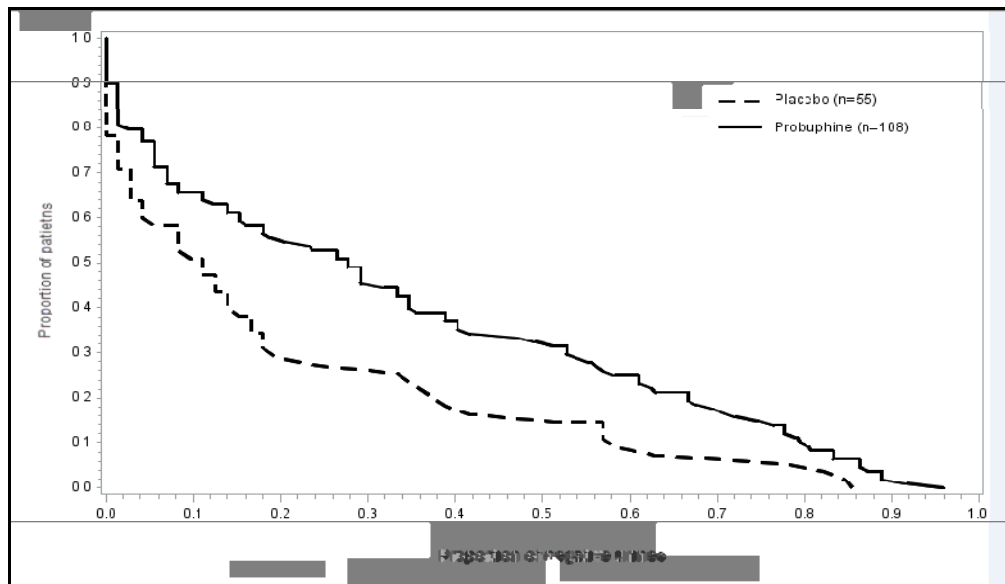
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expedience and not because they are known to have any particular significance), there are fewer patients meeting each threshold. To facilitate comparisons at specific cutoffs, Mr. Petullo also provided tabulations of the proportion of patients meeting 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.

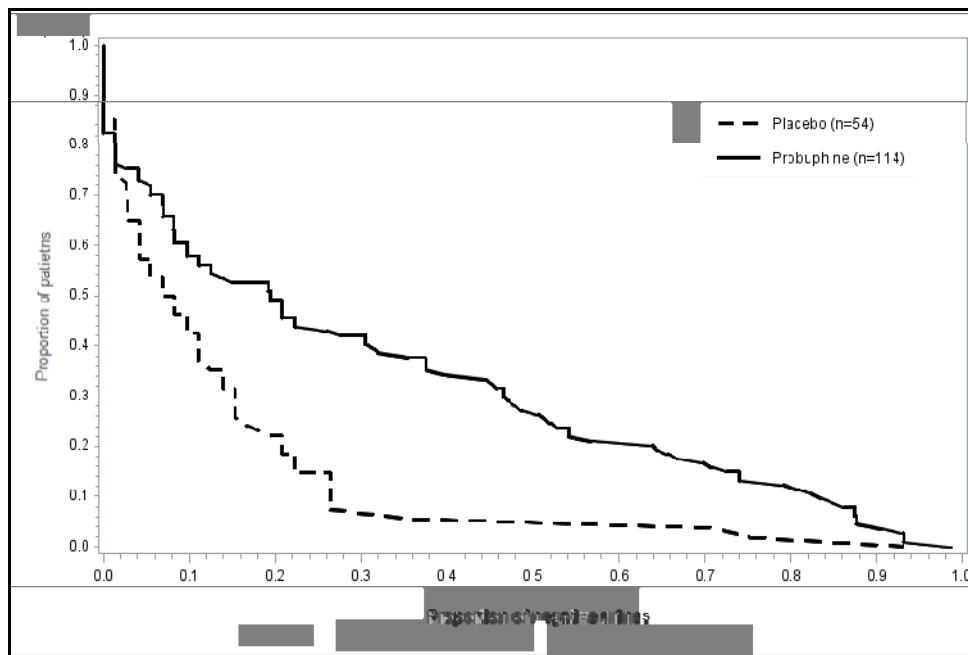
Study PRO-805: Percentage of negative urines, Weeks 1-24

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.

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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.

The clinical and statistical review teams performed a number of additional analyses. One was intended to assess whether allowing a “grace period” of either four or eight weeks, that was intended to allow patients to engage in their treatment, would improve the treatment effect. Another analysis evaluated the impact that actual improvements in social and/or occupational functioning might have had by way of missing visits. Neither of these analyses provided additional evidence of efficacy beyond the level seen in the primary analysis. An assessment of rescue medication use did demonstrate a moderate reduction in rescue use in the Probuphine-treated subjects compared to the placebo-treated subjects. However, many Probuphine-treated subjects continued to require rescue regularly under the protocol-defined paradigm for rescue administration. In the community setting, this careful oversight will not occur and patients needing frequent rescue are likely to resort to illegal, or at best unethical sources for obtaining drug.

I find that the following discussion by Dr. Winchell and the graphic representations of individual patient urine toxicology results prepared by Mr. Petullo provide some of the most compelling information regarding the effectiveness of Probuphine, particularly in the pristine setting of a clinical trial. This information has been reproduced from pages 31 through 33 of Dr. Winchell’s review:

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.

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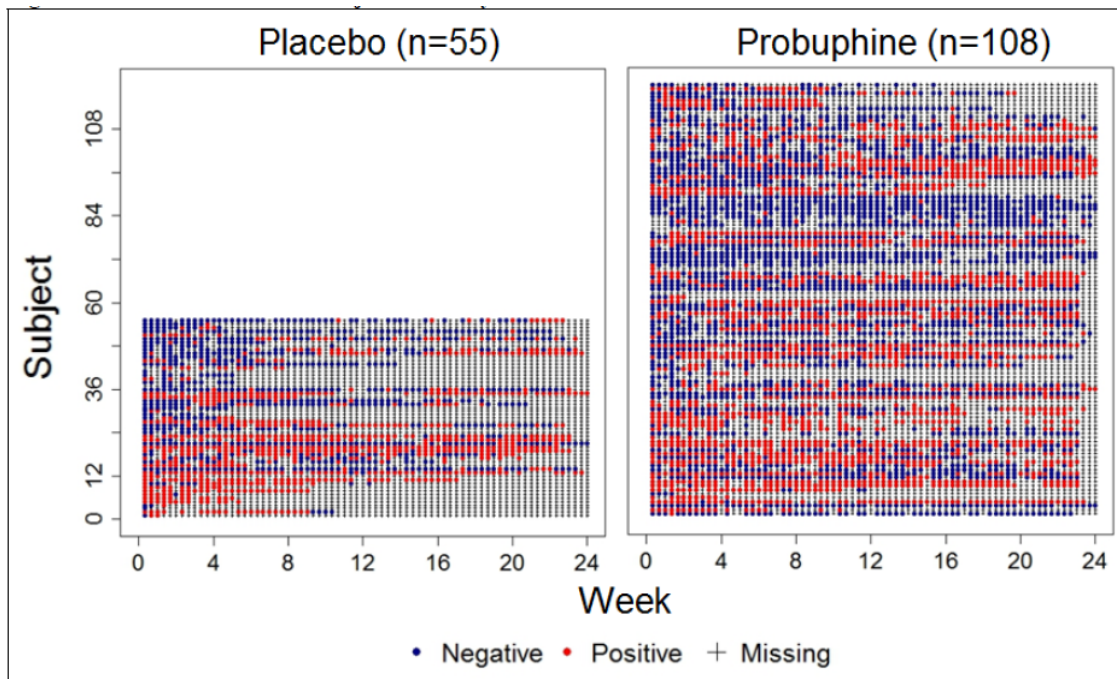
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Petullo also provided a graphic display of the use of rescue medication over time for each patient.

6.4.5.1 Urine Test Results

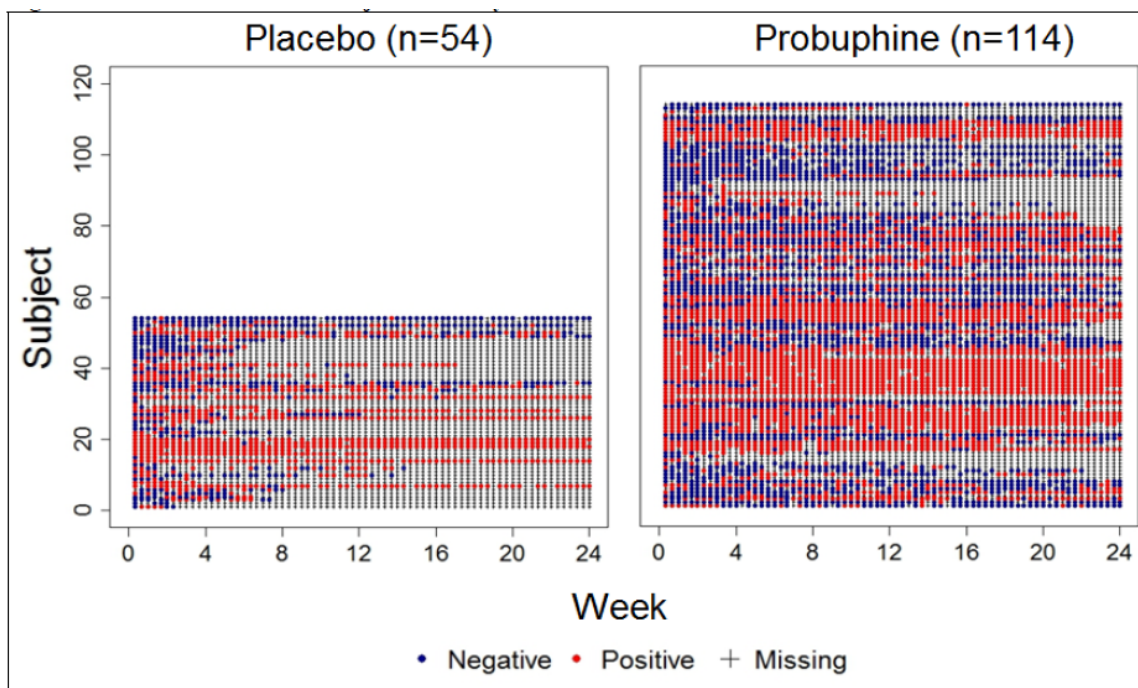
These subject-level analyses are shown below. In these presentations, each individual subject is represented along the y-axis. On the x-axis are the time points during which urine samples were collected. (In these studies, urine samples were collected three times per week). Blue dots are used to represent 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 in the past 10 years 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.

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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 check ups 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 calls into question whether the benefits of “retention in treatment” are going to accrue to these patients.

One additional finding of interest in regard to efficacy noted in Dr. Winchell’s review was that Probuphine subjects with a BMI ≤ 25 tended to have higher plasma buprenorphine and norbuprenorphine concentrations than subjects with a BMI > 25 , and this difference increased with time on study. More than half the subjects fell in the “overweight” or BMI > 25 group. While this could represent an additional problem in regard to efficacy in a large proportion of patients, I reviewed the Applicant’s comments on this finding and their table of purported efficacy correlations, but the clinical outcome and impact remain unclear to me. Further evaluation will be necessary to clarify this initial finding.

The following discussion, reproduced from page 41 of Dr. Winchell’s review, is important as we try to understand the unexpected efficacy results in this program:

...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 was fairly widely used off-label for treatment of withdrawal, at doses of 0.1-0.2 mg.

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*

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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. [My italics]

The italicized section is particularly pertinent to our understanding of the problem. The inadvertently too low doses employed in this development program may have relieved the symptoms of withdrawal, but much higher systemic levels of the drug would be necessary to block the effects of opioids taken to get high. Thus, the patient has the best of both worlds. He can avoid withdrawal signs and symptoms between episodes of using illicitly obtained opioids for abuse; and the source of his treatment is perfectly legitimate. While speculative, this certainly would explain what was demonstrated in the studies conducted for this application.

I concur with the review team that the study has demonstrated that Probuphine has a treatment effect that is better than placebo in some patients, in what is essentially a patient population enriched for responders to buprenorphine.

8. Safety

Overall, 283 subjects were treated with Probuphine in the clinical development program with 85 treated for greater than or equal to 12 months.

There were no deaths in subjects treated with Probuphine in the clinical studies. Serious adverse events occurred in 4% of the Probuphine subjects and 6% of the placebo subjects. The serious adverse events included: accidental injuries, hospitalization for relapse of drug use, complicated opioid withdrawal, abscess and other infections, depression, suicidal thoughts and suicidal actions. There was one serious adverse event related to implantation in a subject who received a placebo implant. This event was cellulitis at the explant site. However, this subject also had pneumonia which may have been the reason for hospitalization.

Discontinuations due to adverse events occurred in 3% of subjects on Probuphine, 2% of subjects on placebo, and 4% of subjects on sublingual buprenorphine. The 6 events in the Probuphine subjects were: implant site pain and/or infection (3), hepatic enzyme increases (2), and breast cancer (1).

The common adverse events were the expected systemic effects seen with buprenorphine and other opioids. Buprenorphine has been known to cause hepatotoxicity and there were cases of elevated liver enzymes, and some elevated bilirubins. There were no Hy's Law cases and no drug-induced liver injury cases. Recent studies of buprenorphine have demonstrated QT prolongation. However, at the time the development program for this product was agreed to, this information had not yet become available and a TQT study was not required for Probuphine. ECGs were performed in some studies. Increases in the QT interval

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were observed in a number of patients, but accurate interpretation of these findings is not possible without a dedicated QT evaluation.

Clearly, one of the most important safety assessments for this product is the evaluation of adverse events associated with implantation and removal of the rods, and any adverse events associated with having the implants embedded in the arm for six months. The following summary of these evaluations has been reproduced from pages 48 through 51 of Dr. Winchell's review:

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, 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 study).

Additionally, 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, 478 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. Study PRO-806 provides experience with 168 insertions and 147 removals, performed by 22 physicians, using the currently-recommended techniques and equipment. An additional 85 insertions using the current methods were performed in PRO-811. 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,

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itching, pain, infection, bleeding, abnormal healing, and any other abnormalities. According to information obtained during OSI inspection, “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.

The table below, from Titan’s Advisory Committee backgrounder, shows the effect of the change in equipment and procedures on the overall rate of implant-site AEs.

Implant Site Adverse Events (>2% of Patients in Any Group) by Preferred Term in Double-Blind Studies PR0-805 and PR0-806

System Organ Class Preferred Term/pre-specified term*	PR0-		PR0-806	
	Probuphine N=108 n(%)	Placebo Implant N=55 n(%)	Probuphine N=114 n(%)	Placebo Implant N=54 n(%)
Any Implant Site AE	63 (58.3)	28 (50.9)	32 (28.1)	14 (25.9)
Implant site pruritus	29 (26.9)	12 (21.8)	5 (4.4)	2 (3.7)
Implant site pain	29 (26.9)	9 (16.4)	6 (5.3)	5 (9.3)
Implant site erythema	27 (25.0)	12 (21.8)	4 (3.5)	0 (0.0)
Implant site haemorrhage	20 (18.5)	8 (14.5)	2 (1.8)	2 (3.7)
Implant site oedema	14 (13.0)	5 (9.1)	2 (1.8)	0 (0.0)
Implant site haematoma	12 (11.1)	9 (16.4)	8 (7.0)	6 (11.1)
Implant site scar	11 (10.2)	8 (14.5)	0	0
Implant site reaction	6 (5.6)	2 (3.6)	1 (0.9)	1 (1.9)
Implant site infection	4 (3.7)	1 (1.8)	0	0
Device expulsion	3 (2.8)	0 (0.0)	0	0
Impaired healing	3 (2.8)	0 (0.0)	0	0
Implant site paraesthesia	2 (1.9)	0 (0.0)	0	0
Implant site rash	1 (0.9)	1 (1.8)	0	0
Complication of device removal	1 (0.9)	0 (0.0)	0	0
Implant site dermatitis	1 (0.9)	0 (0.0)	0	0
Implant site irritation	1 (0.9)	0 (0.0)	0	1 (1.9)
Implant site cellulitis	0 (0.0)	1 (1.8)	0	0
Implant site swelling	0	0	2 (1.8)	0 (0.0)
Procedural pain	0	0	5 (4.4)	0 (0.0)
Procedural site reaction	0	0	3 (2.6)	2 (3.7)
Ecchymosis	0	0	2 (1.8)	0 (0.0)

* In study PR0-805, AEs were identified from case report forms (CRFs) and listing using a pre-specified list

In the open-label studies, rates of implant-site related AEs 45% (any AE) in PRO-807—somewhat lower than the experience in the parent study—and 14% in Study PRO-811. Many of the same clinicians participated in all the studies, so some improvement may

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have been based on increasing familiarity with the procedures. However, the differences between the earlier studies and the later studies provide support for the modifications to the equipment and procedures.

Procedural complications were also reviewed, with a focus on patients experiencing device extrusion or expulsion and on removals which could not be completed on the first attempt. In some patients, the Probuphine rods worked their way through the skin and either protruded partially (extrusion) or fell out (or were pulled out) altogether (expulsion). Six patients (five Probuphine, one placebo) had events of this nature. One patient (Probuphine) had multiple events of implant extrusion and expulsion and had to have her implants replaced on four occasions. All but one of these events (the single placebo patient) occurred in studies using the original insertion tool and training procedures.

There were more difficulties with the removals than with the insertions. In 20 cases (5%), a second attempt was required to remove the implants. This represents a relatively high rate given the small numbers of procedures performed. Although most of these complications occurred in studies using the original insertion tool and removal procedures, 3% of removals in PRO-811 also required more than one attempt. 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 Probuphine implants. They are not radio-opaque. One patient required general anesthesia to complete removal.

Study Identifier	Cases Requiring a Second Attempt at Removal, N (%)
PRO-805	15 (10)
PRO-807 (PRO-805 Extension)	3 (5)
PRO-806	0
PRO-811 (PRO-806 Extension)	2 (3)

The overall experience with insertion and removal of Probuphine using the current equipment and procedures is limited to roughly 250 insertions by fewer than 25 practitioners. Because changes in equipment, techniques, and training procedures were all implemented simultaneously, it is difficult to pinpoint which of these modifications is most important in ensuring safe insertion and removal of Probuphine. The OB/Gyn participants in the Advisory Committee meeting stressed the importance of proper training, and the importance of providers performing procedures frequently and regularly to maintain their skills.

I concur with the review team that no new or unexpected systemic safety signals have been demonstrated during this development program. Further evaluation of the potential for QT prolongation will be necessary. The implantation and particularly the removal procedures do have potential for serious harm to the patients and the training and monitoring for these procedures will need to be carefully defined in the product REMS.

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9. Advisory Committee Meeting

The following summary of the advisory committee meeting held in March has been reproduced from pages 181 through 184 of Dr. Skeete's review. She has formatted her summary of the discussions to follow each of the specific questions posed to the committee members:

1. **DISCUSSION:** Please comment on whether the Applicant conducted adequate dose exploration in the development program to determine the most effective dose.

VOTE: Do the data from the clinical trials provide substantial evidence of effectiveness of Probuphine for the maintenance treatment of opioid dependence?

The committee overall felt that there had not been adequate dose exploration in the development program to determine the most effective dose. The committee expressed concerns about the clinical pharmacology findings which demonstrated that the plasma buprenorphine levels attained with Probuphine are less than levels attained with the target 16 mg sublingual buprenorphine dose. The committee members also had concerns regarding the uncertainties surrounding treatment of patients who require more or less than the target induction dose range of 12 – 16 mg sublingual buprenorphine used in the clinical trials. Moreover, the use of rescue sublingual buprenorphine was viewed as further support of the inadequate dose exploration.

On the voting question, the majority of committee members voted affirmatively (10 voted 'Yes', and 5 voted 'No'). Committee members contended that the data demonstrated that Probuphine was more effective than placebo, as efficacious as other products currently on the market, and that the primary endpoint criteria were met. At the same time, however, the committee members continued to express concerns that optimal dosing had not been determined.

2. **DISCUSSION:** Please comment on the Applicant's assessment of the safety aspect of Probuphine in general, as well as on safety concerns specific to the placement and removal of the implants.

VOTE: Has the Applicant adequately characterized the safety profile of Probuphine in this patient population?

On the whole, the committee did not consider the safety of Probuphine, both as it related to the systemic effects of Probuphine, and the potential safety issues that may be associated with the insertion and removal procedures [*to be of concern*].

Obstetrician/Gynecologists were invited to participate on the panel because of Agency concerns that the potential procedural complications that may arise as a consequence of Probuphine administration could conceivably outweigh any benefits that would be offered to the patient. The Obstetrician/Gynecologists were being asked to provide insight into the issues of safety based on the implantable contraceptives, in particular Norplant, the implantable contraceptive most analogous to Probuphine both from the number of implants used per treatment cycle and the insertion and removal procedures. The Obstetrician/Gynecologists, from their vast experience with these implantable contraceptives expressed that the insertion and removal procedures are not complicated procedures and with appropriate training, most clinicians can be taught to successfully perform the procedures. The key factor driving competency, the

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Obstetrician/Gynecologists contended, is that the implanting health care professional performs enough procedures to become comfortable with the procedures.

The perspective of the Obstetrician/Gynecologists allayed concerns about the procedural safety for this product. However, the committee members still noted that there were differences between the population of patients that would use implantable contraceptives and the population of patients that would use Probuphine. Members felt that training for placement and removal of the implants was important to minimize safety concerns. The majority of the committee agreed that the Applicant had adequately characterized the safety profile of buprenorphine; there were 12 Yes votes (2 voting no, and one abstention). This was because of the prior clinical experience with sublingual buprenorphine which attests to the systemic effects, and the implantable contraceptives, which address the procedural safety associated with the implants and insertion and removal procedures.

3. **VOTE:** Is the Risk Evaluation and Mitigation Strategy (REMS) proposed by the Applicant, which consists of restricted distribution and a training/certification program for healthcare professionals who will implant the product, adequate to address the risks of potential complications associated with the implantation procedure and abuse, misuse, and accidental overdose. Include in your deliberations any concerns related to the proposed model of care and training/certification program.

There was no consensus among the committee members with respect to the adequacy of the REMS proposed by the Applicant to address the risks of potential complications associated with the implantation procedure and abuse, misuse, and accidental overdose. The votes were varied with 5 Yes votes, 4 No votes, and 6 abstentions. The Applicant had revised their REMS shortly before the meeting because they had recently learned that their REMS was not in compliance with DEA and SAHMSA regulations. The REMS described by the Applicant had not yet been submitted to the Agency for review, and as such the Agency was unable to provide perspective on the revised REMS, and at the meeting could only discuss the formal REMS submissions to date. The new submissions are to be reviewed by DRISK, but as they were submitted at the end of the review cycle, there was not enough time for DRISK to review and comment.

4. **DISCUSSION:** Please discuss whether the absence of any information on each of the following matters should be considered a critical deficiency in the application:
 - a. the potential for removal of the implants by non-medical personnel for the purpose of diversion.
 - b. the potential for long-term exposure to the components of the rods if an individual never has the implants removed.
 - c. the potential for patients to require implantation into an arm which has received an implant previously in order to remain on treatment, which would necessitate identification of multiple implantation sites per arm, or use of previously implanted sites.

The committee expressed no concerns about the removal of implants by non-medical personnel for the purposes of diversion or about long-term exposure of the components of the implants. They did, however, express concerns about the treatment duration limitations stemming from the limited implantation sites, but did not view this as a critical deficiency. It was noted that sites other than the arms should be explored, as long-term treatment could be necessary for some patients. During the meeting, it came to light that it may not be necessary to limit implant sites to the inner upper arm.

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5. **VOTE:** Based on the data presented and discussed today, do the efficacy, safety, and risk-benefit profile of Probuphine support the approval of this application?

The committee voted 10-4 in favor of approval of this application. There was one abstention.

The majority of the committee agreed that, based on the data presented and discussed, the efficacy, safety, and risk-benefit profile of Probuphine support the approval of this application. The committee members who voted “Yes” noted that, although they voted “Yes,” additional data were needed to fully assess both the safety and efficacy of Probuphine and that the REMS was still an area of foremost concern. Overall, these members indicated that the benefits outweighed the risks. *Because of the many unresolved issues pertaining to dose-finding and the REMS, the committee’s support of this product appeared to be based, in some part, on the potential of the product, rather than what the currently available safety and efficacy data for the product demonstrate. Additionally, the committee’s favorable opinion appeared to be given in the context of the limited pharmacologic treatment options available for this potentially fatal disease, and the advantage that Probuphine offers in the way of “passive compliance.” Said another way, with Probuphine the difficult choice that patients must make on a daily basis to take their treatment medication rather than taking the substance to which they are addicted is eliminated. The committee members who voted “No” noted that the dose exploration was inadequate, which would also complicate labeling in that the dosing would be limited to only patients who could reach an induction dose of 12 – 16 mg, and expressed concerns with the REMS). The one member who abstained noted similar concerns with the REMS and felt that additional data, particularly regarding patient selection, was needed for a decisive vote.* [my italics]

During the Open Public Hearing, a number of patients, family members, and addiction treatment practitioners spoke passionately about the need for this type of product. Their testimonies were extremely moving and clearly emphasized how important a product that would remove patient compliance from the treatment paradigm could be for opioid addiction patients.

I concur with Dr. Skeete’s summaries of the committee members’ discussions. In particular, note the section of her last summary (Discussion and Vote Number 5) that I have italicized. This is really the central outcome of the committee’s deliberations. Some voted for and some voted against approval; and yet they seemed to reach a consensus that there was potential for enormous benefit from an implantable buprenorphine product based on the impact on compliance, and breaking the cycle of craving and abusing. Nevertheless, they also seemed to reach a consensus that Probuphine may not be that product due to the dosing concerns, minimal efficacy demonstrated, continued drug use by most of the subjects, and the not yet well-defined model of care and training program. Those who voted yes seemed moved to do so by the great need for this type of product. Some who voted for and some who voted against approval also acknowledged that approving this product before it had achieved a level of quality that would assure a reasonable likelihood of successful treatment

could have a significantly negative impact on the future development of similar products, or even on the acceptance of this product by the treatment community.

10. Pediatrics

The following summary of the pediatric issues for this application has been reproduced from page 56 of Dr. Winchell's review:

Although Titan, the sponsor of Probuphine, requested a partial waiver for patients ages (b) (4) years of age only, and a deferral for studies in pediatrics ages (b) (4) years,

An assessment of the feasibility of conducting studies in adolescents, ages 12 to 16 years, with opioid dependence, was recently and reviewed by the Pediatric Review Committee (PeRC), after which the sponsor of that application was granted the full waiver from the requirement for pediatric studies.

Therefore, DAAAP believed that a full waiver would be more appropriate as the population of treatment-seeking, opioid-dependent adolescents has not changed considerably since the time of the feasibility assessment. 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.

11. Other Relevant Regulatory Issues

The major additional regulatory issue is the design and implementation of a REMS for this product. The initial discussions regarding a REMS included an interest in having the plan address the potential for diversion and abuse of Probuphine. However, after extensive internal discussion, it became clear that the likelihood that Probuphine will be widely diverted and abused is extremely small. Even if a patient picks up the prescribed product from a pharmacy with instructions from their prescribing doctor to bring it in for implantation, and the patient diverts the product at that point to sell or extract and inject himself, it would result in his not being prescribed any more Probuphine by the doctor. While the patient could doctor shop to get additional Probuphine, prescribing is already controlled to some degree by DATA 2000 and it is not as simple as obtaining a prescription for most of the other opioid products. Also,

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although extraction of the buprenorphine from the Probuphine rods is relatively easy, the quantity that one could extract from even five rods would be less than a typical month's supply of tablets or films. Finally, as demonstrated in the clinical studies to date, rescue sublingual medication is required in the majority of patients. This, along with the fact that there is a large quantity of sublingual product already in the community and diversion is fairly common, makes the availability of a much more "abuser friendly" formulation likely to limit the amount of extraction attempted with the limited number of rods that will be available.

I do think that there is value in having educational materials regarding the potential for abuse and misuse of, and the proper handling and storage of Probuphine available for patients via a REMS. This would be a similar use of a risk mitigation strategy to the other buprenorphine products approved for the maintenance treatment of opioid dependence.

Nevertheless, the REMS should be focused on assuring that the implantation and removal of the rods are performed by qualified, well-trained individuals only, and that those practitioners are fully aware of their responsibilities under the CSA and DATA 2000. The following summary of the status of the REMS for Probuphine has been reproduced from pages 56 through 58 of Dr. Winchell's review:

11.1 Risk Evaluation and Mitigation Strategy

Titan initially submitted a REMS proposal which had the following goals:

- To maximize effective Probuphine therapy by optimizing the following:
 - patient selection,
 - patient monitoring,
 - insertion and removal procedures by educating healthcare professionals, (Drug Abuse Treatment Act [DATA 2000]-waived physicians and other healthcare providers trained by Titan to perform the Probuphine insertion and removal procedures),
 - implementing a closed process to adequately control distribution and dispensation.

- To ensure safe use of Probuphine by minimizing the risk of misuse, abuse, diversion, accidental poisonings, overdose and complications related to Probuphine and the insertion and removal procedures.

The components of the REMS included a Medication Guide (MG), Communication Plan (CP), Elements to Assure Safe Use (ETASU) and an Implementation System. The ETASU called for health care providers to be certified after participating in a company-sponsored training program, and described the use of a central pharmacy to dispense Probuphine directly to providers within a closed distribution system to ensure that the prescriber was DATA-waived and the implanting practitioner was REMS-certified. The model of care envisioned that a DATA-waived prescriber could transmit a prescription for a specific patient to the central pharmacy, who would then ship the product to the prescriber or to a different person who would perform the implantation procedure. Probuphine would also have to be removed by a REMS certified prescriber, and used Probuphine would be disposed of in medical waste.

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The DRISK team identified a number of concerns with the initial proposal, noting that certain aspects do not conform with the requirements of the Controlled Substances Act. For example, a pharmacy cannot ship the prescription to the physician; it must go to the patient. (A distributor may ship product to a physician for stock supply.) Moreover, there is some lack of clarity over how the used implant (which contains considerable residual drug) should be disposed of. There were also a number of concerns with the model of care. A number of changes to the proposal have been made by Titan, who presented a revised (and not-yet-reviewed) version of the REMS at the Advisory Committee meeting. DRISK has not yet completed a review of the most recent version of Titan's proposal, which now incorporates distribution of product from a distributor to the implanting physician.

It is currently envisioned that the REMS will primarily address the need for health care providers implanting and removing Probuphine to be properly trained and to maintain their familiarity with the procedures. A closed distribution system to ensure that only REMS-certified providers perform the procedures is desirable. Input from the Office of Chief Counsel and Office of Regulatory Policy is currently pending to advise whether any provisions in the Controlled Substances Act or the DATA 2000 preclude FDA from requiring that providers undergo training in the implantation procedures or from implementing a closed system to ensure this.

11.2 Medication Errors Prevention

A Training and Certification Program has been developed by the Applicant and was intended to ensure that clinicians who performed the implant insertion and removal procedures met competency standards and to improve the overall safety of the implant and removal processes. No specific testing of the training program or procedures was included with the NDA; Titan's position was that the procedures were pilot-tested and validated in Studies 806 and 811.

The Division of Medication Error Prevention and Analysis (DMEPA) and the team in CDRH responsible for Human Factors studies were consulted to review issues related to the training program, instruction materials, and directions for use.

Initially, based on the understanding that the product and procedures were essentially the same as Norplant, the review team did not feel that a human factors study or user-performance assessment would be required to support the NDA. However, in the course of review, it became apparent that:

1. The removal procedure differed substantially from the established procedure for removing Norplant, and there was a paucity of clinical experience with this specific procedure, and in training practitioners to perform it, and;
2. The provider population that would be performing the procedures differed substantially from the provider population that inserts and removes Norplant and other implantable contraceptives.

After these points became clear, the DMEPA team felt that the sponsor should provide a comprehensive use-related risk analysis for the product. This analysis should include a comprehensive evaluation of all the steps involved in using the device (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk-

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mitigation strategies employed to reduce any moderate or high risks to acceptable levels, and the method of validating the risk-mitigation strategies.

12. Labeling

Labeling changes recommended by the review team are still being negotiated with the Applicant. Continuation of these discussions will occur during the second cycle review.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Complete Response

- Risk Benefit Assessment

Opioid addiction is a profoundly difficult condition to treat, and most of the available treatments have limited impact due to the need for the patient to comply with the treatment regimen on a daily basis. The one exception is Vivitrol, which is an injectable depot formulation of the opioid antagonist naltrexone. However, addiction specialists believe that agonist therapy is generally more acceptable to patients for the long-term treatment of opioid addiction. All of the available agonist therapies have to be administered at least once daily by mouth. It is not uncommon for patients to continue to abuse their opioid drugs of choice and simply skip the treatment dose, or divert it for abuse by others. Alternatively, due to the challenges of staying in treatment, they discontinue completely and return to illicit opioid abuse full time. Clearly there is a great need for a product that will remove patient compliance from the equation.

Unfortunately, as currently formulated, Probuphine does not appear to be that product. While there was a statistically significant treatment effect compared to placebo in the clinical trials, the effectiveness was extremely limited. This was clearly evidenced by the frequent occurrence of illicit opioids in the Probuphine-treated subjects' urine, and by the continued need for rescue agonist therapy throughout the study by a large proportion of the patients. This finding is consistent with the low systemic exposure levels seen with Probuphine compared to the sublingual buprenorphine products. This low level may provide relief from the signs and symptoms of withdrawal, without full blockade of the opioid receptors, so that patients can continue to abuse illicit opioids and avoid withdrawal between use. So few subjects actually had what could be considered clinically relevant reductions in their opioid use, that only a product with little or no associated risk would have a risk-benefit ratio that would support marketing approval. The potential for serious harm due to

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improper implantation or removal of the Probuphine rods has not been adequately addressed in this application. The model of care and training program are insufficiently clear and robust, and the REMS does not adequately support their implementation.

The members of the advisory committee voted 10 to 4 to approve this application. However, nearly every member, whether they voted for or against approval, expressed concerns about the efficacy, the dose range, and the implantation and removal procedures. While the two OB/GYN physicians were more hopeful that even non-surgically trained practitioners could learn to perform these procedures, there were many concerns expressed by the other members, particularly in regard to removal which is far more complex to perform than insertion. In spite of the final vote, I'm confident that the true message that came out of the committee discussion was that more work is necessary to produce a depot formulation such as this, that will not only be relatively simple and safe to use, but will provide effective treatment of opioid addiction for a clinically relevant proportion of the patient population.

To approve this product now might provide some relief to a small number of patients, but it would provide completely misleading expectations to the larger patient and treatment communities. Wide use may also result in injuries and infections when the rods are implanted or removed by poorly trained, inexperienced, and unmonitored practitioners, and it may well remove any incentive for the industry to develop a formulation, including the collection of adequate dose-ranging data, to treat the larger part of the patient community.

- Postmarketing Risk Management Activities

A REMS will be required as discussed in Section 11, in order to assure the safety of the model of care and the adequacy of training for the implantation and removal of the Probuphine rods. In addition, the REMS will provide for educational materials for patients regarding the abuse potential and the proper handling of the Probuphine rods.

- Postmarketing Study Requirements

If NDA 204442 for Probuphine (buprenorphine hydrochloride implant) for subdermal use is approved, the Applicant will be required to conduct the following study as a postmarketing requirement:

A clinical trial to assess the risk of QT prolongation with subdermal buprenorphine, i.e., a thorough QT (tQT) trial

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/s/

BOB A RAPPAPORT
04/30/2013

Cross-Discipline Team Leader Review

Date	4/17/2013
From	Celia Winchell, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	204442
Applicant	Titan Pharmaceuticals, Inc. (In marketing partnership with Braeburn Pharmaceuticals)
Date of Submission	10/31/2012 (received)
PDUFA Goal Date	4/30/2013
Proprietary Name / Established (USAN) names	Probuphine (buprenorphine hydrochloride) Implant for Subdermal Use
Dosage forms / Strength	80 mg/implant
Proposed Indication(s)	Maintenance treatment of opioid dependence
Recommended:	<i>Complete Response</i>

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1. Introduction

Probuphine is a rod-shaped implant designed to provide sustained delivery of a therapeutic level of buprenorphine, a partial agonist at the μ -opiate receptor, for up to six months when 4 to 5 rods are implanted subdermally. Probuphine is intended as a maintenance treatment for opioid-dependent patients who have been initially titrated to a target dose using sublingual buprenorphine. 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. However, the product delivers a substantially lower dose than the recommended dose of these products.

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.

The Applicant has provided efficacy data from two placebo-controlled trials. While the study design (randomized, placebo-controlled, parallel group study of 6 months' duration) is not novel, some of the analytic approaches and concepts are. The approaches were agreed upon with the Agency during the development program, but the results were not what we expected during these discussions. This review will discuss in detail issues related to the efficacy results and their interpretation. Specifically, I will explain why I do not believe that the dose tested was adequate, and why I do not believe that the results achieved outweigh the risks of buprenorphine treatment.

The Applicant's submission includes safety data from 262 unique patients who were treated with Probuphine, of whom 201 received one course of treatment (24 weeks) and 82 received a second course of treatment (a total of 48 weeks). 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. It is similar in many respects to Norplant, an implantable, progestin-releasing contraceptive which is no longer marketed in the US.

Despite the fact that insertion and removal of Norplant were performed by providers trained in surgical procedures, the product's safety experience identified the potential for various implantation and removal-related complications, some of them with disabling consequences. Similar difficulties may be anticipated with Probuphine, perhaps further complicated by the population of both prescribers and patients. 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 repeatedly 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 μ -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 dependence¹. A sublingual film formulation was approved in 2010. Approximately 10.7 million prescriptions from outpatient retail pharmacies were dispensed and approximately 1 million patients received a dispensed prescription for buprenorphine tablets or films during 2012.

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 μ -receptor. Like methadone, buprenorphine's activity at the μ -receptor was expected to relieve patients' urge to use illicit opioids, but like methadone, the long duration of action would allow patients to achieve a steady state, without the alternating highs and lows associated with opioid abuse that impair daily functioning.

Due to its partial agonist properties, the euphorogenic effects of buprenorphine are 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. This was expected to limit its attractiveness as a drug of abuse.

In addition, 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. This was predicted to serve as a further deterrent to abuse.

Finally, at sufficiently high doses, buprenorphine blocks full opioid full agonists from achieving their full effects, further deterring abuse of these substances for 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 an increasing number of cases of 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, patients could not periodically discontinue use in order to allow the blocking effect to

¹ 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.

dissipate, so that they could experience the effects of their opioids of choice. Probuphine was developed to address these issues.

The recommended dose of sublingual buprenorphine is in the range of 12 mg-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%.

2.1 Background Related to Efficacy Endpoints and Study Design

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 have 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, Titan 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.

A significant effort was expended in trying to establish a definition of a treatment responder that could be applied to the studies; however, no definition of any drug use pattern, short of abstinence, could be identified that was supported by any specific data. Titan also cited literature reports in which group mean percent of clean urine tests were reported; however, because these group means incorporate both complete non-responders, partial responders, and good responders, the group mean value would not be an appropriate choice to define a responder. Therefore, rather than arbitrarily selecting a drug use pattern short of abstinence that would be considered successful, or agreeing a priori that complete abstinence would be an unreasonable expectation, Titan was encouraged to look at the full range of responder definitions, from complete abstinence to no abstinence, but to emphasize the effect of the drug on promoting abstinence or near-abstinence. This analysis is referred to by Titan as the “cumulative distribution function.”

It should be noted that, in these discussions, the emphasis was on trying to define a successful patient in such a way that patients who were clearly clinically successful would not be mis-classified 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. In other words, there was broad agreement that it would not be desirable to “throw the baby out with the bathwater.” However, at no point did the sponsor argue that bathwater itself would be grounds for approval.

2.2 Safety Concerns Related to Surgically Implanted Drugs

The Agency’s previous experience with surgically implanted 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, 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.

While implantable contraceptive methods are generally well-tolerated, procedure-related adverse events are notable for pain, infection, numbness, and scarring at the implant site. Complications such as bleeding or hematoma have also been reported. 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 A.

2.3 Legal and Regulatory Issues Constraining Buprenorphine Treatment

Buprenorphine is a Schedule III Controlled Substance and physicians prescribing Probuphine 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.

It is currently not clear whether the provisions of DATA 2000 require that the physician who implants Probuphine be DATA-waived if the treatment was prescribed by a different physician who holds the DATA waiver. Input from both FDA's legal staff and the DEA are being sought to clarify this issue.

There is also a provision in DATA 2000 which may limit our ability to require a closed distribution system, or to require provider additional training beyond the 8 hours required in the legislation; input is sought on this point as well.

3. CMC/Device

Probuphine is a combination product comprising drug and device constituent components. The drug constituent component is the individual implant or rod that contains buprenorphine and ethylene vinyl acetate (EVA). The device constituent component is the applicator which consists of an obturator and cannula. The CMC review of the drug component 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.

Text below is primarily excerpted from Dr. Jao's review.

- General product quality considerations

The **drug substance** is buprenorphine hydrochloride. 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.

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 buprenorphine. The quality and stability of the registration batches of the drug substance are adequately demonstrated by release and stability data.

The drug product, Probuphine® (buprenorphine HCl implant) is a subdermal implant containing 80 mg buprenorphine hydrochloride USP (BPN) in a (b) (4) mg of ethylene vinyl acetate copolymer (EVA, the only excipient) matrix. 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.

Each implant measures 26 mm in length and 2.5 mm in diameter. Implants are individually packaged into laminated foil pouches. The pouches are terminally sterilized using gamma irradiation.

The manufacturing process of the drug product involves (b) (4) packaging, and terminal sterilization. Various experiments were conducted during pharmaceutical development stage to better understand and optimize the manufacturing process. Adequate in-process and material controls are in place.

The proposed drug product specification is acceptable from 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. The requested shelf life of 36 months is supported by stability data.

Probuphine implants are packaged in a laminated foil pouch (b) (4). No safety issues associated with the container/closure system were identified.

- 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 pending.

The device for delivery of the implants was reviewed by Jacqueline Ryan, CDRH. The text below is primarily from her review.

The Applicator is comprised of three main components:

1. Cannula Needle: Thin walled piercing needle, 10 gauge internal diameter and 60 mm length

2. Insertable Stylet Rod: Obturator used to advance the Probuphine implants to the proper subdermal position; diameter of 0.110 in (2.79 mm), and 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.

3. Cover (Needle Guard): 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 Probuphine.

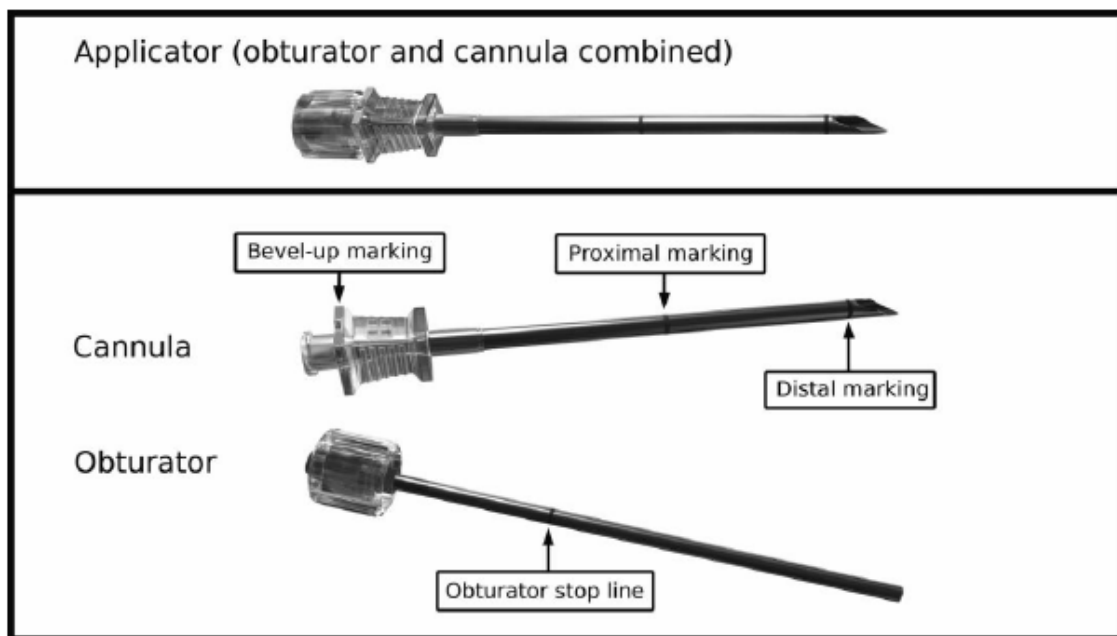


Figure 1: Probuphine Applicator Components

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 Probuphine 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 Probuphine 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 concluded that all aspects of the device were acceptable.

3. Nonclinical Pharmacology/Toxicology

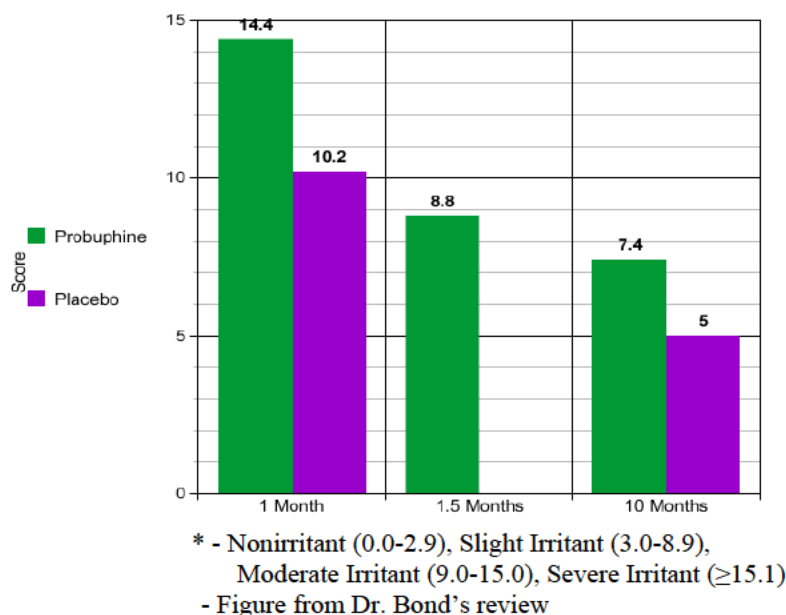
The non-clinical pharmacology/toxicology portion of the application was reviewed by Gary Bond, Ph.D., supervised by Adam Wasserman, Ph.D. Text below is taken primarily from Dr. Wasserman's memo. Much of the pharmacology/toxicology information supporting this application is included by reference to previous 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.

Mean Local Irritation Scores from Implants*



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 notes 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." His review observes:

The approved buprenorphine label includes descriptions of multiple studies for teratogenicity using various routes of administration including IM, SC, IV and oral in rat and rabbit. Carcinogenicity studies conducted in rats and mice utilize daily dietary administration. No nonclinical exposure data was available. Therefore, the doses and findings in the referenced labels are all put into clinical perspective using a body surface area comparison based on daily sublingual dose (mg/m^2). There are no apparent adjustments made for relative bioavailability through these routes. The use of body surface area comparisons is not an ideal means to convey risk in the label even with simple same route animal-human comparisons but becomes increasingly problematic when comparing different routes. For Probuphine, an additional layer of complexity is added by the controlled release properties of buprenorphine from the drug product which is also reflected by the exposure curves. The Applicant proposed to adjust the margins described in the label using mg/m^2 (b) (4)

For the purposes of extrapolating safety margins for carcinogenicity data the C_{avg} may be most appropriate while for reproductive toxicity findings a more conservative use of C_{max} may be most appropriate.

Dr. Wasserman expressed concern that safety margins based on a mg/m^2 body surface area comparison [REDACTED] (b) (4)

[REDACTED] do not provide a meaningful risk assessment, and that bridging toxicokinetic data must be obtained to allow the nonclinical studies cited in the labels to be related to clinical exposures with Probuphine. He noted that this could be accomplished as a post-marketing incorporated as a deficiency if the application receives a Complete Response action, especially if the Applicant will be conducting additional studies to establish the efficacy of higher Probuphine doses which would necessarily be associated with higher clinical exposure.

4. 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.

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 approximately half the trough concentrations observed with 16 mg/day SL buprenorphine at steady state (1.6 ± 0.6 ng/mL). 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 pharmacokinetic parameters of Probuphine, compared to 16 mg/day sublingual buprenorphine tablet, are shown in the table below (Table 12 from Dr. Lee's 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 ^a n=6
C_{max} (ng/mL)	8.61 (6.900)	10.40 (13.400)	4.89 (1.110)	0.91 (0.157)	0.78 (0.128)
T_{max}^b (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_{0-t}^c (ng•hr/mL)	66.25 (35.878)	62.67 (36.397)	113.13 (27.737)	19.60 (3.372)	10.23 (2.264)
AUC_{0-24} (ng•hr/mL)	66.25 (35.878)	62.67 (36.397)	75.191 (24.443)	19.60 (3.372)	10.23 (2.264)
$t_{1/2}^b$ (hr)	11.42 (11.04, 12.09)	7.63	--	--	--
λ_z (hr ⁻¹)	0.0604 (0.00231)	0.0908	--	--	--

λ_z = apparent elimination rate constant; AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to t, where t is the last measurable plasma concentration; C_{max} = maximum observed plasma concentration; $t_{1/2}$ = apparent terminal elimination half-life; T_{max} = 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).

^a Day 57 represents parameters after removal of the Probuphine implants.

^b Median (minimum, maximum) reported for T_{max} and $t_{1/2}$.

^c On Days -1 and -2, AUC_{0-t} represents the AUC from Day -1 or Day -2 Hour 0 through Day 1 or Day -2 Hour 12. On Day 1, AUC_{0-t} 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, elimination, and drug-drug interactions are described in detail in the Suboxone label:

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:

CYP3A4 Inhibitors and Inducers: Subjects receiving SUBOXONE sublingual tablet should be monitored if inhibitors of CYP3A4 such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin) or HIV protease inhibitors and may require dose-reduction of one or both agents. The interaction of buprenorphine with all CYP3A4 inducers has not been studied, therefore it is recommended that patients receiving SUBOXONE sublingual tablet be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered.

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine, has been found to be a moderate CYP2D6 inhibitor in in-vitro studies employing human liver microsomes.

The effect of hepatic impairment on the pharmacokinetics of buprenorphine is unknown. Since the drug is extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine.

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.

5. Clinical Microbiology

The sterility process and controls were deemed acceptable by the Microbiology review. Refer to the Clinical Microbiology review by Dr. Vinayak B. Pawar for additional details.

6. Clinical/Statistical- Efficacy

The efficacy data were reviewed by Rachel Skeete, M.D., M.H.S., medical officer, and David Petullo, M.S., biostatistics reviewer. Mr. Petullo was supervised by Dionne Price, Ph.D. Both reviewers concluded that efficacy was demonstrated, although Dr. Skeete expressed concern about the clinical benefit associated with minor changes in drug-taking behavior. My own conclusions are similar, and are explained in detail below.

Evidence of efficacy is provided from 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 implantation 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.

6.1 Study Design and Endpoints

Both studies were randomized, double-blind, placebo-controlled, parallel group design. Eligible participants included patients 18 to 65 years of age who met DSM-IV criteria for current opioid dependence.

Patients were ineligible to participate if they had received treatment for opioid dependence in the previous 90 days, required opioid treatment of a current chronic pain condition, were considered candidates for short-term detoxification only, met criteria for dependence on other psychoactive substances (nicotine dependence permitted), or used illicit benzodiazepines. Medical reasons for exclusion included elevated hepatic enzymes, bilirubin, or creatinine; anticoagulant treatment; use of CYP3A4 inhibitors; a current AIDS diagnosis; or other medical or psychiatric conditions at investigator discretion.

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 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])

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.

Implantation 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. Visits included assessments of safety (extent of exposure, adverse events [AEs], laboratory evaluations, vital signs, physical examination, electrocardiography [ECG]), concomitant medications) and efficacy (urine toxicology screening, quality of life, withdrawal symptoms and cravings, clinical global impressions [CGI]).

The protocols allowed for administration of supplemental sublingual buprenorphine during the study. 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.

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

Investigators were blind to the urine toxicology results; therefore, supplemental buprenorphine was not provided on the basis of ongoing illicit drug use.

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

After the first two weeks, if a subject required 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 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 ≥ 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, defined as
 - Requiring supplemental sublingual buprenorphine exceeding the following limits, after having received the optional 5th implant:
 - ≥ 3 days per week for 2 consecutive weeks
 - ≥ 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.)

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 implantation procedure was performed by a health care provider who had received training from the sponsor 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 implantation incision. New pieces of

equipment were provided to facilitate removal via this alternate method. Implantation 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 implantation and removal procedures.

As discussed above, because of lack of consensus on what pattern of drug use short of abstinence should be deemed a successful outcome, but recognizing concern that patients might have occasional lapses, a primary endpoint capturing the full range of responses was used. The primary efficacy outcome for both studies was the cumulative distribution function (CDF) of the percent of urine samples negative for opioids.² 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.

6.2 Population

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

² 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 Titan entered Phase 3 of the development program, the Applicant still had some uncertainty about the full duration of therapy with the implant. While Titan 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.

proportion of females were enrolled, and the percentage of subjects with previous treatment history was smaller.

Baseline characteristics were fairly well balanced across the treatment arms, except for a slightly higher proportion of subjects in the Probuphine arm reporting heroin use as their primary opioid of abuse in PRO-806. This is not, however, anticipated to bias results in favor of Probuphine.

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.

6.3 Statistical Methodologies

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.

It is noted that analyses which describe the percent of visits, samples, or weeks that are opioid-free cannot distinguish between patients who require some time to engage in treatment but ultimately attain and sustain abstinence, and patients who have an initial period of abstinence but relapse to regular drug use while still on-treatment. The former patient would be regarded as more successful than the latter. Moreover, if there were a number of patients in the latter category, this might suggest that the duration of effect of the implant had been over-estimated. Therefore, the data were examined using various “grace periods.” In these analyses, drug use during the initial grace period is not included in the calculations. Patients who attained and sustained abstinence by the end of the grace period would be represented as fully abstinent. The data presented below show the results using no grace period, or using a grace period of four months (i.e., only drug use in the final two months “counts”).

6.4 Results

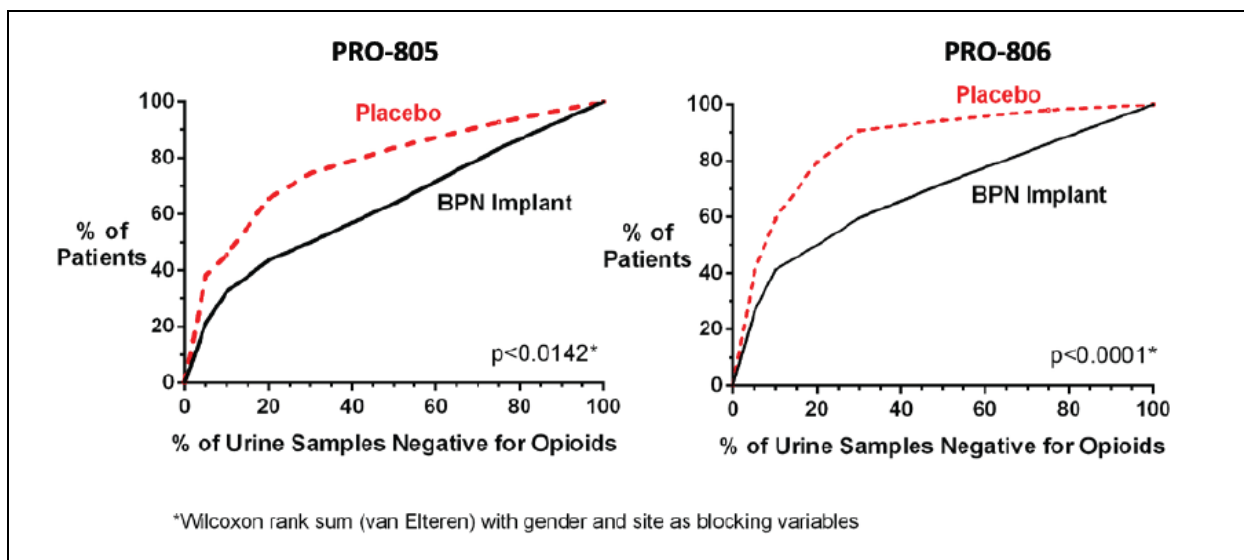
All results presented were obtained by incorporating self-reported use.

6.4.1 Analysis of Urine Samples, Weeks 1-24

6.4.1.2 Applicant’s results

Titan’s graphs 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 Titan’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 Titan’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.

6.4.1.3 Reviewer Analysis

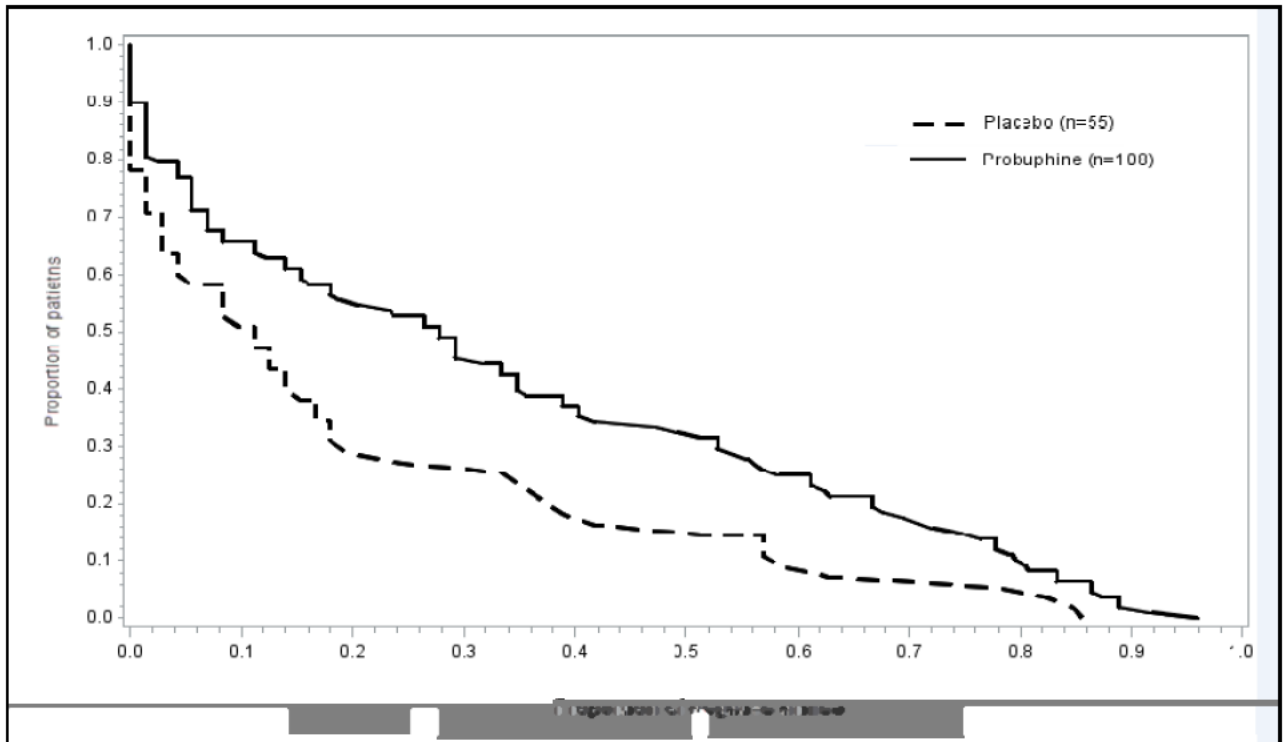
To provide a more intuitive presentation of the study results, Mr. Petullo graphed the data to illustrate the proportion of patients who submitted a particular percentage of negative tests *or better*. Thus, for any individual cutoff value (30%, 50%, 70%, etc., chosen for expedience and not because they 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.

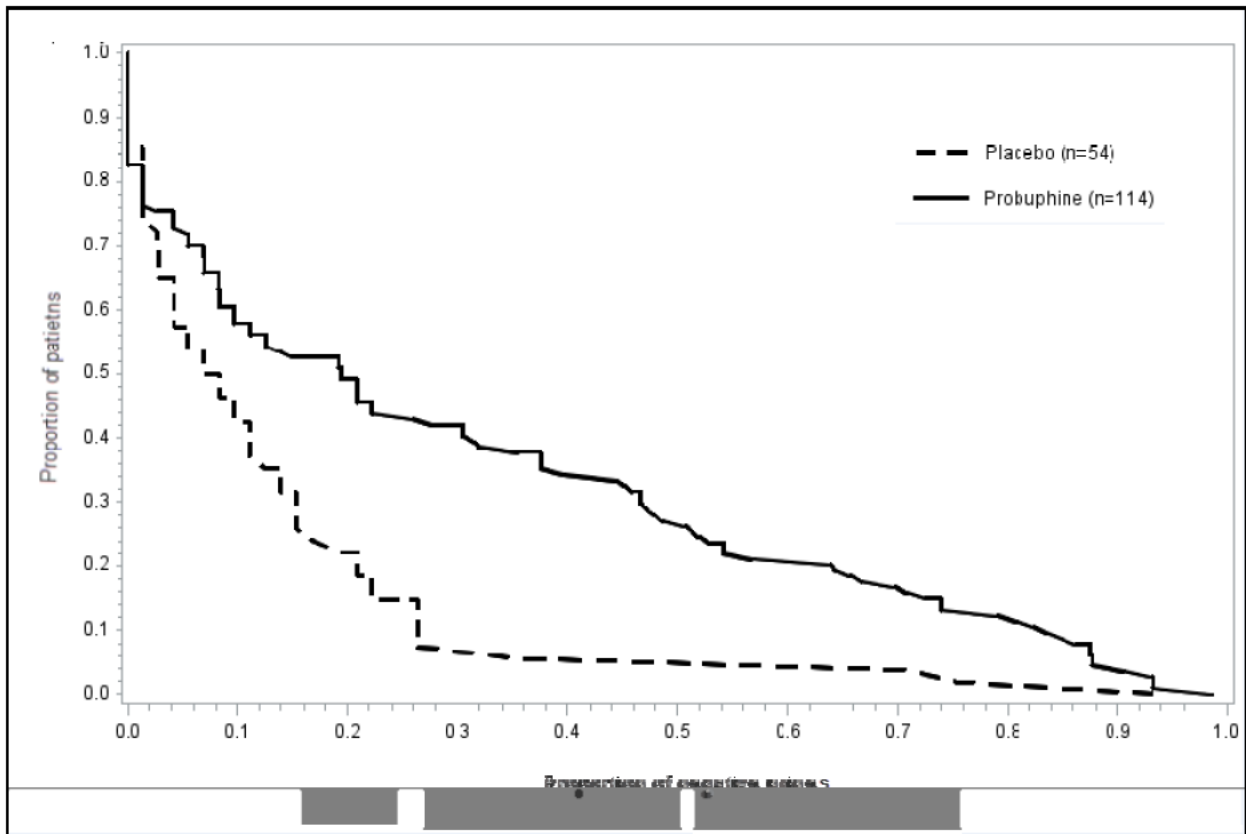
Study PRO-805: Percentage of negative urines, Weeks 1-24

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	-	-

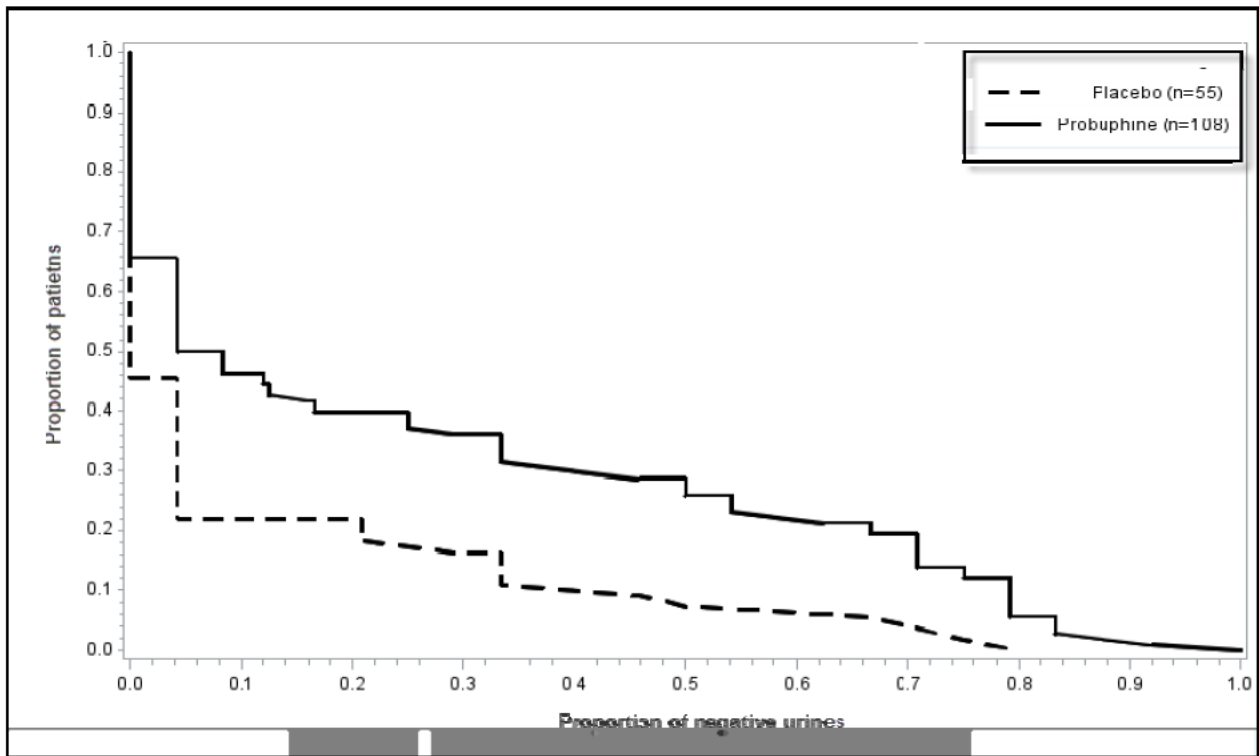
As observed in the PRO-805, the cumulative distribution function and the tabular summary demonstrate that at each given level of the percentage of negative urines, patients on Probuphine in Study PRO-806 were more likely to submit opioid-negative urines. The efficacy findings observed in PRO-805 were, 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.

6.4.2 Analysis of Urine Samples Allowing a Grace Period

In addition to the primary efficacy analyses for the time period of Weeks 1–24, Titan 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. Titan 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. CDFs of percent negative urines for the last 8 weeks of treatment (Weeks 17–24) are presented below.

Study PRO-805: CDF of percent negative urines for Weeks 17-24



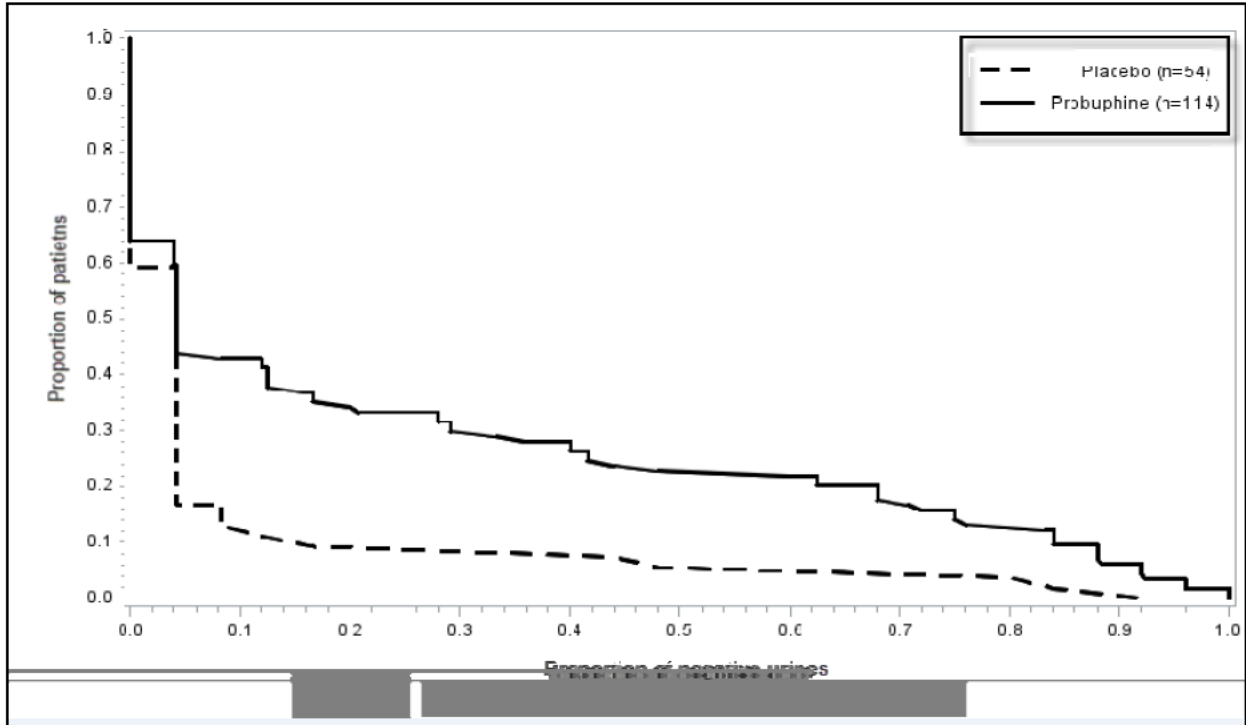
PRO-805: Percent negative urines Weeks 17-24,

Study	% Negative Urines	% of subjects	
		Probuphine	Placebo
PRO-805	≥ 30	36	16
	≥ 50	29	9
	≥ 75	14	4
	≥ 80	6	2
	≥ 85	3	-
	≥ 90	2	-
	≥ 95	1	-
	100	1	-

There was one patient in the Probuphine arm who had no positive or missing urine samples in the final eight weeks, but 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.

CDF of percent negative urines for the last 8 weeks of treatment (Weeks 17-24) for PRO-806 are shown below.

Study PRO-806: CDF of percent negative urines for Weeks 17-24



PRO-806: Percent negative urines Weeks 17-24,

Study	% Negative Urines	% of subjects	
		Probuphine	Placebo
PRO-806	≥ 30	30	9
	≥ 50	23	6
	≥ 75	16	6
	≥ 80	13	6
	≥ 85	10	2
	≥ 90	6	2
	≥ 95	4	-
	100	2	-

There were two patients in the Probuphine arm who had no positive or missing urine samples in the final eight weeks, but, like in Study PRO-805, 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.

6.4.3 Analysis Allowing for Missing Visits

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.

6.4.4 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 Buprenorphine	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.

The table below, which pools data from both efficacy studies, illustrates that over half of the patients who qualified for a fifth implant continued to require rescue medication, although their mean days of use per week and mean milligrams used per week declined.

Summary of Mean Supplemental SL Buprenorphine Use, Studies PRO-805 & PRO-806 (Intent-to-Treat Population)

	Subjects Receiving 4 Implants		Subjects Receiving 5 Implants, Before Implant		Subjects Receiving 5 Implants, After Implant	
	Probuphine	Placebo	Probuphine	Placebo	Probuphine	Placebo
Double-Blind Studies						
Total number of subjects	175	56	47	53	47	53
Number (%) of subjects requiring supplemental SL buprenorphine	65 (37.1)	33 (58.9)	47 (100.0)	53 (100.0)	26 (55.3)	42 (79.2)
Days Used/Week	0.23	0.88	2.03	3.54	0.46	2.16
mg Used/Week	2.61	10.40	23.11	37.72	6.06	25.04

Source: Integrated Summary of Efficacy, p. 58

Titan interpreted the use of rescue medication 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. 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.

Titan 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.

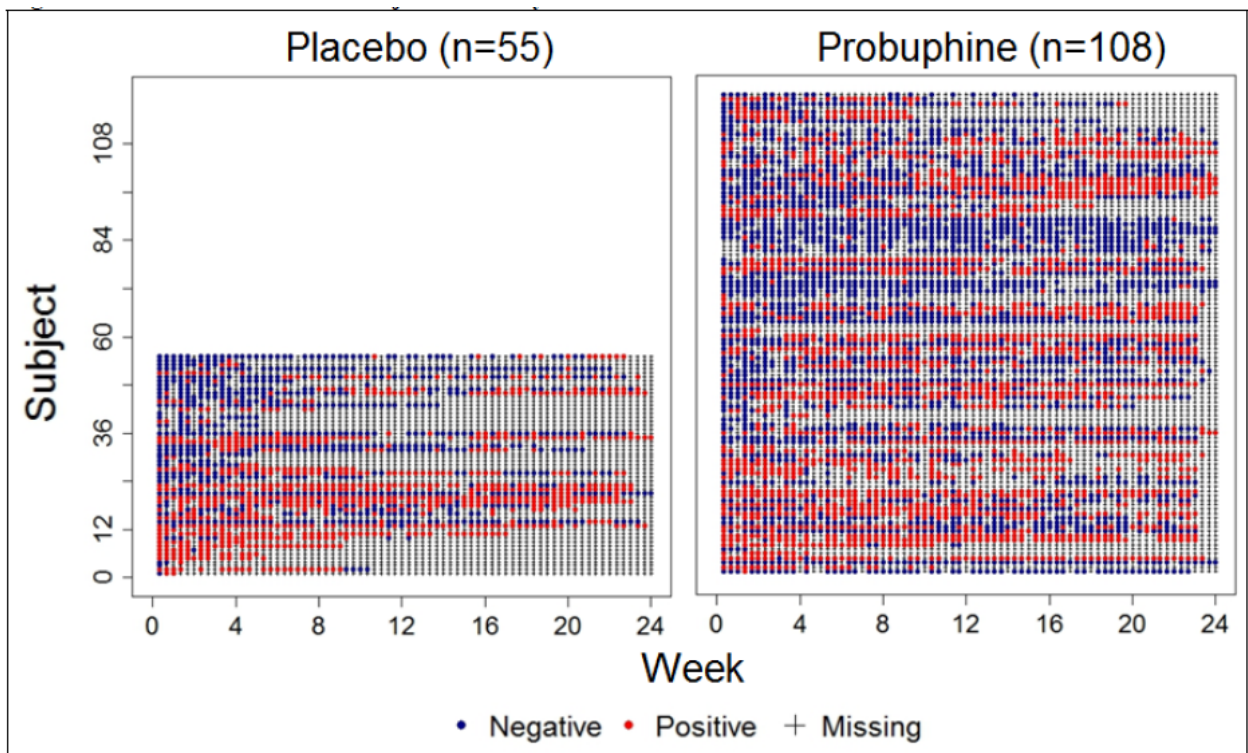
6.4.5 Graphic Depiction of Individual Patient Results

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.

6.4.5.1 Urine Test Results

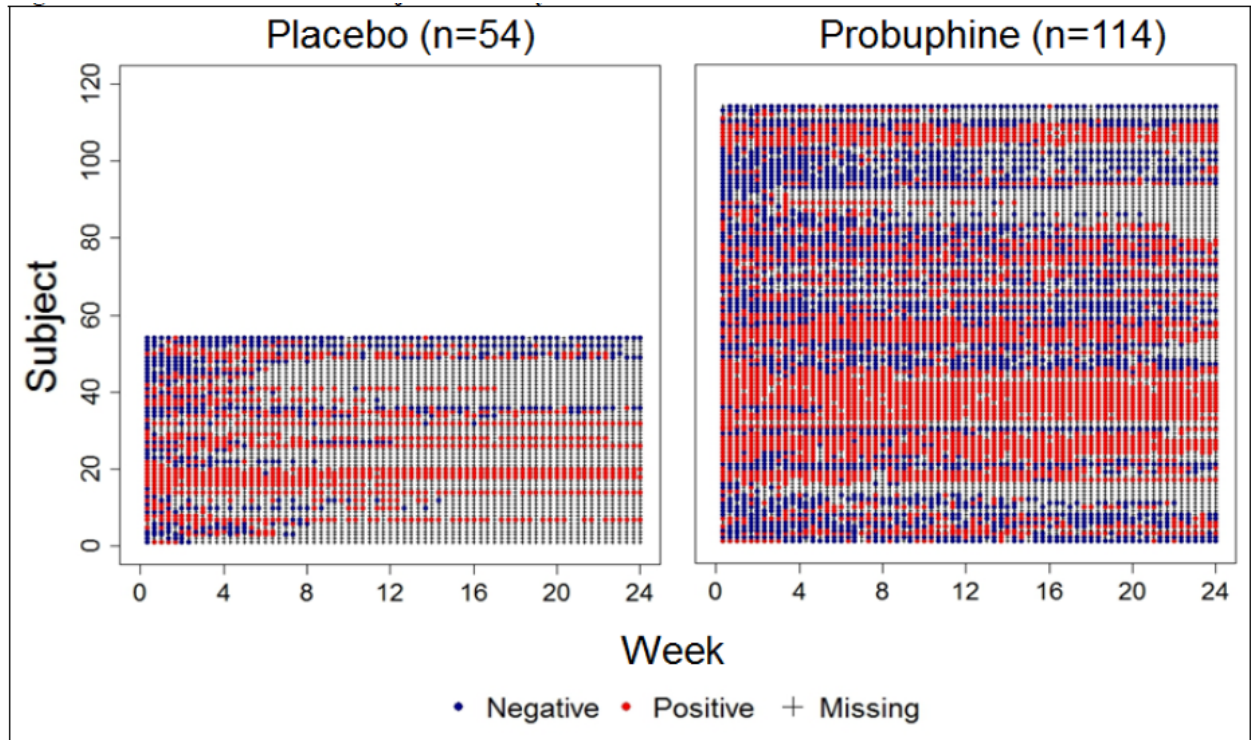
These subject-level analyses are shown below. In these presentations, each individual subject is represented along the y-axis. On the x-axis are the time points during which urine samples were collected. (In these studies, urine samples were collected three times per week). Blue dots are used to represent 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 in the past 10 years 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.

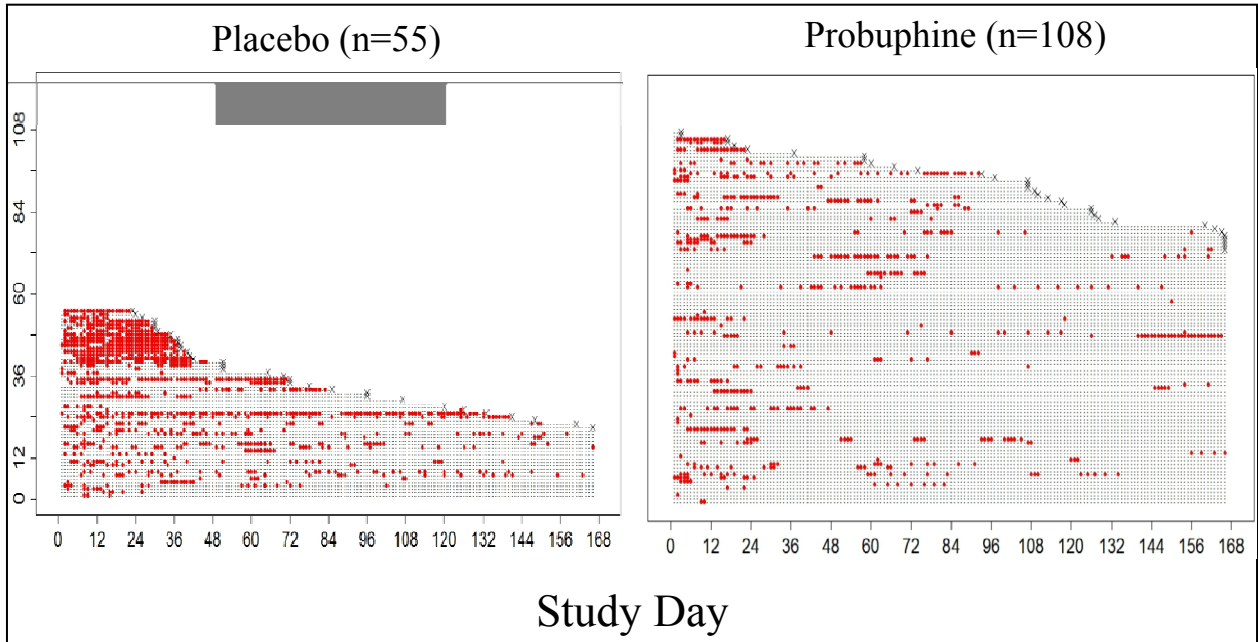
It is striking that patients in the Probuphine studies complied with regular clinic visits over six months, but the protocols may have provided some incentives for them to do so. For example, patients had the prospect of receiving rescue medication at any time and in fact continued to do so sporadically 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 check ups 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 calls into question whether the benefits of “retention in treatment” are going to accrue to these patients.

6.4.5.2 Use of Rescue Medication

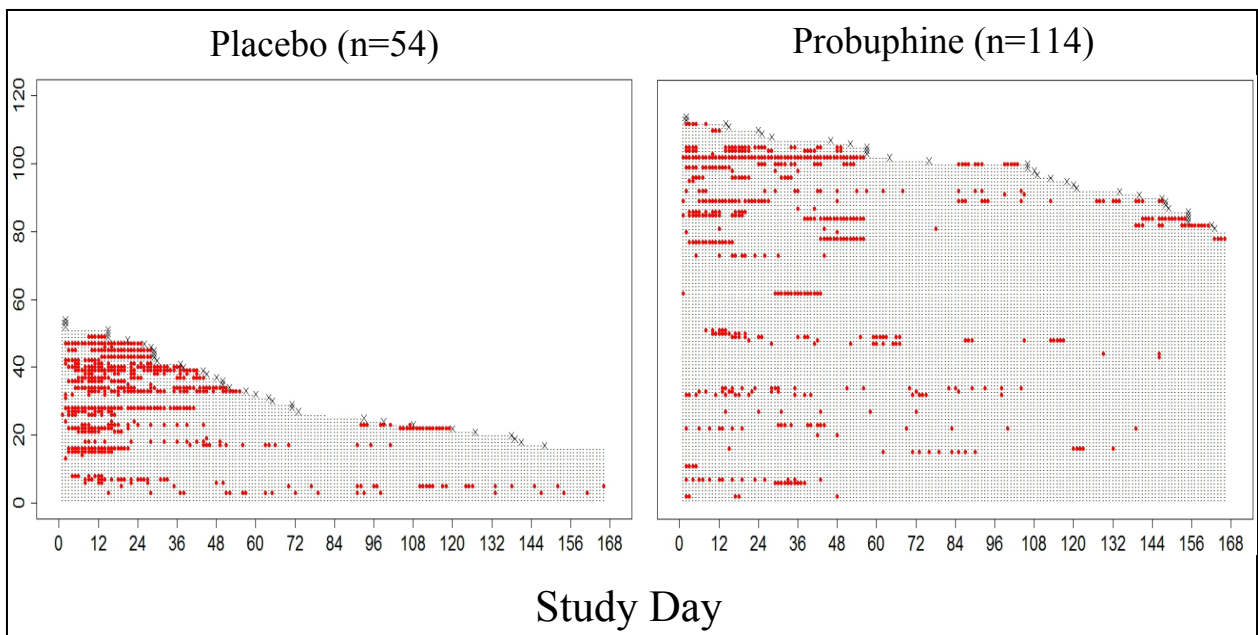
Graphic depictions of the use of rescue medication over time for individual patients are shown in Mr. Petullo’s figures, below. On the y-axis, individual patients are represented. Patients are sorted by date of discontinuation. On the x-axis are the number of days in the trial. The red dots denote any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

6.4.6 Other Endpoints

Titan assessed opioid withdrawal symptoms and craving assessments using the Subjective Opiate Withdrawal Scale, the Clinical Opiate Withdrawal Scale, and a Visual Analog Scale (VAS) for “cravings.” It should be noted that the concept of “craving” is not a well-understood or validated concept and the word may not be understood the same way by all patients.

(b) (4)
The instruments used have also not been developed or evaluated in accordance with the principles laid out in the Agency’s guidance for Patient-Reported Outcome measures. Therefore, (b) (4)
the sponsor’s findings are discussed here for completeness.

Titan found that the LS mean scores for SOWS, COWS, and VAS craving were lower in the Probuphine group compared to the placebo group overall and at weeks 1, 4, 16, and end of treatment. The differences for all measures and all time points were greater in Study PRO-806, where rescue medication was less readily-available, than in Study PRO-805.

Titan also reported results based on Clinical Global Impression instruments, assessing observer impressions of global severity of opioid dependence and global improvement of opioid dependence, and self-reported impressions of opioid use and change in opioid use. Titan conducted a responder analysis on the pooled and study-level CGI-self and CGI-observer data for Week 16 and Week 24 (end of treatment, the visit at which implants were removed). CGI-self and CGI-observer response definitions as determined by the Applicant are as follows:

- CGI-self responders: subjects providing responses of “No problems” or “Borderline problems.”
- CGI-observer responders: subjects providing responses of “No symptoms” or “Borderline symptoms.”

The amount of missing data at the Week 16 time point (as much as 75% of values are missing for the placebo arm) makes it difficult to assess the findings. At the end-of-treatment visit, 56% of Probuphine-treated patients in Study 805 were responders based on self-assessment, vs 36% of placebo-treated patients. In Study 806, the two arms were more similar, at 41% vs 37%.

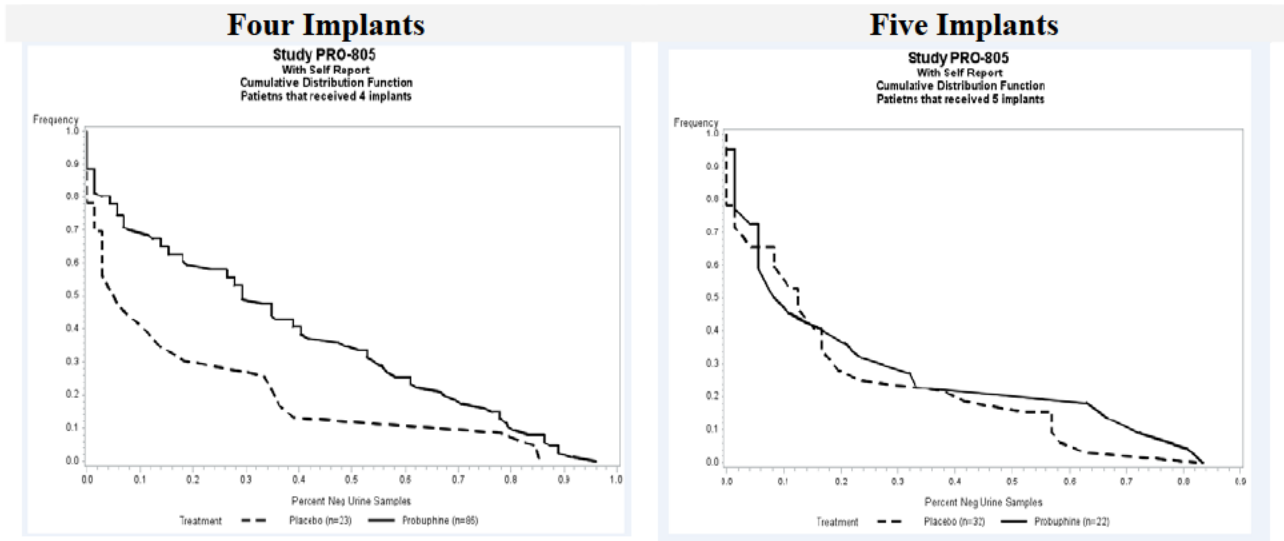
6.4.7 Efficacy Explorations in Subgroups

6.4.7.1 Patients Requiring a Fifth Implant

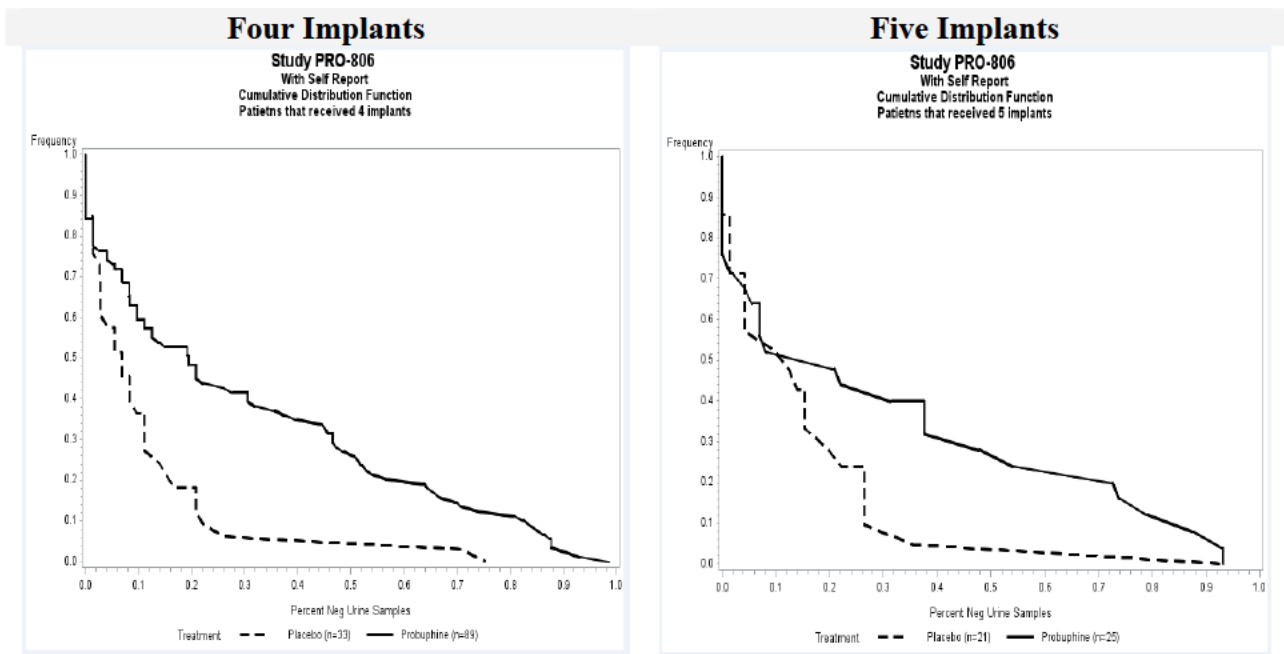
The figures below, generated by Mr. Petullo, illustrate that patients requiring a fifth implant in Study PRO-805 appear not to have benefited, with results similar to placebo-treated patients, while patients in Study PRO-806 who required a fifth implant do seem to have had better

results than placebo-treated patients. This inconsistent result may indicate that patients who do not respond to four implants may not necessarily benefit from a fifth.

PRO-805



PRO-806



6.4.7.2 Other Subpopulations

The primary efficacy endpoint was examined in various subpopulations as defined by the Applicant:

- Gender
- Age (18-35; 36-65)
- Race (White; Black; Other)
- BMI (≤ 25 kg/m²; > 25 kg/m²)
- Primary opioid of abuse (heroin; prescription opioid pain reliever)

Titan performed analysis of the CDF for each of these subpopulations using pooled data from Studies PRO-805 and PRO-806, and reported differences that were statistically significant for both men and women, both subgroups based on age, all race subgroups, and both subgroups defined by primary opioid of abuse. However, in the subset of patients with BMI > 25 kg/m² (49% of the Probuphine patients and 43% of the placebo patients) there was no statistically significant difference in the CDF ($p=0.1438$).

According to Titan, overall, Probuphine subjects with a BMI ≤ 25 tended to have higher plasma buprenorphine and norbuprenorphine concentrations than the BMI > 25 group. The differences between the two groups overall increased with time on study. By Week 24, the BMI ≤ 25 group had 35.4% higher mean plasma buprenorphine levels than the BMI > 25 group (0.696 ng/mL vs. 0.514 ng/mL) and 70.9% higher mean plasma norbuprenorphine levels than the BMI > 25 group (0.340 ng/mL vs. 0.199 ng/mL). This difference in plasma exposure seems to have been sufficient to result in a difference in outcomes. Note that sample size does not seem to be at issue here; the p value for the subset with BMI < 25 was < 0.0001 .

Titan also noted that higher plasma buprenorphine were also seen among females as compared with males receiving Probuphine. Titan concluded that taken together, the subpopulation efficacy analyses discussed here indicate that the effects of Probuphine treatment relative to placebo are the same in the overall population as in the subpopulations examined, with the exception of individuals with higher BMI values.

It must be stressed that a BMI of 25 kg/m² places a patient only in the *overweight* category. Nearly half of the enrolled patients fell into the > 25 kg/m² stratum. Data from the National Health and Nutrition Examination Survey (NHANES) reveal that The age-adjusted prevalence of overweight and obesity combined (BMI ≥ 25) was 68.8% (95% CI, 65.9%- 71.5%) overall, 73.9% (95% CI, 70.0%-77.8%) among men, and 63.7% (95% CI, 60.9%-66.4%) among women. In other words, it appears that Probuphine delivers a dose that is likely to be too low, even by the standards of the primary analysis, to treat most people.

6.5 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. Even after four months of “grace” (in other words, an analysis considering only Weeks 17-24), 1% of Probuphine-treated patients in Study 405 and 2% in Study 406 were

abstinent (vs. none treated with placebo). Allowing that successful patients might miss a visit (perhaps for commendable reasons, such as work responsibilities), we also evaluated how many patients submitted one negative urine sample in each of the final eight weeks of the study, provided self-report of abstinence, and did not submit urine samples to contradict that report. In this analysis, 6% of Probuphine-treated patients (vs no placebo-treated patients) met criteria for abstinence in Study 805, and 4% (vs 2% on placebo) met criteria in Study 806. Stretching our definition of “occasional slip up” to include patients who submitted opioid-negative urine samples on 75% of occasions in the last 8 weeks of treatment, 14% of Probuphine-treated patients met this criterion in Study 805 (vs 4% on placebo), and 16% (vs 6%) in Study 806. On the other hand, 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. Titan has argued that the results were “similar” in the open-label Suboxone arm included in Study 806. However, if Probuphine overcomes the limitations of sublingual buprenorphine by ensuring compliance, one would expect it to be *better*. Notably, it has been extremely difficult to demonstrate the efficacy of oral naltrexone in clinical trials of opiate addiction in any setting lacking enforced or supervised compliance. However, efficacy has been demonstrated using passive compliance (depot) formulations. If the dose delivered by Probuphine were equivalent to the dose delivered by Suboxone 16 mg/day, I have every expectation that the results would be dramatically better, and that superiority to sublingual buprenorphine could probably be demonstrated. 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.

6.5.1 Expected Efficacy of Buprenorphine Treatment

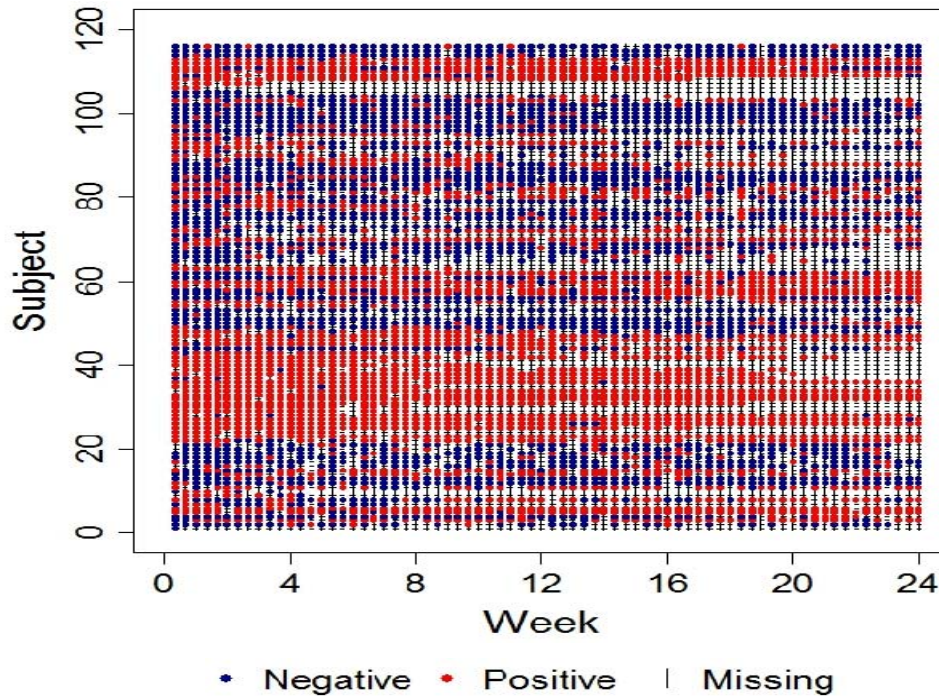
In trying to understand whether the results meet clinical expectations of “success,” I reviewed various sources in literature. The treatment guidelines provided by SAMHSA provide a flow chart that includes dose increases when a patient continues to use illicit drugs; this would imply that ongoing drug 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, I note that 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.

To provide some direct comparison to Suboxone, Titan included an open-label Suboxone arm in Study PRO-806. However, 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 received 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). Parameters of drug use were similar between the Probuphine and sublingual buprenorphine-treated arms—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.

Mr. Petullo provided a subject-level depiction of the urine test results for the open-label arm of Study PRO-806. This illustrates the disappointing results achieved.

Subject-Level Urine Test Results, Open-Label SL buprenorphine arm, PRO-806



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.

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.

6.5.2 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 was fairly widely used off-label for treatment of withdrawal, at doses of 0.1-0.2 mg.

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.

A review of the literature on the relationship between buprenorphine dose and blockade of exogenously administered opioids suggests that the plasma level of buprenorphine produced by Probuphine is simply too low. Comer (2005) evaluated the reinforcing effects of intranasal heroin under three conditions of buprenorphine/naloxone dosing. The authors note that intranasal heroin is one-fourth the potency of intravenous heroin in producing reinforcing effects, and that participants reported being willing to pay \$10-\$20 for the 40 mg dose. Various measures indicated a dose-dependent effect of buprenorphine/naloxone. The subjective effects of a 50 mg i.n. dose of heroin were blocked by 32 mg of buprenorphine but not by lower doses. The number of 50 mg i.n. doses that subjects self-administered was also reduced (but not to the level of a 0 mg sample) by 32 mg buprenorphine and not by lower doses.

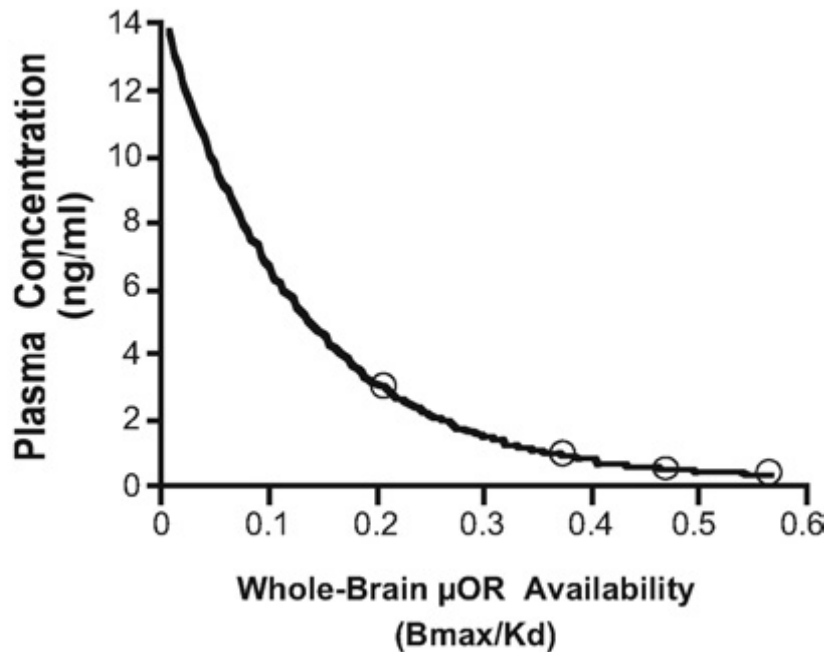
Strain et al found that “maintenance on a daily dose of 4/1 mg sublingual buprenorphine/naloxone is too low to block the effects of 12 mg parenteral hydromorphone, although daily doses as high as 32/8 mg also failed to completely block these effects.” This dose of hydromorphone was estimated by the authors to be equivalent to 80 mg morphine. This study also found that doses of 8 mg/2 mg provided attenuation, but not full blockade of

the effects of 12 mg hydromorphone, there were no significant differences among the 8/1 mg, 16/4 mg, and 32/8 mg doses.

Greenwald (2003) evaluated the ability of buprenorphine at various doses to block the effect of 24 mg hydromorphone i.m. This dose is intended to be equianalgesic to a 100 mg dose of heroin. In this study, 32 mg and 16 mg buprenorphine significantly blocked opioid agonist symptom scores and “high,” but 2 mg buprenorphine did not. This study also measured mu receptor occupancy using PET scanning, and concluded that near-maximal occupancy was achieved at 32 mg, but that the 16 mg dose yielded 85-92% occupancy. Buprenorphine dose dependently occupied 27%–47% of receptors at 2 mg/day 80%–92% at 16 mg/day, and 89%–98% at 32 mg/day.

The same lab (Greenwald 2007) continued this work to attempt to identify the extent of receptor occupancy necessary to achieve blockade of exogenous opioids. Titan made reference to this study during Advisory Committee discussions when asked why the dose of Probuphine was chosen. However, this study differed importantly in several ways from the previous Greenwald study. In the first study, participants were maintained for several days on the dose of buprenorphine and then underwent a single, 24 mg i.m. challenge with hydromorphone. In the second study, participants were maintained for at least 2 weeks on buprenorphine 16 mg/day, then buprenorphine was discontinued. PET scans were performed at 4, 28, 52, and 76 hours to determine how receptor occupancy fell over time. Then, participants were again treated with buprenorphine 16 mg/day for three days and then discontinued. Hydromorphone challenges were then given at 4, 28, 52, and 76 hours so that responses could be correlated to the receptor occupancy levels established in the first part of the study. Agonist symptoms produced by hydromorphone were blocked at 4 hours after buprenorphine was discontinued, but recovered increasingly at 28, 52, and 76 hours. However, in this study, the doses of hydromorphone were 0 mg, 6 mg, 6 mg, and 12 mg, at one hour intervals. At 4 hours after 16 mg, 70% of whole-brain opioid receptors were occupied. The authors concluded that “the threshold for suppressing agonist symptom effects of opioid challenge occurs when about 50%–60% of ORs are occupied (28 h after BUP), although additional benefits accrue when 70% of ORs are occupied (4 h after BUP). This is consistent with previous findings that opioid withdrawal symptom suppression and HYD blockade were obtained at 80% occupancy during 16 mg/d BUP maintenance but not 40% OR occupancy during 2 mg/d BUP maintenance.”

The figure below illustrates the authors’ calculation of the relationship between plasma concentration and receptor availability. It should be noted that availability and occupancy are inversely related, so that the point at which availability is 0.2 corresponds to 80% occupancy. This point is associated with a plasma level between 2 and 4 ng/ml. Recall 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.



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In a fifth study very relevant to the evaluation of the appropriateness of the dose provided by Probuphine, Sigmon et al (2005) evaluated the pharmacokinetic/pharmacodynamic relationship between buprenorphine plasma levels and the blockade of effects of hydromorphone. This study used a depot formulation of buprenorphine, and repeated hydromorphone challenges weekly. The dose of hydromorphone in this study was 3 mg, which is only one-fourth the dose used in the Greenwald studies, and the authors equate it to 10 mg morphine or 10 mg heroin—not a typical dose. In this study, responses to hydromorphone (VAS drug effect) were suppressed for the first three weeks, until the plasma level fell below 0.5 ng/ml. This suggests that the plasma levels associated with Probuphine (0.72-0.83 ng/ml) may be sufficient only to block the effects of very low doses of exogenously-administered opioids.

When asked about their dose at the Advisory Committee meeting, Titan cited the results of the second Greenwald experiment (which was not available at the time they initiated clinical development). It should be noted that the various studies do not support a single conclusion about the relationship between plasma buprenorphine levels, opioid receptor occupancy, and blockade of clinically relevant doses of opioids of abuse.

6.5.3 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 what is the relevance of control of subjective symptoms of withdrawal and “craving” 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. How is this different from other conditions, in which we 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 well being, 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 are looking at a surrogate endpoint of uncertain predictive value. At what level of ongoing drug use can we conclude that the patient's opioid addiction responding or not responding to treatment? Certain measures of other aspects of response were included in the trials, but apart from the issues of lack of validation in accordance with PRO principles, they provide little reassurance. Even if withdrawal symptoms and “craving” scores are lower in Probuphine-treated patients, as noted above, this would have little relevance if it does not translate to a change in drug-use behavior. A Clinical Global Impression of Change measure seems to have been inconsistently administered, with information collected only in a subset of patients (more at Week 24 than at Week 16).

It is possible that information can be brought to bear to support the clinical relevance of the results, but this information was not included in the application.

6.5.4 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.

6.6 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. Furthermore, Probuphine treatment at

the dose regimen studied did not demonstrate efficacy, even in Titan's own primary analysis, in patients with BMI>25; for patients requiring a fifth implant, a difference from placebo was shown in only one of the two trials.

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, and concerns about the adequacy of the dose in overweight patients (even by the standards of the primary analysis), lead me to conclude that the benefits of Probuphine, at the dose tested, are minimal. I believe that the product should be studied at a higher dose, and anticipate that significant clinical benefit would be provided by an adequate dose regimen.

7. Safety

The table below illustrates the extent of exposure to Probuphine in the development program. Just over 200 patients have been treated with Probuphine for six months or longer, and fewer than 100 have been treated for a year.

Cumulative Exposure to Probuphine in Opioid-Dependent Subjects

	Any Exposure	Months				
		≥1	≥3	≥6	≥9	≥12
Double-Blind and Extension Studies						
PRO-805/PRO-807	108	102	96	75	42	38
PRO-806/PRO-811	114	112	108	92	53	47
Open-Label Extension Study						
PRO-807/Placebo → Probuphine	12	12	11	10	n/a	n/a
PRO-811/Placebo → Probuphine	8	8	7	7	n/a	n/a
PRO-811/SL BPN → Probuphine	20	18	16	13	n/a	n/a
Clinical Pharmacology Studies						
TTP-400-02-01	12	12	12	12	n/a	n/a
PRO-810	9	8	0	0	n/a	n/a
Total	283	272	250	209	95	85

Abbreviations: SL = sublingual; BPN = buprenorphine

Source: Adapted from Cumulative Exposure to Probuphine Table submitted in Titan Response to Clinical Queries Provided by Email, Dated March 8, 2013.

The safety database from the **pooled-double blind studies** includes 450 opioid-dependent subjects:

- 222 subjects treated with Probuphine;
- 109 subjects treated with placebo; and

- 119 subjects treated with sublingual buprenorphine

In the **pooled, open-label studies**, there were 147 subjects who received open-label Probuphine treatment in these studies.

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 eight subjects on Probuphine (4%), 7 subjects on placebo (6%), and six subjects on sublingual buprenorphine (5%) 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 accidental injuries, 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.

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 6 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). 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 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 Titan 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.”

In the double-blind studies, events in the hepatic injury SMQ were reported in 8 (4%) of the Probuphine group, 7 (6%) of the placebo group, and 6 (5%) of the sublingual buprenorphine group. In the open-label studies, 10 patients (7%) had one or more event, typically increase in hepatic enzymes.

7.1.2 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 dose used 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.

Increases in QT exceeding 100 msec were observed in a number of patients. Post-baseline values exceeding 500 msec were recorded in two Probuphine-treated and two placebo-treated

patients. Neither increases or values of this magnitude were observed in patients treated with sublingual buprenorphine. Detailed tables may be found on page 171 of Dr. Skeete's review.

7.1.3 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 Titan 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, 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 study).

Additionally, 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, 478 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. Study PRO-806 provides experience with 168 insertions and 147 removals, performed by 22 physicians, using the currently-recommended techniques and equipment. An additional 85 insertions using the current methods were performed in PRO-811. 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, “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.

The table below, from Titan’s Advisory Committee backgrounder, shows the effect of the change in equipment and procedures on the overall rate of implant-site AEs.

Implant Site Adverse Events (>2% of Patients in Any Group) by Preferred Term in Double-Blind Studies PR0-805 and PR0-806

System Organ Class Preferred Term/pre-specified term*	PR0-805		PR0-806	
	Probuphine N=108 n(%)	Placebo Implant N=55 n(%)	Probuphine N=114 n(%)	Placebo Implant N=54 n(%)
Any Implant Site AE	63 (58.3)	28 (50.9)	32 (28.1)	14 (25.9)
Implant site pruritus	29 (26.9)	12 (21.8)	5 (4.4)	2 (3.7)
Implant site pain	29 (26.9)	9 (16.4)	6 (5.3)	5 (9.3)
Implant site erythema	27 (25.0)	12 (21.8)	4 (3.5)	0 (0.0)
Implant site haemorrhage	20 (18.5)	8 (14.5)	2 (1.8)	2 (3.7)
Implant site oedema	14 (13.0)	5 (9.1)	2 (1.8)	0 (0.0)
Implant site haematoma	12 (11.1)	9 (16.4)	8 (7.0)	6 (11.1)
Implant site scar	11 (10.2)	8 (14.5)	0	0
Implant site reaction	6 (5.6)	2 (3.6)	1 (0.9)	1 (1.9)
Implant site infection	4 (3.7)	1 (1.8)	0	0
Device expulsion	3 (2.8)	0 (0.0)	0	0
Impaired healing	3 (2.8)	0 (0.0)	0	0
Implant site paraesthesia	2 (1.9)	0 (0.0)	0	0
Implant site rash	1 (0.9)	1 (1.8)	0	0
Complication of device removal	1 (0.9)	0 (0.0)	0	0
Implant site dermatitis	1 (0.9)	0 (0.0)	0	0
Implant site irritation	1 (0.9)	0 (0.0)	0	1 (1.9)
Implant site cellulitis	0 (0.0)	1 (1.8)	0	0
Implant site swelling	0	0	2 (1.8)	0 (0.0)
Procedural pain	0	0	5 (4.4)	0 (0.0)
Procedural site reaction	0	0	3 (2.6)	2 (3.7)
Ecchymosis	0	0	2 (1.8)	0 (0.0)

* In study PR0-805, AEs were identified from case report forms (CRFs) and listing using a pre-specified list

In the open-label studies, rates of implant-site related AEs 45% (any AE) in PRO-807—somewhat lower than the experience in the parent study—and 14% in Study PRO-811. Many of the same clinicians participated in all the studies, so some improvement may have been based on increasing familiarity with the procedures. However, the differences between the earlier studies and the later studies provide support for the modifications to the equipment and procedures.

Procedural complications were also reviewed, with a focus on patients experiencing device extrusion or expulsion and on removals which could not be completed on the first attempt. In some patients, the Probuphine rods worked their way through the skin and either protruded partially (extrusion) or fell out (or were pulled out) altogether (expulsion). Six patients (five Probuphine, one placebo) had events of this nature. One patient (Probuphine) had multiple events of implant extrusion and expulsion and had to have her implants replaced on four

occasions. All but one of these events (the single placebo patient) occurred in studies using the original insertion tool and training procedures.

There were more difficulties with the removals than with the insertions. In 20 cases (5%), a second attempt was required to remove the implants. This represents a relatively high rate given the small numbers of procedures performed. Although most of these complications occurred in studies using the original insertion tool and removal procedures, 3% of removals in PRO-811 also required more than one attempt. 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 Probuphine implants. They are not radio-opaque. One patient required general anesthesia to complete removal.

Study Identifier	Cases Requiring a Second Attempt at Removal, N (%)
PRO-805	15 (10)
PRO-807 (PRO-805 Extension)	3 (5)
PRO-806	0
PRO-811 (PRO-806 Extension)	2 (3)

The overall experience with insertion and removal of Probuphine using the current equipment and procedures is limited to roughly 250 insertions by fewer than 25 practitioners. Because changes in equipment, techniques, and training procedures were all implemented simultaneously, it is difficult to pinpoint which of these modifications is most important in ensuring safe insertion and removal of Probuphine. The OB/Gyn participants in the Advisory Committee meeting stressed the importance of proper training, and the importance of providers performing procedures frequently and regularly to maintain their skills.

7.2 Other AEs of Interest

Titan performed SMQ searches for various terms of interest to identify signals of CNS or respiratory depression, orthostatic effects, allergic reactions, gastrointestinal symptoms, and psychiatric symptoms. Several of these are labeled effects of buprenorphine. These explorations identified certain events occurring more commonly in Probuphine-treated patients compared to placebo-treated patients, including fatigue, somnolence, nausea, vomiting, and constipation. Dizziness and orthostatic symptoms were reported at a similar rate between Probuphine-treated (8%, 5%) and placebo-treated patients (10%, 5%), but more frequently than in patients treated with sublingual buprenorphine (3%, 1%). These symptoms did not seem to be reported in association with the implant procedure.

7.3 Benzodiazepine Use

Patients who abuse buprenorphine commonly combine it with benzodiazepines, although this practice is dangerous and has been implicated in buprenorphine-related deaths. In the

Probuphine clinical trials, many patients (nearly one-third of the Probuphine group and slightly more in the comparison groups (placebo/SL buprenorphine pooled) continued to use benzodiazepines throughout the observation period, which represents a safety concern.

7.4 Common AEs

The table below, 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.

Common Non-Implant Site Treatment-Emergent Adverse Events ($\geq 5\%$ in the Probuphine group and more commonly than in the Placebo/SL BPN group) in the Pooled Double-Blind Studies

System Organ Class MedDRA Preferred Term	PROBUPHINE N=222 n (%)	Placebo/SL BPN N=228 n (%)
Any Non-Implant Site TEAE	158 (71)	158 (70)
Infections and Infestations	89 (40)	89 (39)
Upper respiratory tract infection	24 (11)	20 (9)
Nasopharyngitis	20 (9)	18 (8)
Gastrointestinal Disorders	67 (30)	54 (24)
Nausea	19 (9)	13 (6)
Constipation	16 (7)	9 (4)
Vomiting	15 (7)	10 (4)
Toothache	14 (6)	7 (3)
Psychiatric Disorders	51 (23)	56 (25)
Depression	14 (6)	8 (4)
Nervous System Disorders	52 (23)	47 (21)
Headache	33 (15)	29 (13)
Dizziness	11 (5)	6 (3)
Musculoskeletal and Connective Tissue Disorders	37 (17)	35 (15)
Back pain	17 (8)	12 (5)
Respiratory, Thoracic and Mediastinal Disorders	35 (16)	20 (9)
Oropharyngeal pain	13 (6)	8 (4)

Source: Modified Version of Post-text Table 8.2.4.1.1

8. 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. Four members of the PDAC, including two psychiatrists (one a child psychiatrist), a statistician, and a consumer representative, attended. 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. Because of the timeline, only government employees and already-appointed SGEs could be considered; over 25 addiction medicine experts were considered and/or screened before identifying individuals who did not have conflict-of-interest issues.

Key issues to be discussed at the meeting related to the clinical meaningfulness of the efficacy results, the adequacy of the safety database in characterizing the risks of the drug, and the adequacy of the sponsor's proposed REMS for managing the risks.

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.

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. Key points in the discussion included Dr. Judith Kramer noting that she was having trouble reconciling sponsor'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.." Dr. Robert Steinbrook expressed agreement with these sentiments, commenting that he would like to think that for a maintenance therapy, the percent of positive urines would be lower. Mr. Michael Yesenko, patient representative, noted that "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? I just had a shot 24 weeks ago. I just had a surgery that requires suture. Twenty-four weeks, I'm still getting positive urines?" Dr. Geri Hewitt noted that the drug "seemed to help some patients" but that she was "heartbroken" by the patients with self-reported drug use and positive tox screens. Dr. Edward Covington 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. Dr. Kramer observed that "we also want a treatment that would realize the potential from an implant such as this to really reduce opioid use maximally and

help these patients long-term. That's what's bothering me, not whether there's some evidence of efficacy. I just feel like there's not been an adequate exploration of dose. There's not been an adequate representation of a model that we can all say, well, that would work in our current system. And it's a complete uncertainty as to how it would play out. And I think that would be a terrible waste to miss our mark in trying to really make an advance here.”

Both Dr. Adam Gordon and Dr. Louis Baxter, addiction medicine providers, observed that it was not a requirement or expectation for a patient in treatment to have “totally clean urines” [paraphrasing Dr. Gordon]. Dr. Baxter observed 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 lack of information about doses other than those tested, saying “When you look at the slide that talks about percent of subjects requiring sublingual buprenorphine, you had 64 percent in PRO-805. And in PRO-806, you had 39 percent....So that's what I'm concerned about, is that we don't approve a quote, unquote, "effective dose" and find ourselves stuck with it later on and have difficulty meeting our patients' needs.”

However, none of the addiction experts provided affirmation that patients in treatment over the course of 6 or even 12 months would be considered successful if only 30% of their urine samples were opioid-negative. Several comments expressed the notion that drug use would reduce over time, but the discussion did not address the data which showed that patterns of use did not seem to change over time when patients were treated with Probuphine. An expert appearing on behalf of Titan, Dr. Andrea Barthwell, 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. And what we're looking for is to give them a steady state, addressing the tremendous biological drive to use drugs while we're beginning to work on the other aspects of their life and provide them some stability. So we're looking to start reducing their drug use, and recognizing that in this setting, patients come to treatment using every 4 to 6 hours. And on an active drug, they may reduce that use to once in a day or two times in a week, and that's a tremendous change in the way in which they're living their life early in treatment...” However, 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, “Dr. Rappaport talked about 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.”

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 their 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 implantation 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. Titan’s expert on the implantation 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. Dr. Hewitt felt that performing 8-10 procedures would render a provider fairly competent, while Dr. Espy pointed out that, for surgical procedures, 15-20 procedures are required to qualify as competent. Dr. Espy noted that certification should be reviewed if providers do not do the procedures regularly. Dr. Gordon observed that the 200-patient limit may prevent DATA-waived physicians from becoming high volume procedure providers. Dr. Espy also observed that providers should be required to have the ability to refer to someone who can do removals of deep implants, which she noted is a specialized skill typically provided at a limited number of facilities.

The participants had difficulty assessing the proposed REMS, because the proposal presented by Titan differed from the one previously provided to FDA for review. Many did express concerns about the feasibility of the treatment model. Although Dr. Laura McNicholas voiced concerns about the privacy implications of the proposed distribution system, no participants questioned the inclusion of such a system in the REMS. Dr. McNicholas, however, did say “I didn’t hear any discussion about...the breakthrough sublingual buprenorphine and how that

will be addressed and physicians educated, and minimize the use of that as part of the REMS procedure.”³

8. Pediatrics

Although Titan, the sponsor of Probuphine, 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)

An assessment of the feasibility of conducting studies in adolescents, ages 12 to 16 years, with opioid dependence, was recently and reviewed by the Pediatric Review Committee (PeRC), after which the sponsor of that application was granted the full waiver from the requirement for pediatric studies.

Therefore, DAAAP believed that a full waiver would be more appropriate as the population of treatment-seeking, opioid-dependent adolescents has not changed considerably since the time of the feasibility assessment. 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.

9. Other Relevant Regulatory Issues

11.1 Risk Evaluation and Mitigation Strategy

Titan initially submitted a REMS proposal which had the following goals:

- To maximize effective Probuphine therapy by optimizing the following:
 - patient selection,
 - patient monitoring,
 - insertion and removal procedures by educating healthcare professionals, (Drug Abuse Treatment Act [DATA 2000]-waived physicians and other healthcare providers trained by Titan to perform the Probuphine insertion and removal procedures),
 - implementing a closed process to adequately control distribution and dispensation.

³ It should be noted that the notion of minimizing the use of sublingual buprenorphine is not likely to be included in the REMS program because this would prevent necessary dose-adjustments in patients who are not responding sufficiently to treatment. However, physicians prescribing sublingual buprenorphine would do so under the applicable REMS for those products.

- To ensure safe use of Probuphine by minimizing the risk of misuse, abuse, diversion, accidental poisonings, overdose and complications related to Probuphine and the insertion and removal procedures.

The components of the REMS included a Medication Guide (MG), Communication Plan (CP), Elements to Assure Safe Use (ETASU) and an Implementation System. The ETASU called for health care providers to be certified after participating in a company-sponsored training program, and described the use of a central pharmacy to dispense Probuphine directly to providers within a closed distribution system to ensure that the prescriber was DATA-waived and the implanting practitioner was REMS-certified. The model of care envisioned that a DATA-waived prescriber could transmit a prescription for a specific patient to the central pharmacy, who would then ship the product to the prescriber or to a different person who would perform the implantation procedure. Probuphine would also have to be removed by a REMS certified prescriber, and used Probuphine would be disposed of in medical waste.

The DRISK team identified a number of concerns with the initial proposal, noting that certain aspects do not conform with the requirements of the Controlled Substances Act. For example, a pharmacy cannot ship the prescription to the physician; it must go to the patient. (A distributor may ship product to a physician for stock supply.) Moreover, there is some lack of clarity over how the used implant (which contains considerable residual drug) should be disposed of. There were also a number of concerns with the model of care. A number of changes to the proposal have been made by Titan, who presented a revised (and not-yet-reviewed) version of the REMS at the Advisory Committee meeting. DRISK has not yet completed a review of the most recent version of Titan's proposal, which now incorporates distribution of product from a distributor to the implanting physician.

It is currently envisioned that the REMS will primarily address the need for health care providers implanting and removing Probuphine to be properly trained and to maintain their familiarity with the procedures. A closed distribution system to ensure that only REMS-certified providers perform the procedures is desirable. Input from the Office of Chief Counsel and Office of Regulatory Policy is currently pending to advise whether any provisions in the Controlled Substances Act or the DATA 2000 preclude FDA from requiring that providers undergo training in the implantation procedures or from implementing a closed system to ensure this.

11.2 Medication Errors Prevention

A Training and Certification Program has been developed by the Applicant and was intended to ensure that clinicians who performed the implant insertion and removal procedures met competency standards and to improve the overall safety of the implant and removal processes. No specific testing of the training program or procedures was included with the NDA; Titan's position was that the procedures were pilot-tested and validated in Studies 806 and 811.

The Division of Medication Error Prevention and Analysis (DMEPA) and the team in CDRH responsible for Human Factors studies were consulted to review issues related to the training program, instruction materials, and directions for use.

Initially, based on the understanding that the product and procedures were essentially the same as Norplant, the review team did not feel that a human factors study or user-performance assessment would be required to support the NDA. However, in the course of review, it became apparent that:

1. The removal procedure differed substantially from the established procedure for removing Norplant, and there was a paucity of clinical experience with this specific procedure, and in training practitioners to perform it, and;
2. The provider population that would be performing the procedures differed substantially from the provider population that inserts and removes Norplant and other implantable contraceptives.

After these points became clear, the DMEPA team felt that the sponsor should provide a comprehensive use-related risk analysis for the product. This analysis should include a comprehensive evaluation of all the steps involved in using the device (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk-mitigation strategies employed to reduce any moderate or high risks to acceptable levels, and the method of validating the risk-mitigation strategies.

11.3 Financial Disclosure

During the OSI inspection of one of the clinical sites, the inspector learned (b) (6)



11.4 Reference to Previous Agency Findings under §505(b)(2)

Titan has referenced both Subutex (NDA 20732) and Suboxone (NDA 20733) in this application, intending for their application to rest in part on the agency's previous findings of safety and efficacy for buprenorphine in these referenced applications. However, both Subutex and Suboxone (tablets) have been withdrawn by the manufacturer, Reckitt Benckiser, from US marketing. The manufacturer states that the withdrawals were for safety reasons. DAAAP has provided the Office of Regulatory Policy with responses to requests for consultative opinions on these marketing discontinuations, and does not believe that either product was withdrawn for reasons of safety, but the Agency has not yet published a relisting determination in the Federal Register.

11.5 Office of Scientific Investigation Inspections

OSI inspections of six clinical sites (most of which served as sites for both studies) were completed. Three sites were each issued a Form FDA 483 citing inspectional observations and preliminary classifications for each of these inspections are Voluntary Action Indicated (VAI). Although regulatory violations were noted, they were deemed unlikely to significantly impact

primary safety and efficacy analyses. The rest of the sites were not issued a Form FDA 483; the preliminary classifications are all No Action Indicated. Final classifications are pending for all sites.

11.6 Abuse Liability

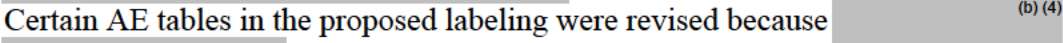
Stephen Sun, M.D. of the Controlled Substances Staff, reviewed the application to evaluate the potential for abuse of Probuphine. Review of adverse events from the clinical trials did not provide any new information to modify the understanding of the effects of buprenorphine. No patients attempted to deliberately remove the implants. However, it is noted that this is possible, and that *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. 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.

10. Labeling

The proprietary name, Probuphine® (buprenorphine HCl implant), was found to be acceptable by DMEPA and OPDP.

The following represent major changes to the sponsor's proposed labeling recommended by the review team:

- Changes were made to the wording of the indication to more clearly identify the population for which the product is intended.
- The Dosage and Administration section did not include any information about providing buprenorphine rescue medication after the initial dose-titration period. The language was modified to indicate that patients might require such treatment and that clinical supervision should be provided to determine when rescue doses should be prescribed.
- Diagrams and photos showing some, but not all, of the steps of Probuphine insertion and removal were included in the proposed labeling. Some discussions are ongoing about how to provide the necessary information without creating a confusing label (and without providing a road map for practitioners who are not REMS-certified). At present, we are exploring placing much of this material on a website that would be maintained as part of the REMS.
- The clinical trials section was revised to provide (b) (4)

- Certain AE tables in the proposed labeling were revised because (b) (4)
 as proposed by Titan, did not seem to be a helpful way to present information about procedural complications.

- Additional information on the use of buprenorphine in pregnancy is proposed by the Maternal Health Team, based on literature review, to provide more up-to-date language reflecting clinical experience accumulated since initial approval of the sublingual tablets.

Review of carton and immediate container labels identified problems that have not been resolved as of this writing, including revisions to the presentation of the strength and the established name. Additionally, one presentation is labeled (b) (4) (containing four implants” and one is labeled (b) (4). It would be more appropriate to identify the four-implant kit as (b) (4).

The Medication Guide has not yet been reviewed. No comments have been received from OPDP or patient labeling teams, because labeling discussions were suspended when it became apparent that pieces related to the REMS would not be available for review. DMEPA also deferred comment on physician training materials pending finalization of the REMS.

11. Recommendations/Risk Benefit Assessment

I am unable to recommend approval of this supplement. I recommend a complete response letter be sent.

The protocol-specified primary endpoint, the cumulative distribution function of opioid-negative urine samples, was agreed upon with Titan out of concern that successful patients not be incorrectly adjudicated as unsuccessful because of too-stringent definitions of success. The CDF approach allows comparisons across all possible definitions, but the intention was not to adjudicate unsuccessful patients as successful. Although the CDF curves were statistically significantly different between the Probuphine and placebo groups, it is difficult to conclude that Probuphine increased the proportion of patients who attained a pattern of drug use that can convincingly be called successful treatment.

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. Furthermore, Probuphine treatment at the dose regimen studied did not demonstrate efficacy, even in Titan’s own primary analysis, in patients with BMI>25; these patients represented nearly half of the enrolled population and nearly two-thirds of the US population. For patients requiring a fifth implant, a difference from placebo was shown in only one of the two trials.

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, and concerns about

the adequacy of the dose in overweight patients (even by the standards of the primary analysis), lead me to conclude that the benefits of Probuphine, at the dose tested, are minimal. I believe that the product should be studied at a higher dose, and anticipate that significant clinical benefit would be provided by an adequate dose regimen. Alternatively, the product might be studied in patients whose buprenorphine requirements are lower. Ideally, patients who are already stable, with established abstinence and stable “recovery,” who have less need for close clinical supervision, would be studied. These would be ideal patients for a product which permits only rare interaction with the prescribing physician.

Although the adverse event experience in the Probuphine development program did not identify new concerning safety issues related to buprenorphine, there are existing concerns which would apply to Probuphine. These include a risk of hepatic injury; the possibility of allergic reactions including anaphylaxis; a signal for QT prolongation; a risk of CNS and respiratory depression, particularly when combined with other depressants; as well as risks of general opioid effects such as orthostatic symptoms. Common adverse events such as nausea, vomiting, and constipation are also associated with buprenorphine and were seen in the Probuphine trials.

Additionally, Probuphine places patients at risk of adverse events and complications attributable to the implantation and removal procedures, and the presence of the indwelling implant. Even in this very small database (just over 200 patients have been treated with Probuphine for six months or longer, fewer than 100 have been treated for a year, and only about half of these were treated using the current implantation/removal techniques, equipment, and training procedures), there were reports of implant site infections, implants extruding through the patient’s skin, deep implantations, and complicated removals requiring more than one attempt, including one case that required general anesthesia. It can be anticipated that the experience of the implant physicians at the clinical sites represents a best-case scenario. Although the Advisory Committee experts were confident that providers could learn the procedures, they did note that training and procedure volume were both essential to attain and maintain competence. If Probuphine can only be inserted by DATA-waived physicians, the 100-patient limit may make it difficult for providers to maintain competence through high volume of procedures.

Finally, buprenorphine can be readily extracted from Probuphine implants. Used implants contain 40% of the original dose. Therefore, this product may be subject to diversion for purposed of abuse before implantation or after removal, or even, conceivably, could be deliberately removed by the patient or someone else.

The following deficiencies should be addressed. In my view, these should be required before approval.

1. Justification of the clinical benefit associated with minor changes in drug-taking behavior
Titan should provide some data or analysis supporting the clinical benefit of patterns of drug use typically observed in the clinical trials. I am not aware of datasets that would provide this information, particularly because most treatment datasets would be complicated by the setting of care, in which frequent visits and clinical contacts are an

integral part of treatment, which is not envisioned to be the case with Probuphine. However, Titan may know of sources of information relevant to this issue.

Alternatively, the two studies described below should be performed.

2. Opioid blockade study

A study should be conducted to evaluate the ability of Probuphine to provide opioid blockade of relevant doses of agonists, to confirm that adequate doses are studied in clinical trials.

3. Study of higher doses of Probuphine

Titan should study substantially higher doses of Probuphine, ideally doses more closely approximating the plasma levels associated with sublingual doses of 12-16 mg/day. Body Mass Index (BMI) should be examined as part of dose finding exploration to ensure that a dose appropriate for a range of patient sizes is identified. The current dose was ineffective, even by Titan's analysis, in patients with BMI>25 (about half the study population and about 2/3 of the US population in general). Ideally, the study should be a double-blind, double-dummy comparison to sublingual buprenorphine, which should be provided under more realistic dosing conditions.

The following are also needed:

4. Human factors usability evaluation

There is a paucity of clinical experience with the Probuphine insertion, and in particular, removal procedure, and with training practitioners to perform it. The provider population that would be performing the procedures differs substantially from the provider population that inserts and removes Norplant and other implantable contraceptives.

Titan should conduct a comprehensive use-related risk analysis including a comprehensive evaluation of all the steps involved in using the device, the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk-mitigation strategies employed to reduce any moderate or high risks to acceptable levels, and the method of validating the risk-mitigation strategies.

5. Risk Mitigation and Evaluation Strategy

A final REMS, acceptable to the DRISK team, which complies with relevant legal and regulatory requirements for Controlled Substance handling and office-based buprenorphine treatment, must be submitted. This REMS should include provisions to ensure that Probuphine procedures are performed only by providers who have been trained in the techniques and demonstrate competence, and who maintain their competence through adequate volume of procedures or through periodic retraining.

The following deficiencies could be addressed as Post-Marketing Requirements (or, in the case of the study in other populations, as a Post-Marketing Commitment).

6. Re-use of previously used implant sites/PK at 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. Titan should study the implantation of Probuphine into previously-implanted sites.

It may also be necessary, should this study reveal that sites cannot be re-used, to study other sites besides the arm.

7. 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.

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

Titan 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.

9. Study of Probuphine in patients with lower sublingual buprenorphine requirements

Titan should study Probuphine in other patient populations who may be more suitable. The current dosing regimen of Probuphine may well be appropriate for some patients. In particular, it may provide an adequate dose for patients who are in long-term, stable, recovery and are maintained on low (6 mg or less) doses of sublingual buprenorphine. These patients require less close clinical supervision and clinical interaction than patients early in treatment, and are likely to be the ideal candidates for a drug product which permits very infrequent contact with the treatment provider.

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APPENDIX A: Insertion and Removal Procedures for Probuphine.

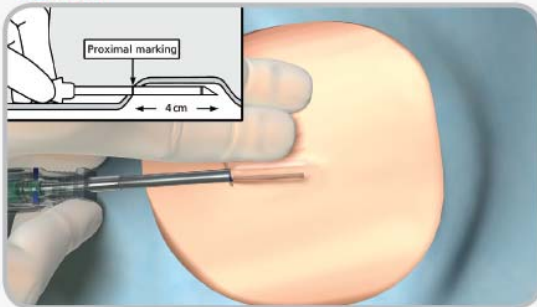
Both procedures begin with locating the appropriate site and obtaining local anesthesia. These steps are omitted below.

Insertion

Insertion is accomplished by making an incision perpendicular to the direction the implants will lie. Relevant sections of the instruction brochure are shown below.

Step 11. Lift the edge of the incision opening with a toothed forceps and create a 2.5-3 mm opening in the subdermal plane with a mosquito forceps. While applying counter-traction to the skin, insert only the tip of the applicator at a slight angle (no greater than 20 degrees), bevel up, into the subdermal space, with the obturator locked fully into the cannula (*Figure 16*). 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. 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 17*).

Figure 17



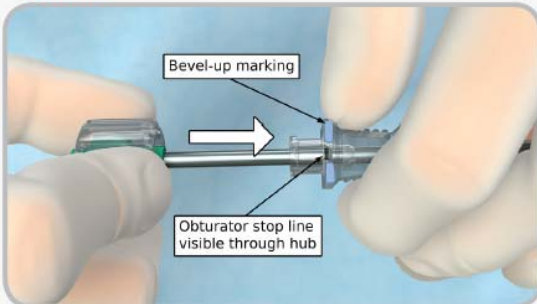
Step 12. While holding the cannula in place, unlock the obturator and remove the obturator.

Step 13. Insert one implant into the cannula (Figure 18), 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 marking**, which indicates the implant is positioned at the tip of the cannula (Figure 19). **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 18

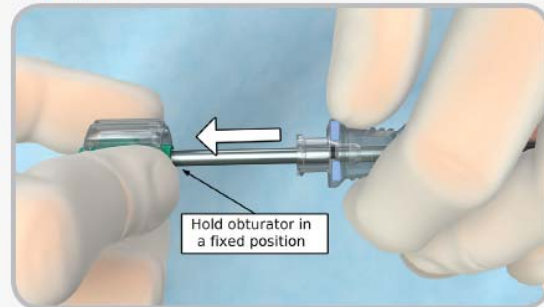


Figure 19



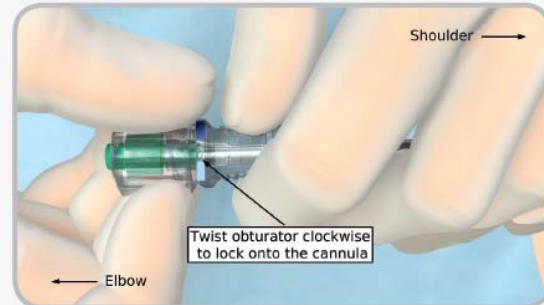
Step 14. While holding the obturator fixed in place on the arm (Figure 20), retract the cannula along the obturator, leaving the implant in place. **Note: do not push the obturator. By holding the obturator fixed in place on the arm and by retracting the cannula, the implant will be left in its correct subdermal position.**

Figure 20



Step 15. Withdraw the cannula until the hub is flush with the obturator, and then **twist the obturator clockwise to lock onto the cannula** (Figure 21). The applicator can now be removed.

Figure 21



Step 16. Always verify the presence of the implant by palpation in the patient's arm immediately after insertion (Figure 22). By palpating both ends of the implant, you should be able to confirm the presence of the 26 mm implant. If you cannot feel the implant or are in doubt of its 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-XXXX.*

Removal

Removal is accomplished by making an incision parallel to the implants. (Note: this differs from the customary method of removal of Norplant implants.) Relevant sections of the instruction brochure are shown below:

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 24*). 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 25*). **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 24

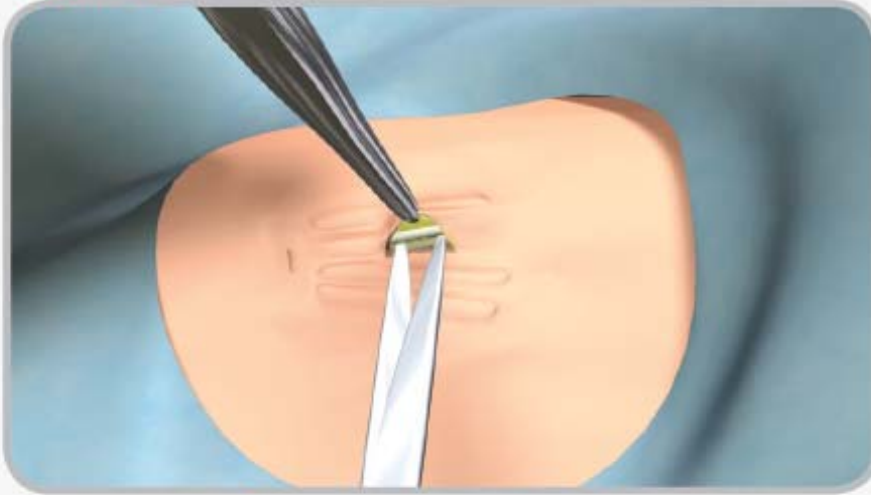


Figure 25



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.

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/s/

CELIA J WINCHELL
04/17/2013

CLINICAL REVIEW

Application Type NDA
Application Number(s) 204442
Priority or Standard Priority

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Reviewer Name(s) Rachel Skeete, MD, MHS
Review Completion Date April 7, 2013

Established Name Buprenorphine implant
(Proposed) Trade Name Probuphine
Therapeutic Class mu-opioid receptor partial
agonist
Applicant Titan Pharmaceuticals Inc.

Formulation(s) Subdermal implant
Dosing Regimen Four 80-mg implants every 6
months following a $\geq$ 3-day
induction with SL
buprenorphine

Indication(s) Maintenance treatment of
opioid dependence

Intended Population(s) Opioid-dependent adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

New Drug Application, NDA 204442, is recommended for Complete Response. The Applicant recently submitted a substantially-revised Risk Evaluation and Mitigation Strategy (REMS) that did not permit review within the timeframe allotted for this NDA review cycle. The REMS has important bearing on the risk-benefit assessment, particularly with respect to the training procedures and the model of care that will be used for Probuphine in clinical practice. These in turn, have bearing, respectively, on procedural safety for this surgically-implantable product in the hands of operators who may not have suitable training and may not practice in suitable environments to perform the insertion or removal procedures, or to manage complications, and in light of this patient population. The model of care is important for an assessment of the advantages that Probuphine is alleged to have with respect to diminished risk of abuse, misuse, and diversion.

Additionally, although efficacy was demonstrated in two controlled trials, the findings were driven by minor changes in drug-taking behavior, whereas what patients and health care providers envision as treatment success, and what was anticipated before the Phase 3 trials were conducted, is that more substantial changes in drug-taking behavior would be achieved. It is conceivable that even minor changes in drug-taking behavior may translate to clinical benefit for the patient, but no discussion or justification to that effect was provided by the Applicant.

1.2 Risk Benefit Assessment

Probuphine[®] is a subdermally implantable formulation of buprenorphine that is intended to provide sustained delivery of buprenorphine for 6 months. This new drug application provides efficacy and safety data intended to support the use of Probuphine for maintenance treatment of opioid dependence, when used as part of a complete treatment program to include counseling and psychosocial support and following induction with sublingual buprenorphine.

Two 24-week Phase 3 safety and efficacy studies were completed to evaluate the efficacy of Probuphine for the maintenance treatment of opioid dependence. In these studies, opioid-dependent patients who had not received treatment for opioid dependence within the previous 90 days, first underwent sublingual buprenorphine induction over a period of 10–16 days, during which they had to be stabilized on 12–16 mg of sublingual buprenorphine for at least 3 consecutive days. Sublingual buprenorphine was discontinued and Probuphine or placebo implants were inserted into the inner upper arm of the patients during an in-office procedure. Implants were indwelling for six months, and were removed in a subsequent in-office procedure. (One

dose increase to add one additional implant was permissible when certain protocol-specified conditions based on use of rescue medication were met). Study treatment was administered in conjunction with standardized, manual-based psychosocial support. All patients were allowed to receive sublingual buprenorphine when certain protocol-defined criteria were met.

The primary efficacy analysis compared the cumulative distribution function (CDF) of the percentage of urine samples negative for opioids in the two treatment groups. Urine samples were collected three times per week. 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, which over the 24 week period amounted to 72 urine samples. Subjects were also asked about their use of illicit opioids approximately every two weeks. If a subject reported opioid use for the past two weeks, any negative urine tests were considered positive for those two weeks. A significant difference was noted between the response profile for placebo and Probuphine in favor of Probuphine for both studies. However, there were no subjects submitting all opioid-negative urines and the largest differences were seen for percentages of negative urines of 30% or better. In other words, 45% of patients treated with Probuphine submitted $\geq 30\%$ opioid-negative urine samples compared with 27% of the subjects on placebo in the first study. As mentioned, no patients submitted 100% opioid-negative urine samples, and 1% and 2% of the subjects on Probuphine submitted $\geq 95\%$ and $\geq 90\%$ opioid-negative urine samples compared with none on placebo. In short, the statistically-significant findings are driven by differences seen among patients who are submitting opioid-negative urine samples approximately one-third of the time, across a period of 24 weeks. A similar pattern was observed in the second study. While efficacy based on the primary endpoint was established in the first trial and replicated in the second trial, it is not clear that these findings translate to any clinically-meaningful benefit for the patient.

Buprenorphine in sublingual form is currently approved for the maintenance treatment of opioid dependence. The target dose for maintenance treatment is 16 mg once daily. Based on a steady-state comparison between Probuphine and the approved treatment at 16 mg/day, the relative bioavailability of Probuphine is approximately one-third that of sublingual 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 substantially lower exposure available with Probuphine may limit the efficacy of the drug as a consequence of providing what may be subtherapeutic levels of buprenorphine for a substantial number of patients. It should be noted that in the first study, 10% of Probuphine-treated patients compared with 5% of placebo-treated patients submitted $\geq 80\%$ opioid-negative urines, and for $\geq 85\%$, it was 6% and 2%, respectively for Probuphine and placebo. It is in this gray area that the efficacy or lack thereof is unclear. Additionally, it is not clear if these patients required rescue medication, because if so, Probuphine offered some buprenorphine exposure but not

enough to obviate the need for sublingual buprenorphine. If a patient's rescue needs are substantial throughout treatment, the advantages of Probuphine are questionable.

In the risk-benefit calculation, the clinical landscape in which this drug would be used is taken into consideration. It is important to bear in mind that there are not many pharmacologic treatments available for the treatment of this serious disease of opioid dependence. Additionally, because this is an implantable formulation of buprenorphine, it eliminates the daily decision that patients must make to take treatment for the addiction or take the substance that the addiction drives them to take. This so-called "passive compliance" could be of great benefit early on in treatment when the drive to use illicit opioids is conceivably strongest. Although this appears to be a tremendous advantage, it is not clear if there is benefit to a patient potentially passively complying with a dose that is too small to help patients achieve abstinence or near-abstinence. On the other hand, one could argue that a reduction in opioid use, even if abstinence or near-abstinence is not achieved, is of some benefit. This could certainly be the case when considering HIV risk and other risks associated with injection drug use. Lastly, this formulation could potentially diminish the risk of abuse, misuse, and diversion, a burgeoning epidemic in the US, by diminishing the use of sublingual formulations of buprenorphine.

Advisory committee consultation was sought for this application, and a meeting of the Psychopharmacologic Drugs Advisory Committee was held on March 21, 2013 to discuss the efficacy and safety data for Probuphine for the maintenance treatment of opioid dependence. The majority of the committee voted in favor of approving this drug product. Although the committee had concerns about inadequate dose-finding, and the unresolved issues pertaining to the Risk Evaluation and Mitigation Strategies, because there are few pharmacologic treatment options available for opioid dependence, because this formulation offers the advantage of "passive compliance", and because efficacy was demonstrated relative to placebo, the committee voted in favor of approving Probuphine for the maintenance treatment of opioid dependence. That being said there was no consensus from the committee about whether efficacy based on analysis that was driven largely by patients who were still using opioids 50 – 70% of the time, (though fewer patients in the treatment arm than in the placebo arm were using at this level), over the course of a six-month period can be considered treatment success. At the same time, there was also no indication that there were concerns among the committee members about the efficacy findings. In truth, there aren't much data available, either clinical trial data or epidemiologic, providing evidence on what a clinically-meaningful change in drug-taking behavior is. In short, when compared to placebo, efficacy was demonstrated, but the clinical meaningfulness of these findings remains uncertain.

The Applicant's submission included pooled safety data from the aforementioned Phase 3 safety and efficacy studies, which was supplemented by data from two follow-on extension studies to each of the primary Phase 3 safety and efficacy studies. As

Probuphine is an implantable formulation of buprenorphine, the safety evaluation focused on the systemic effects from exposure to buprenorphine, the active ingredient, and procedural safety issues associated with insertion and removal procedures. The safety profile of buprenorphine has been fairly well-characterized, and given that Probuphine provides much lower exposure to buprenorphine than the antecedent sublingual formulations, Probuphine could potentially have a more favorable safety profile. As anticipated, review of the Probuphine safety data did not identify systemic safety concerns beyond those consistent with the established safety profile of buprenorphine. Similarly, there were few difficulties with insertion, but a greater number of removal difficulties. It is believed, however, that with appropriate training and if enough procedures are performed, the implanting clinician can become adept at the procedures and safely insert and remove the implants.

Long-acting implantable formulations of agonist treatments for opioid dependence are not currently available in the US. This presents another potential treatment option in the armamentarium available to health care providers to enhance the likelihood that a small subset of patients can have sustained treatment of this disease. The safety profile is considered fairly well-characterized, but the strategies to minimize the risks associated with the procedures have not been evaluated, nor has the model of care which impacts some of the potential advantages of Probuphine, and the assessment of said advantages.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Applicant submitted a proposed REMS with the original NDA submission, but subsequently submitted a substantially-revised REMS proposal, upon learning that the original proposal was not in compliance with controlled substance regulations. The newly proposed REMS was submitted shortly before the writing of this review. The late submission did not permit review during the review cycle for this NDA. Discussions at the advisory committee meeting highlighted the need to ensure that those performing insertion and removal procedures are adequately trained.

1.4 Recommendations for Postmarket Requirements and Commitments

Postmarketing Requirements

1. Human factors usability evaluation

Probuphine requires insertion and removal procedures for administration similar to that used for Norplant. During the development program for Probuphine, the Applicant revised the surgical procedures for removal and modified the associated training program. The new removal procedure differs substantially from the established procedure for removing Norplant, and there is a paucity of clinical experience with this specific procedure, and in training practitioners to perform it.

The provider population that would be performing the procedures differs substantially from the provider population that inserts and removes Norplant and other implantable contraceptives.

Consequently, a comprehensive use-related risk analysis should be conducted for the product. This analysis should include a comprehensive evaluation of all the steps involved in using the device (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk-mitigation strategies employed to reduce any moderate or high risks to acceptable levels, and the method of validating the risk-mitigation strategies.

2. Re-use of previously used implant 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. As such, the impact that re-use of previously used implant sites may have with respect to procedural complications that may occur, for example when there is scarring at a site, has never been evaluated.

3. QT prolongation

The Applicant should be required to evaluate the effect of Probuphine on cardiac conduction.

Postmarketing Commitments

1. Dose-finding study

In the Probuphine clinical development program, no doses higher than those used in the Phase 3 studies were ever explored; it appears that only a minimum effective dose was identified. With the current Probuphine treatment paradigm afforded by the available clinical data, the patient population that can use this drug is restricted to those patients who can be stabilized on a limited range of buprenorphine doses (12 – 16 mg) prior to implantation. A study evaluating the pharmacokinetics, safety and efficacy of Probuphine with higher dose(s) should be performed.

Body Mass Index (BMI) should be examined as part of dose finding exploration. When the primary efficacy endpoint was examined in various subpopulations defined by gender, age, race, primary opioid of abuse, and BMI, for each permutation except BMI, the pooled analysis revealed a significant difference between the Probuphine and placebo groups. For BMI, the pooled analysis revealed a significant difference between the Probuphine and placebo groups among patients with a BMI $\leq 25\text{kg/m}^2$. Conversely, among patients with BMI $> 25\text{kg/m}^2$, the difference between Probuphine and placebo was not significant. It is conceivable that this variation based on BMI is reflective of differential exposure and potentially adequate buprenorphine exposure

in persons with lower BMI. This further substantiates the notion that only a minimum effective dose has been identified in the Probuphine clinical development program.

2. Opioid blockade study

The dose of buprenorphine necessary to treat symptoms of withdrawal is much lower than the dose necessary to block the effects of exogenous opioids. The dose of sublingual buprenorphine recommended in labeling is based on the blocking dose, in order to provide both the reinforcing agonist effects and to provide disincentive to continue illicit opioid use. The data suggest that Probuphine may provide a dose sufficient to palliate the symptoms of withdrawal and potentially the subjective urge to use illicit opioids, but it does not seem to provide a dose that blocks exogenous opioids, as evidenced by many patients who persisted in regular drug use while on Probuphine. A study should be conducted to evaluate the ability of Probuphine to provide opioid blockade to ensure that patients are provided both the reinforcing agonist effects *and* disincentive to continue illicit opioid use in the form of opioid blockade, as is offered by the sublingual formulations at target doses.

3. Treatment Success with Probuphine

Probuphine's efficacy was evaluated in two 24-week controlled clinical trials in which the primary endpoint was a response profile based on the percentage of urines negative for opioids. A significant difference was noted between the response profile for Probuphine and placebo in favor of Probuphine for both studies. The statistically-significant findings were driven by differences observed among patients who were submitting opioid-negative urine samples approximately one-third of the time, across a period of 24 weeks, as opposed to those submitting opioid urines at levels that would suggest abstinence or near abstinence, e.g., $\geq 90\%$ ≥ 95 , or 100% opioid-negative urines. The clinical meaningfulness of these minor changes in drug use behavior are uncertain, and justification should be provided demonstrating that these minor changes in drug-taking behavior are associated with clinical benefit to the patient.

2 Introduction and Regulatory Background

Probuphine[®] is a subdermally implantable formulation of the active ingredient buprenorphine hydrochloride (buprenorphine) in a solid matrix of ethylene vinyl acetate polymer (EVA) that is intended to provide sustained delivery of buprenorphine for 6 months for maintenance treatment of opioid dependence.

The Probuphine NDA is a combination product consisting of drug and device constituent components. The drug constituent component is the individual implant or rod that consists of buprenorphine and EVA. The device constituent component is the applicator which is necessary for insertion of the implants.

The Probuphine NDA is a 505(b)(2) submission relying in part on the Agency's previous findings of safety and efficacy for Subutex and Suboxone SL tablets, which are indicated for maintenance treatment of opioid dependence. Both Subutex and Suboxone have been removed from the US market by the manufacturer, and relisting determinations have not been completed at the time of this writing (although generics are available). The regulatory implications for this application are unclear at this time.

2.1 Product Information

Probuphine[®] is a subdermally implantable formulation of the active ingredient buprenorphine hydrochloride (buprenorphine) in a solid matrix of ethylene vinyl acetate polymer (EVA) that is intended to provide sustained delivery of buprenorphine for 6 months for maintenance treatment of opioid dependence. Buprenorphine, in turn, is a partial agonist¹ at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect. At low doses buprenorphine produces sufficient agonist effect to enable opioid-addicted individuals to discontinue the misuse of opioids without experiencing withdrawal symptoms. The agonist effects of buprenorphine increase linearly with increasing doses of the drug until at moderate doses they reach a plateau and no longer continue to increase with further increases in dose—the “ceiling effect.” Thus, buprenorphine carries a lower risk of certain adverse effects compared to full opioid agonists. In fact, in high doses and under certain circumstances, buprenorphine can actually block the effects of full opioid agonists and can precipitate withdrawal symptoms if administered to an opioid-addicted individual while a full agonist is in the bloodstream.²

It should be noted also that the dose of buprenorphine necessary to treat symptoms of withdrawal is much lower than the dose necessary to block the effects of exogenous opioids. The dose of sublingual buprenorphine recommended in labeling is based on the blocking dose, in order to provide both the reinforcing agonist effects and to provide disincentive to continue illicit opioid use. The data suggest that Probuphine may provide a dose sufficient to palliate the symptoms of withdrawal and potentially the subjective urge to use illicit opioids, but it does not seem to provide a dose that blocks exogenous opioids, as evidenced by many patients who persisted in regular drug use while on Probuphine.

Probuphine is formulated using the ProNeura drug delivery technology. Probuphine[®] (buprenorphine implant) drug product is an implant containing 80 mg buprenorphine hydrochloride USP (BPN) in an ethylene vinyl acetate copolymer (EVA) matrix. The

¹ This means that, although buprenorphine is an opioid, and thus can produce typical opioid agonist effects and side effects such as euphoria and respiratory depression, its maximal effects are less than those of full agonists like heroin and methadone. <http://buprenorphine.samhsa.gov/about.html>

² <http://buprenorphine.samhsa.gov/about.html>

matrix formulation of the implants results in a steady-state delivery of buprenorphine that maintains a stable plasma level of the drug for 6 months.

Each Probuphine implant measures 26 mm in length and 2.5 mm in diameter, with a total weight of 112 mg. Implants are individually packaged into laminated foil pouches. The pouches are terminally sterilized using gamma irradiation. Four implants are administered subdermally in the inner side of the patient's upper arm. Patients may receive a fifth implant, if an increased dose is required. Probuphine must be removed by the end of the sixth month and may be replaced by new implants, in another location, at the time of removal, if continued treatment is desired.

The immediate container closure for each implant is a laminated foil pouch. There will be two packaging configurations with implants and applicators, i.e., four individually pouched implants in a carton with an applicator or one individually pouched implant in a carton with an applicator. The implants will be labeled for storage at 15-30°C (57-86°F).

Trade name:	Probuphine®
Drug established name:	buprenorphine implant
Chemical name:	21-Cyclopropyl-7 α -[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14- <i>endo</i> -ethano-6,7,8,14-tetrahydrooripavine hydrochloride
Drug class:	Mu-opioid receptor partial agonist and kappa-opioid receptor antagonist
Proposed indication:	treatment of opioid dependence
Dose and Administration:	• Four 80-mg implants for six months ○ One dose increase of a single 80-mg implant, as needed, at least two weeks after the initial four implants were inserted • Implants are to be inserted into the inner side of the patient's arm by a qualified health care professional during an in-office surgical procedure • Implants are to be removed by a qualified health care professional six months after placement of the initial four implants in another in-office surgical procedure.
Age groups:	• Adults ○ Full waiver granted for pediatric studies

2.2 Tables of Currently Available Treatments for Proposed Indications

CURRENTLY AVAILABLE TREATMENTS FOR OPIOID DEPENDENCE			
Generic/Chemical Name	Trade Name	Sponsor(s)	Dosage form(s)
Buprenorphine/naloxone	Suboxone and generics (n.b., Subutex no longer marketed by manufacturer in US)	Reckitt Benckiser	• Sublingual tablet
Buprenorphine	Subutex and generics (n.b., Subutex no longer marketed by manufacturer in US)	Reckitt Benckiser	• Sublingual tablet
Buprenorphine/naloxone	Suboxone	Reckitt Benckiser	• Sublingual film
Methadone HCl	Methadose (also generic) Dolophine (also generic) Diskets	Mallinckrodt Roxane	• Oral solution • Bulk powder • Tablet • Dispersible tab • Oral concentrate
Naltrexone HCl	ReVia (also generics)	Duramed	• Tablet
Naltrexone HCl	Vivitrol	Alkermes	• Suspension for intramuscular injection

2.3 Availability of Proposed Active Ingredient in the United States

Buprenorphine in sublingual tablet and film form is approved in the US for maintenance treatment of opioid dependence. Buprenorphine is available as a sublingual tablet (Subutex) and currently generic formulations are being marketed. Buprenorphine is also available in combination with naloxone as a sublingual tablet (Suboxone) and currently generic formulations are being marketed. Buprenorphine is available as a Suboxone film formulation. Parenteral and transdermal formulations of buprenorphine have also been approved for the treatment of pain.

2.4 Important Safety Issues With Consideration to Related Drugs

Buprenorphine: buprenorphine is a partial mu-opioid receptor agonist having mixed agonist-antagonist properties. Important safety issues to consider with respect to related drugs are those safety issues observed in association with pure opioid agonists. Buprenorphine produces typical opioid agonist effects, but they are limited by a ceiling effect. Thus buprenorphine is not anticipated to carry with it the same risks of overdose as seen in other opioid agonists, although it can cause respiratory depression and has been associated with fatal overdose when combined with other depressants. Key safety

concerns related to the drug substance buprenorphine have included hepatic effects, allergic reactions, and potential cardiac conduction effects. The sublingual drug products have been subject to abuse and diversion, and have been implicated in cases of accidental pediatric poisonings. Safety considerations related to buprenorphine formulations are discussed in relevant sections of the safety review, below.

ProNeura: Probuphine is the first drug product formulated using this drug delivery technology.

Surgically-Implanted Drugs: The Agency's previous experience with surgically-implanted products, specifically contraceptive implants, was used to identify potential concerns that could arise with 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, 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.

While implantable contraceptive methods are generally well-tolerated, procedure-related adverse events are notable for pain, infection, numbness, and scarring at the implant site. Complications such as bleeding or hematoma have also been reported. Most significant safety concerns include injuries related to damage of the ulnar or medial cutaneous nerve, which have resulted in permanent disability.

Notably, implantable contraceptive products are inserted and removed by obstetrician/gynecologists, who are surgically trained specialists. 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.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Advice on this new drug application was communicated to the Applicant during a series of Guidance meetings, advice letters, and a pre-NDA meeting. Key recommendations that were provided to the Applicant in each of these settings are summarized.

Primary advice was communicated to the Sponsor during these key regulatory interactions.

- PIND Meeting – April 2001
- IND Opened – December 2004
- Guidance Meeting – February 2005
 - (Clinical Development Plan)
- SPA Request – May 2005
- Guidance Meeting – August 2005
- Protocol Amendment – Sept 2005
- Protocol Amendment – March 2006
- Formal Dispute Resolution Request – Jan 2007
- Guidance Meeting – March 2007
- Protocol Amendment – July 2007
- Suspension of Clinical Development Program – Dec 2008
- Protocol Amendment – October 2009
- Advice Letter – April 28, 2010
- Advice Letter – March 28, 2011
- Pre-NDA Meeting – October 25, 2011

Clinical Trials to Evaluate Probuphine

Titan received guidance on the types of studies that should be included in their clinical pharmacology program and Phase 3 program for Probuphine. A comprehensive clinical pharmacology program should include adequate pharmacokinetic characterization. It was also advised that at least one dose-finding study should be conducted. An adequate dose-finding study was never conducted, and Titan was informed that the dose of four implants for the 6-month window, with an option for a dose increase appeared too low. That is, the systemic exposure of buprenorphine available with 4–5 Probuphine implants appeared to be distinctly lower than the systemic exposure from sublingual buprenorphine/naloxone (16 mg/day). Accordingly, Titan was informed that these potentially inadequate plasma buprenorphine levels would be factored into the risk-benefit assessment for Probuphine.

In order to market Probuphine as initial treatment (as opposed to follow-on treatment in stabilized patients), Titan was informed that two adequate and well-controlled trials would be required.

Clinical Trial Design – Phase 3 Studies

Varied approaches have been applied to clinical trial design for the treatment of opioid dependence. It was in this context that negotiations about the approach to trial design were assumed by the Applicant and Agency. Titan initially proposed [REDACTED] (b) (4)

[REDACTED]

A double-dummy design was also recommended to the Applicant, in order to afford a suitable comparison between Probuphine and a placebo comparator and active control, namely the sublingual buprenorphine formulations which have been approved for maintenance treatment of opioid dependence.

Endpoints and Analytic Approaches

The current paradigm for clinical trials in addiction treatment is evolving, with a shift toward greater focus on individual treatment response rather than group means. Analyses focused on group means (such as mean percent of weeks abstinent) are not considered meaningful, 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.

Because of the shift toward evaluation of individual treatment response, a responder analysis was recommended, rather than an analysis of group means which are difficult to interpret and may obscure individual treatment response. The endpoint was to be based on urine toxicology testing and the Applicant was advised to justify the proposed frequency of urine testing. The Applicant proposed [REDACTED] (b) (4), but previous studies performed urine sampling on a thrice-weekly basis.

A significant effort was expended in trying to establish a definition of a treatment responder that could be applied to the studies; however, no definition of any drug use pattern, short of abstinence, could be identified that was supported by any specific data. Titan also cited literature reports in which group mean percent of clean urine tests were reported; however, because these group means incorporate both complete non-responders, partial responders, and good responders, the group mean value would not be an appropriate choice to define a responder. Therefore, rather than arbitrarily selecting a drug use pattern short of abstinence that would be considered successful, or agreeing a priori that complete abstinence would be an unreasonable expectation, Titan was encouraged to look at the full range of responder definitions, from complete abstinence to no abstinence, but to emphasize the effect of the drug on promoting abstinence or near-abstinence. This analysis is referred to by Titan as the “cumulative distribution function.”

It should be noted that, in these discussions, the emphasis was on trying to define a successful patient in such a way that patients who were clearly clinically successful would not be mis-classified 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.

Recognizing that patients require some time for engagement in treatment, Titan was encouraged to also perform analyses in which a “grace period” was allowed during which drug use was not counted in the assessment of response.

Titan 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, Titan 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 endpoint initially was to be based on urine toxicology data alone; however, when efficacy data from the first Phase 3 trial became available, it was observed that although the urine toxicology findings were more favorable in the Probuphine arm, the patients on Probuphine were reporting illicit drug use more commonly than their placebo counterparts. This was particularly concerning with respect to efficacy because treatment goals, in this case, are to engender meaningful changes in drug-use behavior. It should be noted that these were self-reports of *all* illicit drugs and not illicit opioid use exclusively. Because the self-report data were available, it seemed prudent to use all available sources of data to gain a complete picture of the actual treatment response. In the end, self-report data was also assessed and used for endpoint adjudication.

The length of the trial and the efficacy ascertainment window were also a point of discussion. When Titan entered its Phase 3 development period, there was still uncertainty about Probuphine’s full treatment duration. Titan was operating under the premise that Probuphine would provide sustained delivery of buprenorphine for 6 months, but acknowledged that it may only deliver buprenorphine for four months. Ultimately, Titan judged the extent of delivery to be four months, and accordingly the primary endpoint was to be assessed over a six-month period.

Chronic Treatment

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. Consequently, the Applicant was told that studies assessing the ability to reuse sites were necessary with respect to efficacy, for example, scarring at an implantation site

could impact bioavailability if that same site was later re-used. Similarly, scarring could impact safety by complicating insertion and removal procedures. Ultimately, it was agreed that this study would not be required for filing, but could be submitted after approval, assuming it was completed and submitted in a timeframe that would permit the label to be modified before patients currently being treated would require re-implantation in a previously-implanted arm. This period of time could be as short as one year. (To the Agency's knowledge, this trial has not been initiated.)

2.6 Other Relevant Background Information

Pharmacotherapy for Opioid Addiction Treatment

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 μ -receptor. Like methadone, buprenorphine's activity at the μ -receptor was expected to relieve patients' urge to use illicit opioids, but like methadone, the long duration of action would allow patients to achieve a steady state, without the alternating highs and lows associated with opioid abuse that impair daily functioning.

Due to its partial agonist properties, the euphorogenic effects of buprenorphine are 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. This was expected to limit its attractiveness as a drug of abuse.

In addition, 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. This was predicted to serve as a further deterrent to abuse.

Finally, at sufficiently high doses, buprenorphine blocks full opioid agonists from achieving their full effects, further deterring abuse of these substances for 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 an increasing number of cases of 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, patients could not periodically discontinue use in order to allow the blocking effect to dissipate, so that they could experience the effects of their opioids of choice. Probuphine was developed to address these issues. This application has been granted Priority Review status in recognition of this potential.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Inspection of the case report forms and line listings by the reviewer revealed no major concerns about data quality or integrity. The submission was organized and did not present any major barriers to review. When needed, clinical information requests were sent to the Applicant in order to clarify information in the submission and to provide new information to facilitate the review. Datasets, overall, were in a format that allowed for the reviewer to evaluate and reproduce findings. Case report forms for the latter two phase 3 studies were more readily navigable than those provided for the initial two Phase 3 studies.

3.2 Compliance with Good Clinical Practices

According to the Applicant, the clinical trials in opioid-dependent patients were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. The Applicant also indicates that all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants.

Office of Scientific Investigations Inspection

The Office of Scientific Investigations (OSI) was consulted to review data integrity and quality for selected sites where the Probuphine Phase 3 safety and efficacy trials were conducted. OSI inspected six clinical investigators, covering a total of 11 sites and initially issued a 483 for one of the sites due to incomplete submission of financial disclosure information. The issue was ultimately rectified by the Applicant and the site eventually received a Voluntary Action Indicated (VAI). Otherwise No Action Indicated (NAI) and VAI classifications were issued upon inspection of the selected clinical trial sites. There were no sites that warranted a classification of Official Action Indicated (OAI), e.g., Warning Letter, etc..

3.3 Financial Disclosures

The Applicant's submission included the completed "Certification: Financial Interests and Arrangements of Clinical Investigators" form (Form FDA 3455). The Applicant indicated that the majority of the study investigators are certified as having no Financial Arrangement as defined in 21 CFR 54.2.

There was a single investigator who could not be certified as having no Financial Arrangement as defined in 21 CFR 54.2. The Applicant provided information on the financial arrangements or financial interests that require disclosure as part of Form FDA 3455. Specifically, the Applicant provided information on "any significant payments of

other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria.”



4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

An overview of the key findings from the Chemistry Manufacturing and Controls, Clinical Microbiology, Nonclinical Pharmacology/Toxicology, and Clinical Pharmacology reviews are provided in the respective sections below.

Additionally, important safety issues have come to light in the context of the Division of Medication Error and Prevention Analysis (DMEPA) and Division of Risk Management (DRISK) reviews.

DMEPA

A Training and Certification Program has been developed by the Applicant and was intended to ensure that clinicians who performed the implant insertion and removal procedures met competency standards and to improve the overall safety of the implant and removal processes. No specific testing of the training program or procedures was included with the NDA; Titan's position was that the procedures were pilot-tested and validated in Studies 806 and 811.

Initially, based on the understanding that the product and procedures were essentially the same as Norplant, the review team did not feel that a human factors study or user-performance assessment would be required to support the NDA. However, in the course of review, it became apparent that:

1. The removal procedure differed substantially from the established procedure for removing Norplant, and there was a paucity of clinical experience with this specific procedure, and in training practitioners to perform it, and;
2. The provider population that would be performing the procedures differed substantially from the provider population that inserts and removes Norplant and other implantable contraceptives.

After these points became clear, the DMEPA team felt that the sponsor should provide a comprehensive use-related risk analysis for the product. This analysis should include a comprehensive evaluation of all the steps involved in using the device (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk-mitigation strategies employed to reduce any moderate or high risks to acceptable levels, and the method of validating the risk-mitigation strategies.

DRISK

DRISK identified several concerns with the Applicant's Risk Evaluation and Mitigation Strategy (REMS), as originally proposed. Upon learning that the original proposal was not in compliance with controlled substance regulations, the Applicant substantially revised the REMS. The newly proposed REMS was submitted shortly before the writing of this review. The late submission did not permit review during the review cycle for this NDA. Of note here is that discussions at the advisory committee meeting highlighted the need to ensure that those performing insertion and removal procedures are adequately trained.

4.1 Chemistry Manufacturing and Controls

Probuphine is a combination product comprising drug and device constituent components. The drug constituent component is the individual implant or rod that contains buprenorphine and ethylene vinyl acetate (EVA). The device constituent component is the applicator which consists of an obturator and cannula.

Review of the drug constituent component was performed by the Chemistry Manufacturing and Controls (CMC) review team within the Center for Drug Evaluation and Research (CDER). On review of the data submitted pertaining to Chemistry Manufacturing and Controls, the CMC reviewer concluded that the Applicant on the NDA provided sufficient information to ensure the identify, strength, purity, and quality of the drug product Refer to the CMC review by Dr. Edwin Jao for additional details.

The applicator, or device constituent component, was reviewed by Center for Devices and Radiologic Health (CDRH) reviewers. Refer to the CDRH for additional details.

4.2 Clinical Microbiology

The sterility process and controls were deemed acceptable by the Microbiology review. Refer to the Clinical Microbiology review by Dr. Vinayak B. Pawar for additional details.

4.3 Preclinical Pharmacology/Toxicology

The nonclinical review team identified a signal of local irritation effects of of the Probuphine and placebo implants. Probuphine (buprenorphine + EVA) implants appear to have increased local toxicity above that observed with the placebo implants (EVA only). Refer to Section 7.2.3 Special Animal and/or In Vitro Testing of this clinical review for additional details of the local toxicity findings. Refer to Nonclinical Review by Dr. Gary Bond for complete details of the nonclinical evaluation for this NDA.

4.4 Clinical Pharmacology

Two clinical pharmacology studies, namely TTP-400-02-01 and PRO-810 were submitted in support of the Probuphine NDA, and were reviewed in detail by the Clinical Pharmacology Team. On review of these studies, and compared to the reference listed product for this NDA, sublingual buprenorphine/naloxone (as Suboxone) the Clinical Pharmacology review team noted the following.

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 lower than the trough concentrations observed with 16 mg/day SL buprenorphine at steady state (1.6 ± 0.6 ng/mL; the Time 0 value on Day 1 of Probuphine insertion is the trough value from the last SL dose since the last SL buprenorphine administration was 24 hours before the implant insertion). From this information, it appears that buprenorphine steady-state concentrations from four implants are approximately half as much as that of the trough concentration obtained from 16 mg/day SL buprenorphine administration. 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%.

Refer to the Clinical Pharmacology review by Dr. David Lee for additional details.

4.4.1 Mechanism of Action

The mechanism of action for buprenorphine is summarized in the Suboxone label:

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor.

4.4.2 Pharmacodynamics

The subjective effects and physiologic effects are summarized in the Suboxone label:

Subjective Effects:

Comparisons of buprenorphine to full opioid agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect.

In opioid-experienced subjects who were not physically dependent, acute sublingual doses of buprenorphine/naloxone tablets produced opioid agonist effects which reached a maximum between doses of 8/2 mg and 16/4 mg buprenorphine/naloxone.

Opioid agonist ceiling-effects were also observed in a double-blind, parallel group, dose-ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg), placebo and a full agonist control at various doses. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid-experienced subjects who were not physically dependent. Both active drugs produced typical opioid agonist effects. For all measures for which the drugs produced an effect, buprenorphine produced a dose-related response. However, in each case, there was a dose that produced no further effect. In contrast, the highest dose of the full agonist control always produced the greatest effects. Agonist objective rating scores remained elevated for the higher doses of buprenorphine (8-32 mg) longer than for the lower doses and did not return to baseline until 48 hours after drug administration. The onset of effects appeared more rapidly with buprenorphine than with the full agonist control, with most doses nearing peak effect after 100 minutes for buprenorphine compared to 150 minutes for the full agonist control.

Physiologic Effects:

Buprenorphine in IV (2, 4, 8, 12 and 16 mg) and sublingual (12 mg) doses has been administered to opioid-experienced subjects who were not physically dependent to examine cardiovascular, respiratory, and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared to placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O₂ saturation, or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3-hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed.

The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after

buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O2 saturation to the same degree.

4.4.3 Pharmacokinetics

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 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 ^a n=6
C _{max} (ng/mL)	8.61 (6.900)	10.40 (13.400)	4.89 (1.110)	0.91 (0.157)	0.78 (0.128)
T _{max} ^b (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 _{0-t} ^c (ng•hr/mL)	66.25 (35.878)	62.67 (36.397)	113.13 (27.737)	19.60 (3.372)	10.23 (2.264)
AUC ₀₋₂₄ (ng•hr/mL)	66.25 (35.878)	62.67 (36.397)	75.191 (24.443)	19.60 (3.372)	10.23 (2.264)
t _{1/2} ^b (hr)	11.42 (11.04, 12.09)	7.63	--	--	--
λ _z (hr ⁻¹)	0.0604 (0.00231)	0.0908	--	--	--

λ_z = apparent elimination rate constant; AUC₀₋₂₄ = area under the plasma concentration-time curve from time 0 to 24 hours; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to t, where t is the last measurable plasma concentration; C_{max} = maximum observed plasma concentration; t_{1/2} = apparent terminal elimination half-life; T_{max} = 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).

^a Day 57 represents parameters after removal of the Probuphine implants.

^b Median (minimum, maximum) reported for T_{max} and t_{1/2}.

^c On Days -1 and -2, AUC_{0-t} represents the AUC from Day -1 or Day -2 Hour 0 through Day 1 or Day -2 Hour 12. On Day 1, AUC_{0-t} represents the AUC from Day 1 Hour 0 through Day 2 Hour 36, relative to the time of insertion.

Buprenorphine distribution, metabolism, elimination, and drug-drug interactions are described in detail in the Suboxone label:

Distribution:

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

Naloxone is approximately 45% protein bound, primarily to albumin.

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. Naloxone undergoes direct glucuronidation to naloxone-3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.

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 and naloxone has a mean elimination half-life from plasma ranging from 2 to 12 hours.

Drug-drug Interactions:

CYP3A4 Inhibitors and Inducers: Subjects receiving SUBOXONE sublingual tablet should be monitored if inhibitors of CYP3A4 such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin) or HIV protease inhibitors and may require dose-reduction of one or both agents. The interaction of buprenorphine with all CYP3A4 inducers has not been studied, therefore it is recommended that patients receiving SUBOXONE sublingual tablet be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered.

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine, has been found to be a moderate CYP2D6 inhibitor in in-vitro studies employing human liver microsomes. However, the relatively low plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic doses are not expected to raise significant drug-drug interaction concerns.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Probuphine clinical development program comprises two primary Phase 3 safety and efficacy trials, identified as PRO-805 and PRO-806, and two corresponding follow-on extension studies to the primary studies, identified as PRO-807 and PRO-811, respectively. The development program also includes, two clinical pharmacology

studies, specifically a pharmacokinetic trial, identified as TTP-400-02-01, and a bioavailability study with respect to Suboxone, PRO-810.

Efficacy data derive from clinical trials PRO-805 and PRO-806. Safety data derive from Studies PRO-805, PRO-806, PRO-807, and PRO-811. The clinical pharmacology studies also contribute limited safety data. Clinical pharmacology data derive from TTP-400-02-01 and PRO-811 and are under review by the clinical pharmacology team. Additional limited pharmacokinetic data are contributed by the Phase 3 primary and extension studies.

Table 1 Table of Studies/Clinical Trials in the Probuphine Clinical Development Program

Study No. & Title	Design/ Status	Study Treatments	Population	Duration	Location/ # of Centers
P3 S&E Trials					
PRO-805 A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study of Probuphine in Patients with Opioid Dependence	P3, DB, R, PC trial with 2:1 randomization Probuphine to placebo Initiated: Apr 2, 2007 Completed: Jun 19, 2008	4 Probuphine subdermal implants (80 mg buprenorphine per implant) (5 if protocol-specified criteria met) 4 Placebo subdermal implants (5 if protocol-specified criteria met) All: SL BPN as needed	N = 163 opioid-dependent subjects • Probuphine: n= 108 • Placebo: n=55 Median age: 35 (19 – 62) Gender: 69% male	Single dose; 24 weeks	US 23 centers
PRO-806 A Randomized, Placebo and Active-Controlled, Multi-Center Study of Probuphine in Patients with Opioid Dependence	P3, DB, R, PC and OL AC trial with 2:1:2 randomization Probuphine, placebo, SL BPN Initiated: Apr 22, 2010 Completed: May 12, 2011	4 Probuphine subdermal implants (5 if protocol-specified criteria met) 4 Placebo subdermal implants (5 if protocol-specified criteria met) SL BPN 12–16 mg once daily All: SL BPN as needed	N = 301 opioid-dependent subjects (301 enrolled; 287 received study drug) • Probuphine: n= 114 • Placebo 4 implants: n=54 • SL BPN n=119 Median age: 33 (18 – 60) Gender: 61% (175/287) male	Single dose; 24 weeks	US 20 centers
P3 Extension Trials					
PRO-807 (PRO-805)	Open-label; Extension	4 Probuphine subdermal	N = 62 opioid-dependent	Single dose; 24 weeks	US 15 centers

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Study No. & Title	Design/ Status	Study Treatments	Population	Duration	Location/ # of Centers
extension)	Initiated: Mar 20, 2008 Completed: Feb 19, 2009	implants (5 if protocol-specified criteria met) All: SL BPN as needed	subjects Median age: 37 range (20 – 62) Gender: 71% male		
PRO-811 (PRO-806 extension)	Open-label; Extension 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 Median age: 37 (19 – 61) Gender: 66% male	Single dose; 24 weeks	US 18 centers
Clinical Pharmacology Studies					
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 • 2 Probuphine implants n=6 • 4 Probuphine implants n=6 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

5.2 Review Strategy

For efficacy evaluation, data from the Phase 3, double-blind, safety and efficacy trials, PRO-805 and PRO-806, were examined separately. Studies PRO-805 and PRO-806 were two Phase 3 safety and efficacy studies conducted to assess whether efficacy could be established in the first trial, and if so, replicated in the second, based on comparisons made between the Probuphine and placebo arms with respect to analyses of efficacy endpoints. The efficacy information that was reviewed was primarily from the PRO-805 and PRO-806 study reports and accompanying datasets. Analyses of these data were performed by the primary Statistics Reviewer, David Petullo, who reproduced the Applicant's analyses to ensure that they were replicable and conducted additional analyses deemed important for efficacy ascertainment and for arriving at a better understanding of the clinical relevance of the findings.

For safety evaluation, data from the Phase 3, double-blind, safety and efficacy trials, PRO-805 and PRO-806, were pooled, as were the data from the Phase 3, open-label, extension studies, PRO-807 and PRO-811 (PRO-805 and PRO-806 extension trials, respectively). Additionally, limited safety data were available from the clinical pharmacology studies TTP-400-02-01 and PRO-810, and were used to supplement and complement safety data provided by the major contributors to the safety database, namely the Phase 3 double-blind and extension studies. The safety information that was reviewed was primarily from the Integrated Summary of Safety (ISS). Safety information included in the individual study reports for the respective studies was referenced when additional detail beyond that included in the ISS was needed.

5.3 Discussion of Individual Studies/Clinical Trials

The Probuphine clinical development program comprises two primary Phase 3 safety and efficacy trials, identified as PRO-805 and PRO-806, two corresponding extension studies to the primary studies, identified as PRO-807 and PRO-811, respectively, as well as two clinical pharmacology studies, specifically a pharmacokinetic trial, identified as TTP-400-02-01, and a bioavailability study with respect to Suboxone, PRO-810. A description of the studies follows.

Clinical Pharmacology Studies:	TTP-400-02-01 & PRO-810
Phase 3 Safety and Efficacy Trials:	PRO-805 & PRO-806
Phase 3 Extension Trials:	PRO-807 & PRO-811

INTEGRATED SUMMARY OF PROTOCOLS

The trials in the Probuphine clinical development program had a number of parallels. The studies are described collectively, and specific protocol elements that differ across the studies are emphasized.

All studies enrolled opioid-dependent patients who received sublingual buprenorphine either before enrollment or as open-label treatment during an induction phase of the study. Once a target dose of sublingual buprenorphine was achieved either on entry to the study or for three consecutive days during an induction phase, sublingual buprenorphine was discontinued, and Probuphine (or placebo) implants were inserted into the upper arm in an in-office surgical procedure. Implants were intended to remain indwelling for 24 weeks and removed in another in-office surgical procedure at the end of the 6-month treatment cycle.

Study Population

All studies enrolled opioid-dependent adults. Patients with dependence on any other psychoactive substances besides opioids or nicotine (e.g., alcohol, sedatives) were excluded. In general, patients who received treatment for opioid dependence within the previous 90 days, candidates for only short-term opioid treatment or detoxification therapy, and patients with chronic pain requiring opioids for treatment were also excluded from participation.

Outpatient Induction with SL Buprenorphine

The studies included an induction period with SL buprenorphine treatment in the form of sublingual (SL) Subutex tablets or Suboxone tablets to ensure tolerability, safety, and adequate control of opioid withdrawal symptoms and “cravings” in subjects who had not received pharmacotherapy for opioid dependence for at least 90 days prior to screening. SL Subutex tablets were used for induction during a portion of Study PRO-805 and SL Suboxone was used otherwise in the studies. Subjects had to successfully complete induction in order to be transitioned to either Probuphine implants, placebo implants or, in the case of Study PRO-806, to a defined starting dose of 12–16 mg of SL buprenorphine. All studies included in the pooled data defined successful induction as achieving a stable 12–16 mg daily SL buprenorphine dose for a minimum of 3 consecutive days within 8–16 days of having started the induction process after Screening. Subjects in TTP-400-02-01 were maintained on a dose of 8 mg to 16 mg SL Subutex prior to enrollment; this was an eligibility criterion.

24-week Treatment Period

Following successful induction, meaning that the subject had reached a stable target dose of sublingual buprenorphine for a minimum of three consecutive days within 8 to 16 days of having started the induction period, subjects began double-blind treatment

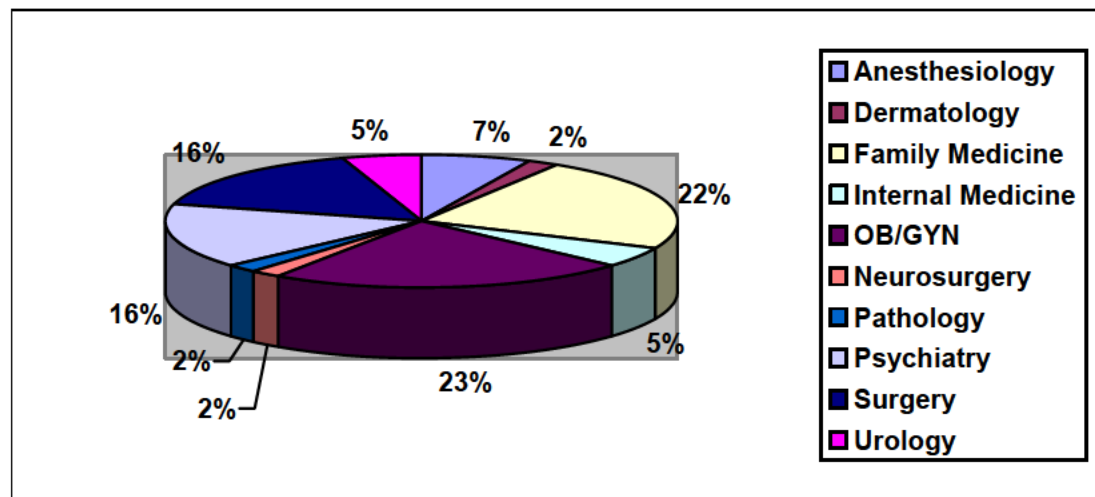
with four Probuphine or placebo implants or open-label treatment with sublingual buprenorphine at 12 – 16 mg/day.

24-week Treatment Period: Implant Insertion (Initial 4 Implants) and Removal

Implantation

Within 12 to 36 hours after the last induction dose of SL buprenorphine, Probuphine was inserted in the subject's inner upper arm in a brief, in-office procedure. All implant insertion and removal procedures were performed by trained health care providers at the clinical study sites. (The HCPs who performed implant insertion and removal procedures were licensed physicians who by his/her respective practice can be categorized as follows: approximately 7% Anesthesiology; 2% Dermatology; 23% Family Medicine; 5% Internal Medicine; 23% OB/GYN; 2% Neurosurgery; 2% Pathology; 16% Psychiatry; 16% Surgery; and 5% Urology. The breakdown is illustrated graphically below.)

Figure 1 Implanting Physicians by Specialty



Source: Reviewer-generated based on Response to Information Request

For Studies PRO-806, PRO-811, and PRO-810, modified surgical equipment (applicator and removal clamp), surgical techniques, and training were implemented. These modifications were intended to reduce implant-procedure-related issues.

For the open-label extension studies, the opposite arm as that implanted in the preceding double-blind study was used in the majority of cases. There were 6 cases where this was not possible: 3 each for Studies PRO-807 and PRO-811, all of whom had been treated with Probuphine in the preceding double-blind study. In these instances, re-implantation occurred in a different area on the same arm.

Explantation

At the end-of-treatment visit or at early discontinuation, all implants were removed in a brief, in-office procedure.

24-week Treatment Period: Open-label Sublingual Buprenorphine Treatment

PRO-806 included an open-label sublingual buprenorphine treatment arm. Subjects' dose levels were to remain within 12 to 16 mg/day SL buprenorphine throughout the 24-week treatment period.

Sublingual Buprenorphine Rescue and Additional Implant/Dose Increase

All subjects were allowed to receive limited supplemental rescue SL buprenorphine in increments of ≥ 2 mg. In the TTP-400-02-01, rescue medication was permissible, as clinically indicated. In the other studies, rescue medication was permissible based on the following pre-specified criteria, or at the investigator's discretion:

- Withdrawal symptoms with a score of >12 on the COWS
- Cravings with a score of >20 mm on the opioid-cravings VAS
- Subject request for supplemental SL buprenorphine deemed appropriate by the investigator

In PRO-805, PRO-807, and PRO-810, one or more of the criteria had to be met. In PRO-806 and PRO-811, all three criteria had to be met. As with the induction phase, supplemental SL buprenorphine was provided in the form of either SL Subutex tablets (Studies TTP-400-02-01 and part of PRO-805) or SL Suboxone tablets (all other studies).

Subjects requiring supplemental SL buprenorphine were required to obtain supplemental SL buprenorphine at their clinic/pharmacy for each dose. Supplemental Suboxone SL buprenorphine doses were to be administered under observation at the clinic/pharmacy to ensure compliance. A staff member served as witness that the SL tablet had completely dissolved under the subject's tongue. A maximum of 3 days of take-home dosing of Suboxone was provided for weekends/holidays or other circumstances at the discretion of the investigator, and a daily Suboxone take-home dosing log was given to the subject for drug accountability.

For all studies except the pharmacokinetics (PK) studies TTP-400-02-01 and PRO-810, subjects with the following SL buprenorphine requirements were to have received one additional implant:

- ≥ 3 days per week of supplemental SL buprenorphine for 2 consecutive weeks
- ≥ 8 days of supplemental SL buprenorphine over 4 consecutive weeks

Subjects were allowed to refuse the recommended additional implant, but were discontinued from the study in those circumstances. This occurred in 1 Probuphine and

2 placebo cases in Study PRO-806 only. The additional implant was not inserted within the first 2 weeks after initial implant insertion to allow for stabilization of blood levels.

In Study PRO-806, subjects in the open-label SL buprenorphine group were allowed to receive a dose increase of 2 to 4 mg arriving at a fixed dose not to exceed 16 mg/day as determined by the Investigator, if they met the above dose-increase criteria.

An investigator's decision to allow a subject to receive supplemental SL buprenorphine or a fifth implant was made on the basis of clinical signs and symptoms of opioid withdrawal symptoms or cravings, not on the basis of plasma buprenorphine levels or illicit drug use. (Investigators were blind to the results of urine toxicology tests.)

Subjects in the open-label sublingual arm were also allowed one dose reduction in response to an adverse event and if deemed clinically appropriate by the investigator. Subjects unable to tolerate 12 mg/day were discontinued from the study. Dose reductions were not permitted for subjects treated with Probuphine or placebo implants.

Psychosocial Counseling

Subjects were to receive an adequate amount of both pharmacologic and psychosocial treatment at all times while on study. For the double-blind studies PRO-805 and PRO-806, all subjects attended twice-weekly manual-guided drug counseling during study Weeks 1 through 12 and weekly drug counseling during Weeks 13 through 24. For Studies PRO-807 and 811, manual-guided individual drug counseling was provided as clinically indicated. Weekly manual-guided drug counseling was required of all subjects in Study PRO-810. Counseling was not provided for the first study, Study TTP-400-02-01.

Subject Early Withdrawal

Protocol specified criteria for early withdrawal from the study included:

- subject request
- subject non-compliance defined as refusal or inability to adhere to the study protocol:
 - if a subject missed 9 consecutive urine collections after the baseline visit, the subject was considered non-compliant and was withdrawn from the study;
 - if a subject missed 6 consecutive counseling sessions after the baseline visit, the subject was considered non-compliant and was withdrawn from the study;
 - any other instances of refusal or inability to adhere to the study protocol, as determined by the PI);
- treatment failure, defined as having either of the following supplemental buprenorphine needs any time after an implant or open-label sublingual buprenorphine dose increase:
 - ≥ 3 days/wk of supplemental SL buprenorphine for 2 consecutive wks

- ≥8 days of supplemental SL buprenorphine over 4 consecutive wks
- Subjects already at maximum dose in the OL SL buprenorphine group (16 mg) were considered treatment failures the first time the above SL buprenorphine requirements were met
- 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 >7 days”) that, in the judgment of the investigator, affected assessments of clinical status to a significant extent, required discontinuation of drug, or both;
- requirement for continual use of opioid analgesics >7 days or general anesthesia for surgery;
- at the request of Titan, regulatory agencies, or the Institutional Review Board (IRB);
- loss to follow-up.

Study Assessments

Similar safety measures were evaluated in each of the studies included in the pooled database and included extent of exposure, TEAEs, and vital signs (pupillary diameter and concomitant medications were collected in the individual study reports but were not evaluated in the pooled safety analyses). Information in regard to these outcomes was collected at each visit. Laboratory evaluations, physical examinations, and ECG were performed less frequently, per study protocol.

Study Visit Schedule

Subjects returned to the clinic numerous times during the study period for the collection of safety, efficacy, and PK data.

- Studies PRO-805 and PRO-806 had visits 3 times a week for intensive urine toxicology screening; the extension studies, PRO-807 and PRO-811, employed less frequent testing.
- Studies TTP-400-02-01 and PRO-810 were PK studies that required in-patient subject stays for approximately 3 days around the time of implantation, and also required a 24-hour post-removal inpatient period for elimination-phase blood sampling.
- In all studies except for PRO-811, subjects returned to the site for a follow-up visit 2 weeks post-removal. Study PRO-811 had the follow-up visit at 4 weeks post-removal.
- Subjects were contacted by phone for a safety assessment within 1 to 5 weeks post-removal.

Review of Individual Study Protocols:
Phase 3 Safety and Efficacy Trials

PRO-805

Title:	A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study of Probuphine in Patients with Opioid Dependence	
Protocol & Amendment Dates	• Protocol No. PRO-805: March 7, 2006 • Amendment No. 1: September 1, 2006 • Amendment No. 2: April 4, 2007	
Study Initiation & Completion Dates	• Initiation: April 2, 2007 • Completion: June 19, 2008	

PRO-805 Objective/Rationale:

The *primary objective* was to determine the efficacy of Group A (4 Probuphine implants) versus Group B (4 placebo implants) in the treatment of patients with opioid dependence over 16 weeks of treatment³.

The *key secondary objective* was to determine the efficacy of Group A versus Group B in the treatment of patients with opioid dependence over treatment weeks 17–24. Additional secondary objectives were to assess the efficacy and safety of Probuphine in patients with opioid dependence over 16 and 24 weeks of treatment.

³ When Titan entered Phase 3 of the Probuphine clinical development program, the Applicant still had some uncertainty about the total duration of therapy with the Probuphine implants. While the Applicant was operating under the premise that the implant provided buprenorphine for a total of six months, they acknowledged that it was possible that it only delivered active drug for four. As such, when they proceeded with the PRO-805 clinical trial, the strategy taken was to use a four-month window for the primary analysis and to subsequently also evaluate the six-month time period. The second Phase 3 study to replicate findings would be of six month duration if it worked for that whole time period during the initial study and a four-month duration if it worked for the lesser of the time periods. Since Titan judged that the implant lasts for six months, the fourth month evaluations are no longer of relevance.

PRO-805 Overall Study Design

This was a randomized, double-blind, placebo-controlled, multi-center study of Probuphine in patients with opioid dependence. After meeting initial screening criteria, patients underwent induction with sublingual (SL) buprenorphine (as Subutex [(original protocol and Amendment 1] and later Suboxone [Amendment 2]). Subjects were to reach a target dose of 12–16 mg/day within 10 days of Screening, and were to receive a fixed dose of 12–16 mg/day of SL buprenorphine (BPN) for a minimum of three consecutive days prior to randomization. Following successful induction, subjects were randomized 2:1 to receive 4 Probuphine implants (Group A) or 4 placebo implants (Group B) that were to remain in place for six months.

The protocol called for all patients to attend manual-guided psychosocial counseling per a version of the Individual Drug Counseling Manual. The protocol also permitted receipt of supplemental SL BPN if clinically indicated, if meeting one or more of the following protocol-defined guidelines:

- Withdrawal symptoms with a score of >12 on the COWS
- Cravings with a score of >20 mm on the opioid-cravings VAS
- Subject request for supplemental SL buprenorphine deemed appropriate by the investigator

PRO-805 Study Population: Planned enrollment was 150 patients at approximately 30 study sites. The protocol specified that subjects had to first meet a set of initial screening criteria, and then another set of randomization criteria at the end of sublingual induction, in order to be randomized.

Initial Screening Criteria (Prior to Induction)

Inclusion Criteria

- Adults, ages 18–65 years
- Current opioid dependence by DSM-IV criteria
- Reliable means of contraception

Exclusion Criteria

- Acquired Immune Deficiency Syndrome (AIDS) diagnosis
- Laboratory criteria: AST or ALT $\geq$ 3xULN; Total bilirubin $\geq$ 1.5xULN; and/or creatinine $\geq$ 1.5xULN
- Treatment for opioid dependence (e.g., methadone, BPN), within previous 90 days
- Current diagnosis of chronic pain requiring opioids for treatment
- Candidates for only short-term opioid treatment or opioid detoxification therapy
- Pregnancy or lactation
- Hypersensitivity or allergy to BPN- or EVA-containing substances or naloxone
- Use of agents metabolized through CYP 3A4
- Anti-coagulant therapy (such as warfarin) or INR > 1.2
- Other psychoactive substance dependence other than opioids or nicotine (e.g., alcohol, sedatives) per DSM-IV criteria
- Benzodiazepine use other than physician-prescribed use
- Significant medical or psychiatric symptoms or dementia which in the opinion of the Investigators would preclude compliance with the protocol, patient safety, adequate cooperation in the study, or obtaining informed consent

- Concurrent medical conditions (such as severe respiratory insufficiency) that may prevent the patient from safely participating in study; and/or any pending legal action that could prohibit participation and/or compliance in study
- Clinical study participation within the previous 8 weeks

Randomization Criteria (Following induction)

- Continue to meet all inclusion criteria
- Meet no exclusion criteria
- Underwent induction with SL BPN to a dose of 12–16 mg/day as clinically appropriate within 10 days of screening (and received a fixed dose of 12–16 mg/day SL BPN for at least 3 consecutive days immediately prior to randomization).
 - Patients who underwent induction with SL BPN to a dose < 12 mg/day or > 16 mg/day were ineligible
- No significant withdrawal symptoms (defined as a score ≤ 12 on the Clinical Opiate Withdrawal Scale [COWS])
- No significant cravings for opioids (defined as a score ≤ 20-mm on the 100-mm Opioid Craving VAS)

PRO-805 Study Procedures

PRO-805 Study Procedures: Study Treatments

Sublingual Buprenorphine Induction

Subjects underwent induction with sublingual (SL) buprenorphine (BPN) as Subutex® (original protocol and Amendment 1) and later Suboxone® (Amendment 2). Induction was to have been completed within 10 days of Screening. Patients were to receive a fixed dose of 12–16 mg/day SL BPN for at least 3 consecutive days immediately prior to randomization.

Implants (Probuphine or Placebo) and Implantation

Following induction, SL BPN was to be discontinued and implants inserted 12–24 hours after the last SL BPN dose. It was recommended in the protocol that implants be inserted into the non-dominant arm. The insertion of Probuphine or placebo implants was to be into the inner side of the upper arm and performed under local anesthesia using a specialized applicator provided by Titan. For at least 30 minutes following insertion by medically qualified study staff, the protocol stipulated that patients be monitored closely for adverse events (AEs) and vital signs. The protocol allowed for an additional implant to be inserted at least 2 weeks after the initial implantation if the patient met protocol-defined criteria based on supplemental sublingual buprenorphine dosing (described in the *Supplemental Sublingual Buprenorphine Dosing* section below in this review).

Implant Packaging and Storage

The protocol described the packaging and storage of the implants as follows:

Each implant is individually packaged in a foil-lined pouch and (b) (4). Pouched implants are labeled and packaged into an individual Patient Kit (Box). All Initial Implant Kits contain either 4 Probuphine implants or 4 placebo implants. The Initial Implant Kit assigned to the patient is determined by the assigned treatment group. All Implant Dose Increase Kits contain only 1 implant, either a Probuphine implant or a placebo implant.

Patients will receive Implant Dose Increase Kits based upon the assigned treatment group.

All Patient Kits (Boxes) should be stored at room temperature (15–25°C [59–77°F]), in a secured, double locked area and in accordance with applicable laws, regulations and institutional requirements. Detailed dispensing records must be maintained, including date received, quantity received, date dispensed, and remaining inventory.

After implant removal, all implants should be returned as outlined in the MOP.

Supplemental Sublingual Buprenorphine Dosing

The protocol permitted supplemental SL buprenorphine (Suboxone[®]) during the study. The rules guiding administration of sublingual buprenorphine dosing, per protocol, were as follows:

Patients were to meet 1 or more of the following criteria:

1. Withdrawal symptoms scoring > 12 on Clinical Opiate Withdrawal Scale (COWS)
2. Request for dose increase by patient deemed appropriate by physician
3. Cravings > 20 mm on the Opioid Craving Visual Analog Scale (VAS)

The primary reason for the patient's need for Supplemental SL buprenorphine was to be noted in the Case Report Form (CRF).

Supplemental SL buprenorphine was to be administered in increments of 2 mg or more as clinically indicated. Investigators were advised that, as is the case when using other opioid agonist medications, a period of time should elapse between supplemental SL buprenorphine doses in order to determine clinical response. Investigators were advised that peak buprenorphine blood levels with Probuphine are seen within the first day post-implantation and that any supplemental SL buprenorphine, if needed soon after implantation, must be prescribed bearing that in mind.

Supplemental SL buprenorphine doses were to be administered under observation at the clinic/pharmacy and witnessed by a staff member to ensure that the SL tablet had completely dissolved under the patient's tongue. A maximum of 3 days of take-home dosing of Suboxone was allowed for weekends/holidays or other circumstances at the discretion of the investigator.

Dose Increases and treatment failures

Supplemental sublingual buprenorphine use thresholds were used to determine whether dose increases were required, and to establish treatment failure.

- Implant dose increase (1 additional Probuphine or Placebo implant): SL buprenorphine requirement ≥ 3 days/week for 2 consecutive weeks or ≥ 8 days over 4 consecutive weeks
 - The one additional implant could be inserted any time after the first 2–4 weeks following the initial insertion of 4 implants
[To allow for stabilization of blood levels, the additional implant (Implant Dose Increase) was not to be inserted within the first 2 weeks after insertion of the initial 4 implants]
- Treatment Failure: After implant dose increase, patient continued with same supplemental SL BPN needs that led to implant dose increase

Implant Removal

As stipulated in the protocol, patients had implants removed under local anesthesia through a small incision during the End of Treatment Visit.

Psychosocial Counseling

Manual-guided psychosocial counseling was required for all patients. Counseling (frequency, duration, training, etc.) was to be provided per a version of the US National Institutes of Health/National Institute on Drug Abuse Manual titled "Individual Drug Counseling."⁴ Counseling sessions were scheduled to take place 2 days per week during Weeks 1–12, then 1 day per week during Weeks 13–24. Additional counseling could be provided as clinically indicated; however, under certain circumstances, the additional counseling may have constituted a treatment failure. If a patient missed 6 consecutive counseling sessions after the Baseline Visit, the patient was considered non-compliant and was required to be withdrawn from the study.

PRO-805 Study Procedures: Blinding Mechanisms

Implant group assignments were double-blinded. The patient, investigational site personnel, Titan, and Titan designees directly involved in the conduct and/or monitoring of this study were not to be aware of the treatment group assignments.

The Implanting Physician and their staff were not to be informed of the treatment group assignments; however, since the placebo implants have a slightly different appearance than the Probuphine implants, the protocol dictated that the following would be agreed upon in a signed document by the Implanting Physician and the Investigator in order to maintain the blind:

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

Each implant was to be sealed in a foil-lined pouch such that the implant could not be seen from the outside of the sealed pouch. The implants were then packaged in a sealed Patient Kit (Box) that was to be opened only by the Implanting Physician and/or his/her staff.

⁴ Reference cited: Mercer D, Woody G. Individual Drug Counseling: adapted from the Naltrexone and Fluoxetine for Heroin Addiction Study; Philadelphia Veterans' Affairs Medical Center

PRO-805 Study Procedures: Evaluations and Procedures

The following evaluations and procedures took place over the course of the study as outlined in the Schedule of Events table that immediately follows this listing of evaluations and procedures:

Evaluation/Study-Specific Procedure	Comments
Informed Consent Form (ICF)	
Eligibility Criteria Review	
Randomization	
Medical History and Medication History	
Psychiatric History (MINI)	
Physical Examination	
Vital Signs	
Implant Insertion	Initial implantation, and implant dose increase if protocol-specified criteria were met.
Implant Site Examination/ Treatment Compliance	
Quality of Life (QOL)	Assessed via the Addiction Severity Index (ASI), which was to be utilized at Baseline, and follow-up questions on the ASI were to be utilized for subsequent visits at Weeks 16, 24 or early termination.
Withdrawal Symptoms and Cravings	Subjective Opiate Withdrawal Scale (SOWS), Clinical Opiate Withdrawal Scale (COWS), Opioid Craving Visual Analog Scale (VAS)
Illicit Drug Use Self-Report	Patients were to be questioned about illicit drug use. The drug name, number of days used, daily use, average cost per day, and whether the patient 'got high' was to be documented.
Clinical Global Impression – Self	Patients were to rate their current severity of opioid related problems and their improvement in symptoms of opioid dependence from baseline, using a 7-point Likert-type scale.
Clinical Global Impression – Observer	The treating physician and study personnel were to rate the patient's severity of opioid dependence covering 8 specific problem areas, using a 7-point Likert-type scale, as well as global severity of opioid dependence over the last week and the patient's degree of global improvement since baseline using a 7-point Likert-type scale.
Psychosocial Counseling	Manual-guided psychosocial counseling
Electrocardiogram (ECG)	

Evaluation/Study-Specific Procedure	Comments	
Clinical Laboratory Evaluations	Hematology	Hematocrit, Hemoglobin, red blood cells (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RBC Morphology, white blood cells (WBC) with differential, and platelets
	Chemistry (including liver profile)	Urea nitrogen, calcium, bicarbonate, chloride, creatinine, glucose, magnesium, potassium, sodium, albumin, alkaline phosphatase, amylase, AST (SGOT), ALT (SGPT), total bilirubin, total cholesterol, gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), lipase, total protein
	Coagulation	Prothrombin time (PT), INR
	Pregnancy Test	Serum or urine; females of child bearing potential only
	Urine Toxicology	Illicit opioids (including prescription analgesics, excluding BPN and its metabolites), amphetamines, antidepressants, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, methaqualone, phencyclidine, phenothiazine, propoxyphene
	Other	Plasma BPN and norBPN levels, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV)
Supplemental Sublingual Buprenorphine		
Implant Removal		
Adverse Events	- AEs occurring after induction and for up to 14 days after study drug treatment discontinuation (i.e., removal of implants) were required to be documented. - AEs designated as study drug related, and all serious AEs, were to be followed until resolution or stabilization. - AEs reported by the patient at times other than specified in the Schedule of Events should also have been recorded.	
Concomitant Medications / Procedures		
Telephone Contact	Patients were to be contacted by telephone 1 week ($\pm$ 2 days) after the removal of implants to capture any AEs that occurred since removal. Patients who completed the study and chose to enter the extension study were not to complete this visit.	

Table 2 Schedule of Events

Event	Screening		Baseline ³	Implant	Post-Implant ⁴	Treatment ⁶		End of Treatment ⁸	Follow-Up	
	Pre-Induction ¹	During Induction ² (Up to 10 days)								
Week				0		Urine Collection Visits Weeks 0–23	Weeks 1 ⁷ , 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20	24	25	26
Visit Number	S1	S ₂ (S2, S3, etc.)	1	2	3	M, W, F	4–14	15		16
Informed Consent	•									
Eligibility Criteria Review ⁸	•		•							
Randomization ⁵			•							
Medical History/Medication History MINI, v.5.0	•									
Substance Abuse History and Treatments	•									
Physical Examination ⁹	•		•				Week 16	•		
Vital Signs ¹⁰	•	•	•	• ^{11,12}	•		•	•		•
Implant Site Examination/Treatment Compliance ²³					•		•	•		•
Dispense Treatment Identification Card				•						
Quality of Life Questionnaire			•				Week 16	•		

Event	Screening		Baseline ³	Implant	Post-Implant ⁴	Treatment ⁶		End of Treatment ⁸	Follow-Up	
	Pre-Induction ¹	During Induction ² (Up to 10 days)								
Week				0		Urine Collection Visits Weeks 0–23	Weeks 1 ⁷ , 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20	24	25	26
Visit Number	S1	S ₂ (S2, S3, etc.)	1	2	3	M, W, F	4–14	15		16
Withdrawal Symptoms and Craving (SOWS, COWS, Opioid Craving VAS) ³²	•	•	• ¹³	• ¹⁴			Weeks 1, 4, 8, 12, 16 and 20	•		•
Illicit Drug Use Self-Report	•	•	•				•	•		•
CGI - Self	•						Week 16	•		
CGI - Observer	•						Week 16	•		
Psychosocial Counseling ^{30,31}							See Drug Counseling Manual			
ECG	•		•				Week 4	•		
Pregnancy Test ¹⁵	•		• ¹⁶				Weeks 4, 8, 12, 16 and 20	•		

Clinical Review
 Rachel Skeete, MD, MHS
 NDA 204442
 Probuphine® (buprenorphine implant)

Event	Screening		Baseline ³	Implant	Post-Implant ⁴	Treatment ⁶		End of Treatment ⁸	Follow-Up	
	Pre-Induction ¹	During Induction ² (Up to 10 days)								
Week				0		Urine Collection Visits Weeks 0-23	Weeks 1 ⁷ , 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20	24	25	26
Visit Number	S1	S ₂ (S2, S3, etc.)	1	2	3	M, W, F	4-14	15		16
Hematology and Chemistry	•	• ¹⁷					Weeks 1, 4, 12, 16 and 20	•		
Coagulation Profile	•	• ¹⁷					Weeks 1, 4, 12, 16 and 20	•		
Urine Toxicology ¹⁸			•			M, W, F	•	•		
Plasma BPN/norBPN levels ¹⁹			•	• ¹⁹			Weeks 1, 4, 8, 12, 16 and 20	•		
HBV, HCV, HIV ²⁰	•									
Induction (SL BPN)		•	• ²¹							
Implant ^{21, 22}				Insertion				Removal		
Supplemental SL BPN (Suboxone [®]) ²⁴						If needed (protocol-defined)				
ONE Implant Dose Increase ^{21, 25}							Anytime > 2 Weeks, if needed (protocol-defined)			
Adverse Events ²⁶		•	•	• ²⁷	•		•	•	•	•

Event	Screening		Baseline ³	Implant	Post-Implant ⁴	Treatment ⁶		End of Treatment ⁸	Follow-Up	
	Pre-Induction ¹	During Induction ² (Up to 10 days)								
Week				0		Urine Collection Visits Weeks 0-23	Weeks 1 ⁷ , 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20	24	25	26
Visit Number	S1	S ₂ (S2, S3, etc.)	1	2	3	M, W, F	4-14	15		16
Concomitant Medications/ Procedures		•	•	•	•		•	•		•
Wound Care Information Sheet ²⁸				•				•		
Telephone Contact ²⁹										•

1. Pre-Induction Visit assessments and procedures may be performed over a period of 3 days.
2. At least one visit will occur during the Induction period. The visits during Induction should be numbered S2, S3, S4, etc. Any additional assessments performed that are not listed above must be recorded on the appropriate CRF. Patients should receive a fixed dose of 12-16 mg/day SL BPN for at least 3 days immediately prior to randomization.
3. Baseline procedures/evaluations should be completed within 48 hours prior to the Implant Visit. If necessary, these procedures/evaluations can be completed at the Implant Visit, but PRIOR to, implantation.
4. The Post-Implant Visit must be 1 day after the Implant Visit.
5. All Treatment visits will be conducted within a window of ± 2 days.
6. Discuss the option to enter the extension study with patients who complete 24 weeks of treatment.
7. Week 1 Visit should occur 7 ± 2 days after Implant Visit.
8. Prior to initiating Induction for this study, Inclusion and Exclusion criteria must be met. Prior to Randomization, the criteria for Randomization must be met.
9. A complete physical exam of all major body systems will be performed.
10. Vital signs (temperature, blood pressure, pulse rate, and respiration rate) along with pupil diameter and weight will be measured; height is measured at Baseline Visit only.
11. Vital signs (temperature, blood pressure, pulse rate, and respiration rate) will be measured just prior to implantation (Initial as well as Implant Dose Increase, as applicable) then every 15 minutes after implantation for at least 30 minutes.
12. IMPLANT DOSE INCREASE ONLY: Vital Signs (temperature, blood pressure, pulse rate, and respiration) along with pupil diameter and weight will be measured within 48 hours prior to Implant Dose Increase. Study Staff other than Implanting Physician and/or Staff should measure the vital signs.
13. Must be performed prior to Randomization on day of Randomization to ensure that COWS score ≤ 12 and Opioid Craving VAS score ≤ 20-mm.
14. Withdrawal symptoms and craving assessments must be performed PRIOR to implantation. Implanting Physician or Implanting Staff may not perform assessments.
15. A serum pregnancy test at Screening and End of Treatment Visit will be collected. A urine pregnancy test will be required at Baseline PRIOR to Randomization and then every 4 weeks thereafter (for women of childbearing potential).
16. Urine pregnancy test must be performed prior to Randomization on day of Randomization.
17. Required blood tests must be performed after the patient has reached a dose of Suboxone[®] of 12-16 mg/day for 3 consecutive days and PRIOR to Randomization.

18. Urine samples will be collected Monday, Wednesday, and Friday ($\pm$ 1 day) throughout the study. Urine samples must be collected starting the first Monday, Wednesday, or Friday following implantation so that a total of 72 urine samples will be collected through End of Treatment. If a patient misses 9 consecutive urine collections after Baseline Visit, the patient will be considered non-compliant and will be withdrawn from the study.
19. Plasma for BPN/norBPN levels should be collected 12–24 hours after the most recent SL BPN dose, prior to implantation (for Initial Implant [Baseline] and Implant Dose Increase).
20. It is the Investigator's responsibility to be familiar and comply with all laws and regulations that apply to HIV, HBV, HCV and testing of blood.
21. SL BPN should be discontinued 12–24 hours prior to implantation.
22. Implantation must occur between 12–24 hours after the last SL BPN dose.
23. The implant site will be visually inspected. If there is any evidence of removal (or attempted removal), the patient will be withdrawn from the study and all implants will be removed (if applicable).
24. Patients may receive Supplemental SL BPN (Suboxone[®]) anytime after implantation if patient meets protocol-defined criteria. This will be administered under observation at the clinic/pharmacy except for take home weekend/holiday doses (See Section 6.5.1). Investigators are advised that peak BPN blood levels after Probuphine are seen within the first day post-implantation. Any Supplemental SL BPN, if needed soon after implantation, must be prescribed bearing that in mind.
25. Patients may receive one additional implant anytime after 14 days of the initial implantation if patient meets protocol-defined criteria (See Section 6.5.2). Patients will again undergo the following: Implant Visit, Post-Implant Visit, and Week 1 Visit and all subsequent visits until a TOTAL of 24 weeks from date of initial implant.
26. AEs that are reported by the patient at times during the study other than during the visits as specified above (i.e., at any clinic visit) must be recorded.
27. Patients will be monitored for at least 30 minutes after implantation for AEs.
28. Wound Care Information Sheet will be given to the patient after each insertion/removal procedure.
29. Patients will be contacted by telephone 1 week $\pm$ 2 days after removal of implants to capture any AEs that occurred since removal.
30. If any patient requires > 1 additional day per week of counseling (See Section 8.2) for 4 consecutive weeks (i.e., > 3 sessions per week during weeks 1–12 and > 2 sessions per week during weeks 13–24), the patient will be considered a treatment failure.
31. If a patient misses 6 consecutive counseling sessions after Baseline Visit, the patient will be considered non-compliant and will be withdrawn from the study.
32. If a patient reports of cravings or withdrawal symptoms at a visit where the measures are not scheduled, the SOWS, COWS and Opioid Craving VAS may be administered.
33. HBV, HCV and HIV testing is required unless a site's IRB prohibits such testing.

Source: PRO-805 protocol Amendment #2

PRO-805 Study Procedures: Patient Early Withdrawal Criteria

Protocol-specified criteria for early withdrawal from the study included:

- subject request
- subject non-compliance defined as refusal or inability to adhere to the study protocol:
 - if a subject missed 9 consecutive urine collections after the baseline visit, the subject was considered non-compliant and was withdrawn from the study
 - if a subject missed 6 consecutive counseling sessions after the baseline visit, the subject was considered non-compliant and was withdrawn from the study
 - any other instances of refusal or inability to adhere to the study protocol, as determined by the PI)
- treatment failure, defined as having either of the following supplemental buprenorphine or counseling needs any time after an implant dose increase:
 - $\geq$ 3 days/wk of supplemental SL buprenorphine for 2 consecutive wks
 - $\geq$ 8 days of supplemental SL buprenorphine over 4 consecutive wks
 - > 1 additional day per week of counseling for 4 consecutive weeks (i.e., > 3 sessions per week during Weeks 1–12 and > 2 sessions/ week during Weeks 13–24)
- 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 would, in the judgment of the investigator, affect assessments of clinical status to a significant extent, require discontinuation of drug, or both
- requirement for continual use of opioid analgesics >7 days or general anesthesia for surgery
- at the request of Titan, regulatory agencies, or the Institutional Review Board (IRB)
- loss to follow-up

Patients who met the above criteria were to be seen for an End of Treatment Visit, for implant removal and clinical evaluations as outlined for that visit.

PRO-805 Study Procedures: Safety Considerations

Data Safety Monitoring Committee

A Data Safety Monitoring Committee (DSMC) was to be established to safeguard the interests and safety of the study participants.

Concomitant Medications

- Opioid Analgesics – If continual use required for > 7 days, implants were removed and the subject withdrawn from study. Same in cases where general anesthesia was required for surgery.
- Cytochrome P450 3A4 inhibitors and inducers
 - Subjects excluded if on CYP3A4 inhibitors. Medical monitor was to be consulted if these inhibitors were required during study. Examples of CYP3A4 inhibitors included azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), and HIV protease inhibitors (e.g., ritonavir, indinavir, and saquinavir)
 - Use of CYP 3A4 inducers, such as phenobarbital, carbamazepine, phenytoin and rifampicin, were to be avoided. Medical monitor was to be consulted prior to starting any patients on any of these agents.
- Sedatives – use of other narcotic analgesics, sedative-hypnotics, benzodiazepines, phenothiazines, other tranquilizers, or other CNS depressants was to be minimized during Probuphine treatment. Medical monitor consultation required if these sedatives were required during study.

Treatment Identification Card

Patients were to receive a card indicating that they were participating in a placebo-controlled clinical research study and may be receiving buprenorphine via a subcutaneous implant. The card was to be presented to health care providers by the patient in the event of an emergency or requirement for medications such as opioid analgesics.

Wound Care Information Sheet

Patients were to receive written instructions explaining how to care for the surgical site after implant insertion and/or removal.

Implant Site Examination

The implant site was to be visually inspected for evidence of erythema, edema, itching, pain, infection, bleeding, abnormal healing, and any other abnormalities. If there was any evidence of *removal*, the patient was to confirm the removal of some or all of the implants, and the patient was to be withdrawn from study. If there was evidence of *attempted removal*, the patient was to be withdrawn from the study and all implants were to be removed. If, upon removal, the Implanting Physician had difficulty locating the implants, they were advised that ultrasound could be used to facilitate their localization. Due to the non-biodegradable nature of the Probuphine and placebo implants, it was considered vital that no patient be lost to follow-up to ensure that proper implant removal and Follow-Up Visits were completed.

Possible Impairment

Patients were instructed to avoid operating heavy machinery and exercise caution in activities requiring alertness, such as driving, during the first few days after implant insertion or until such

time that they were reasonably certain that their ability to engage in such activities was not adversely affected.

PRO-805 Statistical Considerations

Titan outlines the following statistical methods for the protocol.

Sample Size Justification

The primary analysis will evaluate the efficacy of Probuphine versus placebo via a stratified Wilcoxon rank sum (van Elteren) test comparing the cumulative distribution functions of the percentages (%) of urine samples negative for illicit opioids between groups at 16 weeks. The test will be stratified on gender and (pooled) site. In order to detect a shift of 20% between the placebo and active arms using a 2-sided alpha of 0.05 and 80% power, approximately 150 patients will be required. This was to take into account the 2:1 randomization, normal distributions without stratification with a common standard deviation of 30% as a conservative powering model, and an attrition rate of approximately 40%.

Stratification and Randomization

Titan indicates that in a previously published study on Subutex[®], women were less likely to give clean urine samples regardless of dose, indicating that gender may be an important prognostic factor.⁵

To control for this, randomization was stratified by gender. Stratification was also to be by site. Due to the size of the study, it was expected that patients would be balanced for various other baseline factors, including age.

Patients were to be randomized in a 2:1 ratio (active:placebo). Randomization was to be performed centrally in blocks within strata (gender, site). An imbalanced randomization was chosen in order to increase exposure to Probuphine and decrease the number of patients receiving placebo implants.

Analysis Populations

The following analysis populations were defined:

- Intention-to-Treat (ITT) – all patients who were randomized and received an implant. Analyses based on this population grouped patients according to the treatment they were randomized to receive, regardless of actual treatment received, and is the primary analysis population.
- Efficacy Evaluable (EE) – all patients treated with implants who remained on study for at least 4 weeks of efficacy evaluation
- Safety – all patients treated with implants

Analysis Methodology

General Conventions:

- Missed urine samples were considered positive.

⁵ References cited:

1. NDA 20-732 / NDA 20-733. (2002). Summary Basis of Approval for Subutex (NDA 20-732) and Suboxone (NDA 20-733). 8 October 2002. Retrieved on 2 December 2004 from http://www.fda.gov/cder/foi/nda/2002/20-732_20-733_Subutex.htm.
2. Ling W, Wesson DR. Clinical efficacy of buprenorphine: comparisons to methadone and placebo. *Drug and Alcohol Dependence* 2003; 70:S49-S57.

- After a patient was withdrawn from study (e.g. treatment failure), their urine samples from that point onward were to be considered positive.
- All tests were to be conducted at $\alpha = 0.05$, 2-sided, unless otherwise specified.
- Missing values in COWS, SOWS, and Craving VAS were imputed using the Last-Observation-Carry-Forward mechanism.

Efficacy Analysis:

- Primary Analysis: The primary analysis was to determine if the cumulative distribution of % urine samples negative at week 16 (during weeks 1 to 16) in the Probuphine implant group (Group A) was significantly greater than that in the placebo implant group (Group B). This primary efficacy analysis was to be conducted on the ITT population. It was to compare the cumulative distribution functions of % negative urines at 16 weeks between Group B and Group A using a stratified Wilcoxon rank sum (Van Elteren) test using gender and (pooled) site as stratification factors. This analysis was to be supported by presentation of the cumulative distribution functions by treatment group. Pooling of sites was by geographic region using an algorithm determined before database lock and unblinding. Thrice weekly urine samples were to be taken throughout the entire treatment period (6 months). The denominator for percentage urine samples for the primary endpoint was to be all possible urine samples that could have been collected since implantation through month 4 (week 16 of the study), which would be 48 urine samples per patient (i.e., missed visits/samples would be considered positive, and after a patient was withdrawn from study, their urine samples from that point onward were considered positive).

Although as originally planned, the ascertainment window for the primary analysis was Weeks 1 to 16, the ascertainment window that was ultimately used was Weeks 1 to 24. When Titan entered Phase 3 of the Probuphine clinical development program, the Applicant still had some uncertainty about the total duration of therapy with the Probuphine implants. While the Applicant was operating under the premise that the implant provided buprenorphine for a total of six months, they acknowledged that it was possible that it only delivered active drug for four. As such, when they proceeded with the PRO-805 clinical trial, the strategy taken was to use a four-month window for the primary analysis and to subsequently also evaluate the six-month time period. The second Phase 3 study to replicate findings would be of six month duration if it worked for that whole time period during the initial study and a four-month duration if it worked for the lesser of the time periods. Since Titan judged that the implant lasts for six months, the fourth month evaluations are no longer of relevance.

- Secondary Analyses

Secondary efficacy outcome measures included:

- Cumulative distribution function of the percent of urine samples negative for illicit opioids over weeks 17–24 of treatment
- Mean percent urines negative for illicit opioids
- Proportion (%) of study completers
- Mean total number of weeks of abstinence
- Mean maximal period of continuous abstinence
- Mean total score on the Subjective Opioid Withdrawal Scale (SOWS)
- Mean total score on the Clinical Opiate Withdrawal Scale (COWS)
- Mean subjective opioid craving assessment (VAS)
- Patient and physician rated Global Improvement
- Pharmacokinetic analyses

- **Additional Analyses**

The following endpoints were considered exploratory:

- Self-report of illicit drug use (opioids, amphetamines, barbiturates, benzodiazepines, cocaine, methadone)
 - Supplemental SL buprenorphine use
 - Quality of Life
- **Safety Analysis:** Adverse event, vital sign, patient disposition and reason for study termination, concomitant medications, and laboratory evaluation summaries were to provided based on analyses of safety data.

Key Protocol Amendments:

PRO-805 initiated April 2, 2007; Completed June 19, 2008

Amendment #1 (September 1, 2006)

- Additional stratification by site
- Manual-guided psychosocial counseling: a revised version of the US National Institutes of Health/National Institute on Drug Abuse Manual titled “Individual Drug Counseling” will be utilized. This revised version has been adapted for the treatment of opioid dependence.
- Exclusion criteria clarified: “Candidates for only short term OPIOID TREATMENT or opioid detoxification therapy,” and “Current anti-coagulant therapy (SUCH AS WARFARIN) or an INR>1.2.”
- Additional criteria for induction added: Additional criteria for induction of “and receive a dose of 12–16 mg/day SL BPN for at least 3 days prior to randomization.”
- Additional Criteria for early withdrawal:
 - If a patient misses 6 consecutive counseling sessions after Baseline Visit, the patient will be considered non-compliant and will be withdrawn from the study.
 - “At the request of Titan, regulatory agencies, or IRB.”
 - Lost to follow-up
- Addition of the frequency of counseling sessions: 2 days per week during Weeks 1–12, then 1 day per week during Weeks 13–24.
- Wound Care information sheet added
- The requirement to “perform an ultrasound if evidence of removal or attempted removal is observed” has been removed since this was grounds for withdrawing the patient from the study. The patient will be withdrawn from the study, and all implants will be removed (if applicable).
- Urine toxicology: Addition of the following: “The temperature of a urine sample within 4 minutes of voiding should fall within the range of 32 degrees Celsius to 37.7 degrees Celsius (90 degrees Fahrenheit to 100 degrees Fahrenheit). If test results are outside these ranges, the patient will be asked to immediately provide another urine sample. If this second sample is outside of the temperature range, the sample will be counted as 'missing', and documented on the appropriate CRF.”
- Clarification throughout the Schedule of Events for Supplemental SL BPN and Implant Dose Increase: “if patient meets protocol-defined criteria.”

Amendment #2 (April 4, 2007)

- Revision of primary and secondary efficacy endpoints
- Changed “Subutex®” to “Suboxone®.”

- Additional sublingual buprenorphine criterion added for dose increase (additional implant) and definition of Treatment failure.
- Addition of “sedative hypnotics” to list of sedatives.
- Additional wording added: “HBV, HCV, HIV testing is required unless a site’s IRB prohibits such testing.”
- Addition of “Clinical Global Impression – Self.”
- Addition of “Clinical Global Impression – Observer.”
- Addition of “Psychiatric History and MINI” to the list of assessments/procedures for the Pre-Induction Visit.
- Addition of “MINI (Mini International Neuropsychiatric Inventory, Version 5.0).”

Study Outcome:

Subject Characteristics:

A total of 348 subjects were screened and 163 were enrolled with 108 randomized to treatment with Probuphine and 55 randomized to treatment with placebo.

Enrollment By Center:

PRO-805 was conducted in the US and randomized patients at 18 sites. Enrollment was distributed among centers as shown in the table below.

Site №	Institution Name and Site Investigators	Enrollment
02	Behavioral Pharmacology Research Unit Behavioral Biology Research Center Johns Hopkins University School of Medicine/Bayview Campus Baltimore, MD PI: Bigelow, George, PhD Cansino, Catherine, MD Harrison, Joseph A. Hsu, Pilan Jamshidi, Roxanne, MD Nanda, Leticia V, NP Singh, Rameet, MD Strain, Eric C., MD Umbricht, Annie, MD	N = 11 patients • Probuphine: n = 7 • Placebo: n = 4
04	New York VA Medical Center New York, New York PI: Casadonte, Paul, MD Ballert, Erik, MD Lautin, Andrew, MD Lorin, Jeffrey, MD Rotrosen, John, MD Thakkar, Vatsal, MD	N = 18 patients • Probuphine: n = 13 • Placebo: n = 5
06	Providence Behavioral Health Services Everett, Washington	N = 3 patients • Probuphine: n = 2

Site No	Institution Name and Site Investigators	Enrollment
	PI: Dickinson, William E., DO Abbott, Stephanie, PharmD De Jong, Randall, ARNP Patz, John D., DO	Placebo: n = 1
07	St. Luke's Roosevelt Hospital Center Behavioral Sciences Research Unit, 11 th Floor New York, New York PI: Rosenthal, Richard N., MD Ajwani, Neena, BA Cummings, Allegra, MD McGahee, Wendy, MD Merchan, Luz M., CCRC Posner, Daniel, MD	N = 1 patient - Probuphine: n = 0 - Placebo: n = 1
09	UCLA Los Angeles, California PI: Ling, Walter, MD Chim, David, DO Dickerson, Daniel, DO Heinzerling, Keith, MD Miotto, Karen, MD Modir, Shahla Mooney, Larissa Torrington, Matthew	N = 13 patients - Probuphine: n = 9 - Placebo: n = 4
11	Duke University Medical Center Durham, North Carolina PI: Patkar, Ashwin, MD Mannelli, Paolo Marks, David McCain, Karen	N = 11 patients - Probuphine: n = 8 - Placebo: n = 3
12	Wayne State University School of Medicine Department of Psychiatry and Behavioral Neuroscience Detroit, Michigan PI: Greenwald, Mark, PhD Cederlind, Lark Christensen, Carl, MD, PhD Eadie, Michael, MD Lundahl, Leslie H. Pihlgren, Eric M., PhD Steinmiller, Caren L., PhD Stine, Susan M.	N = 6 patients - Probuphine: n = 4 - Placebo: n = 2
17	SSTAR: Stanley Street Treatment & Resources Fall River, Massachusetts PI: Bailey, Genie L., MD Alexandre, Holly, MD Arena, Andrea MD Holmes, Katherine, MD Putney, Andrew, MD	N = 6 patients - Probuphine: n = 5 - Placebo: n = 1

Site No	Institution Name and Site Investigators	Enrollment
19	University of Pennsylvania Treatment Research Center Philadelphia, Pennsylvania PI: Kampman, Kyle M., MD Callahan, Patricia Dackis, Charles, MD Dumon, Kristoffel, MD Woody, George E., MD Yu, Elmer, MD, FASAM	N = 18 patients • Probuphine: n = 12 • Placebo: n = 6
20	Northwest Behavioral Research Center Roswell, Georgia PI: Banov, Michael D., MD Bay, Scot, MD Calhoun, Cathie, APRN Jay, Daniel, MD	N = 5 patients • Probuphine: n = 3 • Placebo: n = 2
21	VA Medical Center Puget Sound Healthcare System Seattle, Washington PI: Saxon, Andrew J., MD Bigda, Susan, RN Bondurant, Timothy, MD Bounkeua, Phoumy, PA Buchholz, Jonathan Cornell, Teresita Dandala, Kalyan Farsje, Lisa Ferguson, Laura, MD Fukuda, Yoko, MD Malte, Carol Meredith, Charles, MD Olley, Jennifer Raugi, Gregory J., MD Reoux, Joseph, MD Robinson, Joseph Sullivan, Norah, ARNP Wruck, Kevin	N = 3 patients • Probuphine: n = 1 • Placebo: n = 2
25	Pahl Pharmaceutical Research, LLC Oklahoma City, Oklahoma PI: Pahl, Jorg J., MD Zaza, Ali, MD	N = 13 patients • Probuphine: n = 8 • Placebo: n = 5
26	Amit Vijapura, MD and Associates Jacksonville, Florida PI: Vijapura, Amit, MD Fricke, Gus F., ARNP Hunt, John B., MD Jacobs, Jr., William S. Mitchell, Kelly, LMHC	N = 12 patients • Probuphine: n = 8 • Placebo: n = 4
	North County Clinical Research	

Site No	Institution Name and Site Investigators	Enrollment
27	Oceanside, California PI: Isacescu, Valentin, MD Dumas, Diane, PsyD Lindamood, Timothy, MD Mays, C. Hugh, MD	N = 4 patients • Probuphine: n = 2 • Placebo: n = 2
30	Synergy Clinical Research National City, California PI: Ishaque, Saleem, MD Bari, Mohammed A., MD Delgado, Christine Jenkin, Frederick D., DO Paniccia, Gregory S., MD Petersen, Franklyn A., CCRC Vassilenko, Ekaterina, MD Villalpando, Yvette, CCRC	N = 12 patients • Probuphine: n = 8 • Placebo: n = 4
31	Scientific Clinical Research North Miami, Florida PI: Segal, Scott D., MD Andrade, Steven Bravo, Patricia Brovender, Herman A., MD Chavoustie, Steven E., MD, FACOG Cisneros, Wendy L., PsyD Gomez, Alexander M. Hall, Damien Marsh, Julie L., PhD Martin, Paul McKenzie, Rochelle Montero, Judith, PsyD Munoz, Jose L., Jr., CCMA Nelson, Alberta, OA Rego, Cynthia A. Rodriguez, Gustavo, BA Spears, Antonio, OA Webber-Lind, Briana, PsyD	N = 15 patients • Probuphine: n = 10 • Placebo: n = 5
32	Fidelity Clinical Research Lauderhill, Florida PI: Flaherty, David H., DO Andrade, Steven Bravo, Patricia, MD Brovender, Herman A., MD Chavoustie, Steven E., MD, FACOG Cisneros, Wendy L., PsyD Gomez, Alexander M. Hall, Damien Marsh, Julie L., PhD Martin, Paul McKenzie, Rochelle	N = 10 patients • Probuphine: n = 7 • Placebo: n = 3

Clinical Review
 Rachel Skeete, MD, MHS
 NDA 204442
 Probuphine® (buprenorphine implant)

Site No	Institution Name and Site Investigators	Enrollment
	Montero, Judith, PsyD Munoz, Jose L., Jr., CCMA Nelson, Alberta, OA Punjwani, Sohail, MD Rego, Cynthia A Rodriguez, Gustavo, BA Spears, Antonio, OA Webber-Lind, Briana, PsyD	
33	Psych Care Consultants Research St. Louis, Missouri PI: Malik, Azfar, MD Albanna, Faisal, MD Malik, Maheen, MD Malik, Shazia, MD Turner, W. Edward, MD	N = 2 patients • Probuphine: n = 1 • Placebo: n = 1

Source: Table generated by Reviewer from Financial Disclosure, Response to Office of Scientific Investigation Information Request, and Demography datasets.

Patient Disposition:

Patient disposition is shown in Table 12 in section 6.1.3 below.

PRO-805 patient disposition information is also summarized for the individual PRO-805 trial in greater detail in the following table.

Table 3 Patient Disposition PRO-805

Number of Patients in ITT Population [a]	Placebo N = 55	Probuphine N = 108	Total N = 163	P-Value [c]
Patient Completed Study (Weeks 1-24)	17 (30.9%)	71 (65.7%)	88 (54.0%)	<.0001
Patient Withdrew Early (Weeks 1-24)	38 (69.1%)	37 (34.3%)	75 (46.0%)	
Patient Completed Study (Weeks 1-16)	28 (50.9%)	88 (81.5%)	116 (71.2%)	<.0001
Patient Withdrew Early (Weeks 1-16)	27 (49.1%)	20 (18.5%)	47 (28.8%)	
Reason for Patient Early Withdrawal (Weeks 1-24) [b]				
Patient non-Compliance				
Patient missed 6 consecutive counseling sessions	7 (18.4%)	12 (32.4%)	19 (25.3%)	
Patient missed 9 consecutive urine collections after baseline visit	1 (2.6%)	2 (5.4%)	3 (4.0%)	
Refusal or inability to adhere to the study protocol	4 (10.5%)	7 (18.9%)	11 (14.7%)	
Treatment failure				
Patient required >= 3 days per week of Supplemental SL buprenorphine for 2 consecutive weeks or >= 8 days of Supplemental SL buprenorphine Over 4 consecutive weeks any time after Implant Dose Increase	2 (5.3%)	3 (8.1%)	5 (6.7%)	
Patient required > 1 additional day per week of counseling for 4 consecutive weeks (i.e., > 3 sessions per week during weeks 1-12 and > 2 sessions per week during weeks 13-24)	17 (44.7%)	0 (0.0%)	17 (22.7%)	
Evidence of implant removal or attempted removal of the implant	17 (44.7%)	0 (0.0%)	17 (22.7%)	
Unacceptable or intolerable treatment-related AE	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Pregnancy	0 (0.0%)	1 (2.7%)	1 (1.3%)	
Use of other treatments for opioid dependence	0 (0.0%)	4 (10.8%)	4 (5.3%)	
Use of any investigational treatment	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Patient request	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Intercurrent illness or circumstances that would, in the judgment of the investigator, affect assessments of clinical status to a significant extent, require discontinuation of drug, or both	9 (23.7%)	8 (21.6%)	17 (22.7%)	
Requirement for continual use of opioid analgesics > 7 days or general anesthesia for surgery	0 (0.0%)	0 (0.0%)	0 (0.0%)	
At the request of Titan Pharmaceuticals, regulatory authority or IRB	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Lost to Follow-Up	4 (10.5%)	10 (27.0%)	14 (18.7%)	
Other	0 (0.0%)	1 (2.7%)	1 (1.3%)	

Note: A completer for weeks 1-16 was defined as a patient that did not discontinue within 113 days after receiving an implant. A completer for weeks 1-24 was defined as a patient that completed the full 24 weeks of treatment. Patient 04014's reason for early withdrawal had been updated to treatment failure, due to use of supplemental SL buprenorphine.
 [a] The ITT population included all patients who had been randomized and had received an implant.
 [b] Percentage for each reason was based on the total number of patients early withdrawn.
 [c] P-Value was from Cochran-Mantel-Haenszel (CMH) stratified on gender and pooled site.

Source: PRO-805 Clinical Study Report, p. 100 – 1

The most common reasons for early withdrawal were treatment failure, non-compliance, patient request, and loss to follow-up.

Rescue medication use was the key factor in determining treatment failure. Recall that patients were to be discontinued from the study, per protocol, if they required rescue medication exceeding certain parameters, or missed more than a specified number of visits. Not surprisingly, a number of patients on placebo required rescue medication exceeding these limits and were therefore discontinued from the protocol. This has some potential to bias results because all urine samples collected after discontinuation were adjudicated as positive.

In this instance, loss to follow-up is a safety consideration because patients on Probuphine needed to return to have the implants removed, so those lost to follow-up may still have the implants in place. The consequences, if any, of Probuphine implants remaining in place indefinitely, are unknown.

Demographics:

Patient demographics and baseline characteristics are presented in the following tables and also shown in Table 10 in section 6 below.

Table 4 Patient Demographics PRO-805

	Placebo N=55	Probuphine N=108	Total N=163
Sex			
Male	40 (72.7%)	72 (66.7%)	112 (68.7%)
Female	15 (27.3%)	36 (33.3%)	51 (31.3%)
Race			
American Indian or Alaska Native	0 (0.0%)	5 (4.6%)	5 (3.1%)
Asian	1 (1.8%)	0 (0.0%)	1 (0.6%)
White	40 (72.7%)	82 (75.9%)	122 (74.8%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	1 (0.9%)	1 (0.6%)
Black or African American	6 (10.9%)	14 (13.0%)	20 (12.3%)
Other	8 (14.5%)	6 (5.6%)	14 (8.6%)
Ethnicity			
Hispanic or Latino	12 (21.8%)	12 (11.1%)	24 (14.7%)
Not Hispanic or Latino	43 (78.2%)	96 (88.9%)	139 (85.3%)
Age^a (yrs)			
n	55	108	163
Median	39.0	33.0	35.0
Mean (SE)	39.3 (1.58)	35.8 (1.06)	37.0 (0.89)
CI (Mean)	(36.09,42.42)	(33.71,37.90)	(35.22,38.72)
Range (minimum/maximum)	20/61	19/62	19/62

KEY: CI=confidence interval; SE=standard error; yrs=years
^a Calculated as the difference between Date of Birth and Date of Informed Consent, in years.

Source: PRO-805 Clinical Study Report, p. 54

Table 5 Patient Baseline Characteristics PRO-805

	Placebo N=55	Probuphine N=108	Total N=163
Meets DSM-IV criteria for opioid dependence			
Yes	55 (100.0%)	108 (100.0%)	163 (100.0%)
No	0 (0.0%)	0 (0.0%)	0 (0.0%)
First Diagnosed in 2002-2007	40 (72.7%)	78 (72.2%)	118 (72.4%)
First Diagnosed in 1996-2001	4 (7.3%)	17 (15.7%)	21 (12.9%)
First Diagnosed in 1990-1995	6 (10.9%)	8 (7.4%)	14 (8.6%)
First Diagnosed in 1984-1989	1 (1.8%)	1 (0.9%)	2 (1.2%)
First Diagnosed in 1978-1983	3 (5.5%)	1 (0.9%)	4 (2.5%)
First Diagnosed in 1972-1977	1 (1.8%)	1 (0.9%)	2 (1.2%)
First Diagnosed in 1966-1971	0 (0.0%)	2 (1.9%)	2 (1.2%)
Current primary opioid of abuse			
Heroin	34 (61.8%)	69 (63.9%)	103 (63.2%)
Prescription opioid pain reliever	21 (38.2%)	39 (36.1%)	60 (36.8%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)
Previously treated for substance abuse/dependence			
Yes	36 (90.0%)	73 (86.9%)	109 (87.9%)
No	4 (10.0%)	11 (13.1%)	15 (12.1%)
Missing	15	24	39

KEY: DSM-IV= Diagnostics and Statistical Manual of Mental Disorders revision IV.
 NOTE: Percentages were based on total number of subjects with non-missing records.

Source: PRO-805 Clinical Study Report, p. 55

Overall, the groups were similar across demographic variables. Generally, the enrolled subjects were White, non-Hispanic/Latino males in their early to late 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.

Dosing Information:

All patients received four implants initially. Exposure to implant data are summarized in the following table:

Outcome Statistics	Placebo N=55	Probuphine N=108	Overall N=163
Weeks of Exposure to Implant			
n	55	108	163
Median	16.6	24.0	24.0
Mean (SE)	16.0 (1.26)	21.8 (0.69)	19.8 (0.66)
CI of Mean	13.42, 18.49	20.41, 23.15	18.51, 21.12
Range (minimum/maximum)	3/34	0/43	0/43

KEY: CI=confidence interval; SE=standard error.

Source: PRO-805 Clinical Study Report, p. 73

Twenty-two (20.4%) of the Probuphine subjects and thirty-two (58.2%) of the placebo subjects received a one implant dose increase to a fifth implant.

Major Protocol Violations

The following major protocol violations were noted:

Probuphine

(b) (6)	• Received disallowed med – methadone. Pt. put into detox after his probation officer tested his urine. Pt. was required to take methadone while at the detox center.
	• At implant visit, only 3 of 4 implants received, 4 th fell on the floor and was contaminated so given at a later date.
	• pt. never received fixed dose of 12 mg for 3 consecutive days, pt. only took 8 on 10/15
	• had exclusionary VAS score of 048 at baseline (i.e., baseline opioid craving > 20)
	• VAS score exclusionary
	• VAS score exclusionary
	• VAS score exclusionary

Source: Listing xxx 'Yes' answers

Placebo

(b) (6)	• Did not meet inclusion criteria of VAS < 20. Although pt was stabilized to an induction dose of 16mg/day, he received only 8 mg on his last day of induction (due to coordinator oversight – see note to file) which destabilized him and lead to increase
	• implanted with COWS > 20
	• took disallowed medication – methadone
	• VAS score of 37 mm, and randomized due to staff oversight, COWS = 2, SOWS = 0

Source: 'Yes' answers, PRO-805 Clinical Study Report, Appendix 16.2.2 (Listing 35)

The distribution of protocol violations, both number and type, was similar across the treatment arms, and not anticipated to materially impact interpretation of the efficacy findings.

Efficacy Results are reported and discussed in Section 6, below.

Safety Results are discussed in Section 7, below.

PRO-806

Title:	A Randomized, Placebo and Active-Controlled, Multi-Center Study of Probuphine in Patients with Opioid Dependence	
Protocol & Amendment Dates	• Protocol No. PRO-806: October 30, 2009 • Amendment No. 1: February 17, 2010 • Amendment No. 2: June 11, 2010 • Amendment No. 3: September 28, 2010	
Study Initiation & Completion Dates	• Initiation: April 22, 2010 • Completion: May 12, 2011	

PRO-806 Objective/Rationale:

The *primary objective* was to confirm the efficacy of Probuphine versus placebo in adult subjects with DSM-IV-TR defined opioid dependence, over Weeks 1–24 of outpatient treatment, through the assessment of thrice-weekly urine toxicology results.

The *key secondary objectives* were to evaluate the efficacy of Probuphine versus placebo in adult subjects with DSM-IV-TR defined opioid dependence, over Weeks 1–16 and Weeks 17–24 of outpatient treatment, through the assessment of thrice-weekly urine toxicology results; and to demonstrate non-inferiority of Probuphine versus SL BPN in adult subjects with DSM-IV-TR defined opioid dependence, over Weeks 1–24 of outpatient treatment, through the assessment of thrice-weekly urine toxicology results.

It should be noted here that Titan was informed that an open-label sublingual arm would not be appropriate [REDACTED] (b) (4) and that they should consider a double-dummy design for the trial. Titan later explained that [REDACTED] (b) (4). Additionally, throughout the development program, when Titan was considering a non-inferiority study only, Titan had been informed that an appropriate NI margin has not been established.

Another secondary objective was to evaluate additional measures of efficacy and safety across the three treatment groups, over 16 and 24 weeks of treatment.

PRO-806 Overall Study Design

This was a randomized, placebo- and active-controlled, multi-center study of Probuphine in adult outpatients with opioid dependence. After meeting initial screening criteria, patients underwent induction with sublingual (SL) buprenorphine (as Suboxone). Subjects were to reach a target dose of 12–16 mg/day for a minimum of three consecutive days, immediately prior to randomization and within 16 days⁶ of the start of induction, to be randomized. Following successful induction, subjects were randomized 2:1:2 to receive 4 Probuphine implants (Group A) or 4 placebo implants (Group B) that were to remain in place for six months, or open-label treatment with 12–16 mg/day SL buprenorphine.

⁶ 10 days in PRO-805

The protocol called for all patients to attend twice-weekly manual-guided drug counseling during study Weeks 1–12 and weekly drug counseling during Weeks 13–24, as described in the Individual Drug Counseling Manual. The protocol also permitted receipt of limited supplemental sublingual buprenorphine if clinically indicated, if subjects met *all* of the following criteria:

- Withdrawal symptoms with a score of >12 on the COWS
- Cravings with a score of >20 mm on the Opioid Craving VAS
- Subject request for supplemental SL buprenorphine deemed appropriate by physician

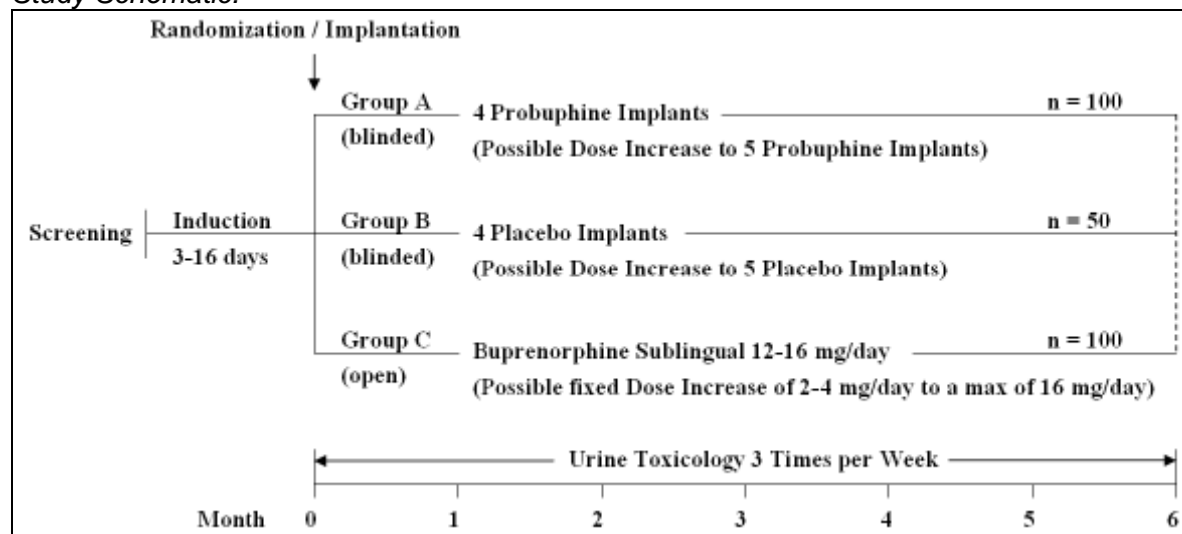
In PRO-805 they had to meet one or more vs. all three of the above protocol-defined guidelines, as required in PRO-806.

(Note: there was less sublingual buprenorphine use in Study PRO-806 compared with PRO-805, likely because of the stricter criteria that needed to be satisfied in order to receive supplemental).

The protocol stipulated a requirement for implant dose increases in the Probuphine and placebo implant arms based on a predetermined frequency of rescue sublingual buprenorphine usage. Similarly, subjects in the OL sublingual buprenorphine arm could receive a dose increase of 2–4 mg, arriving at a fixed dose, not to exceed 16 mg/day as determined by the Investigator under certain protocol-specified conditions. One dose reduction was also permitted for subjects in this arm, under certain circumstances, but the new dose could not be lower than 12 mg/day.

For all arms of the study, the protocol-defined criteria for treatment failure were based on supplemental SL buprenorphine needs following the implant dose increase in the implant arms, or a dose increase to 16 mg in the OL sublingual buprenorphine arm.

Study Schematic:



Source: PRO-806-A3 protocol, p. 10

PRO-806 Study Population: Planned enrollment was 250 patients at approximately 20–25 study sites. The protocol specified that subjects had to meet a set of initial entry criteria prior to the SL buprenorphine induction phase (and in certain instances, specific laboratory criteria

could have been met after starting induction). An additional set of randomization criteria needed to be satisfied at the end of sublingual induction in order to be randomized.

Initial Screening Criteria (Prior to Induction)

Inclusion Criteria

- Adults, ages 18–65 years
- Current opioid dependence by DSM-IV-TR criteria
- Reliable means of contraception

Exclusion Criteria

- Acquired Immune Deficiency Syndrome (AIDS) diagnosis
- Medication-assisted treatment for opioid dependence (e.g., methadone, buprenorphine), within previous 90 days
- Current diagnosis of chronic pain requiring opioids for treatment
- Candidate for only short-term opioid treatment (<6 mos) or opioid detoxification therapy
- Pregnancy or lactation
- Hypersensitivity or allergy to BPN- or EVA-containing substances or naloxone
- Use of agents metabolized through CYP3A4
- History of coagulopathy within past 90 days and/or anti-coagulant therapy such as warfarin
- Psychoactive substance dependence other than opioids or nicotine (e.g., alcohol, sedatives) per DSM-IV-TR criteria
- Significant medical or psychiatric symptoms, cognitive impairment, or other factors which in the opinion of the Investigator would preclude compliance with the protocol, patient safety, adequate cooperation in the study, or obtaining informed consent
- Current medical conditions such as severe respiratory insufficiency that may prevent the patient from safely participating in study; or any pending legal action that could prohibit participation or compliance in study
- Investigational drug use within the previous 8 weeks
- Previous exposure to Probuphine, or prior implantation with a placebo implant in the context of a Probuphine clinical trial

Exclusion Criteria (Prior to or After Starting Induction)

If clinically indicated, subjects were permitted to start induction prior to receiving the Screening Visit laboratory results, so long as they met all other Inclusion/Exclusion Criteria above. Subjects were eligible for randomization to treatment only if they did not meet the following exclusion criteria:

- Laboratory criteria: AST or ALT $\geq$ 3xULN; Total bilirubin $\geq$ 1.5xULN; and/or creatinine $\geq$ 1.5xULN
- Clinically significant low platelet count

Randomization Criteria (Following induction)

- Continued to satisfy all inclusion and exclusion criteria
- Underwent induction with SL buprenorphine to a dose of 12–16 mg/day as clinically appropriate within 16 days (vs. 10 days in PRO-805) of start of induction and received a fixed dose of 12–16 mg/day SL buprenorphine for at least 3 consecutive days immediately prior to randomization.
 - Patients who underwent induction with SL buprenorphine to a dose < 12 mg/day or > 16 mg/day were ineligible
- No significant withdrawal symptoms, scoring $\leq$ 12 on the Clinical Opiate Withdrawal Scale [COWS]
- No significant cravings for opioids, scoring $\leq$ 20 mm on the 100-mm Opioid Craving Visual Analog Scale (VAS), as measured at Baseline visit

PRO-806 Study Procedures

PRO-806 Study Procedures: Study Treatments

Sublingual Buprenorphine Induction

Subjects underwent induction with sublingual (SL) buprenorphine (BPN) as Suboxone[®]. Induction was to have been completed within 16 days of Screening (within 10 days of Screening in PRO-805). Patients had to receive a fixed dose of 12–16 mg/day SL buprenorphine for at least 3 consecutive days immediately prior to randomization in order to be eligible for randomization.

Implants (Probuphine or Placebo) and Implantation

Following induction, SL buprenorphine was to be discontinued and implants inserted 12–36 hours after the last SL buprenorphine dose (12–24 hours in PRO-805). The protocol made an allowance for small (2–4 mg) doses of SL buprenorphine to be administered during the 12 hours prior to implantation, at the Investigator's discretion, for the clinical management of subjects' withdrawal symptoms in advance of their insertion procedures. Additionally, the protocol allowed for delay of implantation in certain circumstances, and stated that: "In the case of extenuating circumstances where implantation must be significantly delayed and the Investigator wishes to extend induction into the day following the Baseline Visit or beyond, the Investigator must consult the Titan Medical Monitor to discuss the case and receive Titan approval, in order for the subject to remain in the study. Some baseline assessments may need to be repeated, depending on the circumstances and the length of the delay." (*The allowances for small doses of SL buprenorphine and delayed implantation were PRO-806 specific and not specified in PRO-805*).

The protocol specified that implantation under the skin, usually into the inner side of the subject's upper arm, was to be performed using a specialized investigational applicator provided by Titan. According to the protocol, the Probuphine Applicator that was to be used in PRO-806 is similar in design to the commercially-approved applicators currently used for the insertion of other implantable drugs, such as Implanon[®]. (New applicator used in PRO-806). The protocol specified that at the discretion of the implant physician, an alternative site other than the upper arm may be used, following consultation with the Titan Implant Medical Monitor. (*Preceding info PRO-806 specific*). Subjects were to be monitored closely for adverse events and vital signs for at least 30 minutes following insertion by medically qualified study staff. The protocol permitted insertion of an additional implant (dose increase) any time after 2 weeks had elapsed since the initial Dosing Visit, under protocol-defined criteria that were based on supplemental sublingual buprenorphine dosing (described below in the *Supplemental Sublingual Buprenorphine Dosing* section of this review).

Implant Packaging and Storage

The protocol described the packaging and storage of the implants as follows:

Each implant is individually packaged in a foil-lined, (b) (4) pouch. Pouches are then sterilized using gamma radiation. Pouched implants are labeled and packaged into an individual Patient Kit (Box). All Initial Implant Kits contain 4 Probuphine implants or 4 placebo implants. The Initial Implant Kit assigned to the patient is determined by the assigned treatment group. All Implant Dose Increase Kits contain only 1 implant, either a

Probuphine implant or a placebo implant. Patients will receive Implant Dose Increase Kits based upon the assigned treatment group.

All Patient Kits should be stored at room temperature (15–25°C [59–77°F]), in a secured, double locked area and in accordance with applicable laws, regulations and institutional requirements. Detailed drug accountability records must be maintained, including the dates shipments are received, the quantity of material received, the dates dispensed, the running inventory, and the unused quantities returned to Titan's drug supply vendor at the end of the trial.

After implant removal, all implants should be packaged and shipped to appropriate laboratory vendor, as outlined in the Study Manual of Procedures.

Open-Label (OL) Sublingual (SL) Buprenorphine (BPN) Treatment

Subjects in this treatment arm received open-label sublingual buprenorphine 12 to 16 mg/day and the treatment doses were to be taken once per day. The protocol permitted one dose reduction for subjects in the OL SL buprenorphine arm, in response to an adverse event, and if deemed clinically appropriate by the Investigator; the new dose was not to be lower than 12 mg/day. Subjects who were unable to tolerate 12 mg/day were to be withdrawn. Following a dose reduction, the subject was not permitted to receive a subsequent dose increase. Dose increases of 2–4 mg were also permitted, arriving at a fixed dose, not to exceed 16 mg/day as determined by the Investigator. Dose increases were permitted when pre-specified criteria for buprenorphine use were met (as described in the next section on *Supplemental Sublingual Buprenorphine Dosing*). The protocol permitted subjects in the OL SL buprenorphine to be provided with up to 7 days of treatment with SL buprenorphine at a time.

Supplemental Sublingual Buprenorphine Dosing

The protocol permitted supplemental SL buprenorphine (Suboxone®) during the study. However, SL buprenorphine was not supposed to be used for 24 hours prior to the collection of the pharmacokinetic sample.

The rules guiding administration of sublingual buprenorphine dosing, per protocol, were as follows:

Patients were to meet all of the following criteria (*1 or more for PRO-805*):

1. Withdrawal symptoms scoring > 12 on COWS
2. Request for dose increase by patient deemed appropriate by physician
3. Cravings > 20 mm on the Opioid Craving VAS

The primary reason for the administration of Supplemental SL BPN was to be noted in the Case Report Form (CRF).

Supplemental SL buprenorphine was to be administered in increments of 2 mg or more, as clinically indicated. Investigators were advised that, as is the case, when using other opioid agonist medications, a period of time should elapse between supplemental SL buprenorphine doses in order to determine clinical response. Investigators were advised that peak buprenorphine blood levels with Probuphine are seen within the first day following insertion of the implants and were advised to be very cautious when prescribing supplemental SL buprenorphine during that time.

Subjects requiring supplemental SL buprenorphine were required to obtain it at their study clinic or pharmacy. Supplemental SL buprenorphine doses were to be administered under observation at the clinic in order to verify that the SL tablet had completely dissolved under the subject's tongue. A maximum of 3 days of take-home SL buprenorphine was allowed for weekends, holidays, or other circumstances at the discretion of the investigator; a daily SL buprenorphine take-home dosing log was to be completed by subjects receiving take-home doses.

Subjects were reminded to bring the dispensed treatment SL buprenorphine to every visit. To detect diversion and monitor compliance, SL buprenorphine tablets were to be counted by the site staff at every urine collection visit.

Dose Increases and treatment failures

- Implant dose increase (1 additional Probuphine or Placebo implant): SL buprenorphine requirement ≥ 3 days/week for 2 consecutive weeks or ≥ 8 days over 4 consecutive weeks
 - The one additional implant could be inserted any time after the first 2–4 weeks following the initial insertion of 4 implants
 - [To allow for stabilization of blood levels, the additional implant (Implant Dose Increase) was not to be inserted within the first 2 weeks after insertion of the initial 4 implants]
 - The additional implant was to be placed in the same arm as the initial four implants, unless an alternative site was deemed clinically necessary by the implanting clinician.
 - Refusal to receive a dose increase when these criteria were met was considered noncompliance and resulted in withdrawal from study
- SL buprenorphine dose increase (OL SL buprenorphine arm): SL buprenorphine requirement ≥ 3 days/week for 2 consecutive weeks or ≥ 8 days over 4 consecutive weeks
 - SL buprenorphine dose increase of 2–4 mg, arriving at fixed dose not to exceed 16 mg/day as determined by the Investigator, and attained within a week's time
- Treatment Failure:
Supplemental sublingual buprenorphine use thresholds were used to determine whether dose increases were required, and to establish treatment failure.
 - *Probuphine or Placebo Implant arms:* After implant dose increase or SL buprenorphine dose increase, patient continues with same supplemental SL buprenorphine needs that led to implant dose increase
 - *OL SL Buprenorphine arm:* Subjects already at maximum dose in OL SL buprenorphine group (16 mg) considered treatment failures the first time the above SL buprenorphine criteria met

Following implant or SL buprenorphine dose increases, the protocol called for subjects to attend a second cluster of associated visits as outlined in the Schedule of Events.

Implant Removal

As stipulated in the protocol, patients would have implants removed under local anesthesia through a small incision during the End of Treatment Visit

Psychosocial Counseling

All subjects were to attend twice-weekly manual-guided drug counseling during study Weeks 1 – 12 and weekly drug counseling during Weeks 13 – 24, as described in the Individual Drug

Counseling.”⁷ Additional counseling could be provided as clinically indicated; however, under certain circumstances, additional counseling may also have constituted a treatment failure.

PRO-806 Study Procedures: Blinding Procedures

Implant group assignments were double-blinded. The patient, investigational site personnel, Titan, and Titan designees directly involved in the conduct and/or monitoring of this study were not to be aware of the treatment group assignments for the implant groups.

The Implanting Physician and their staff were not to be informed of the treatment group assignments; however, since the placebo implants have a slightly different appearance than the Probuphine implants, the protocol dictated that the following was to be agreed upon in a signed document by the Implanting Physician and the Investigator in order to maintain the blind:

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

Each implant was to be sealed in a foil-lined pouch such that the implant cannot be seen from the outside of the sealed pouch. The implants were then packaged in a sealed Patient Kit (Box) that was to be opened only by the Implanting Physician or his/her staff.

PRO-806 Study Procedures: Evaluations and Procedures

The following evaluations and procedures took place over the course of the study as outlined in the Schedule of Events table that immediately follows this listing of evaluations and procedures:

Evaluation/Study-Specific Procedure	Comments
Informed Consent Form (ICF)	
Eligibility Criteria Review	
Randomization	By Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS) managed by Titan.
Medical History and Medication History	

⁷ Reference cited: Mercer D, Woody G. Individual Drug Counseling: adapted from the Naltrexone and Fluoxetine for Heroin Addiction Study; Philadelphia Veterans' Affairs Medical Center

Evaluation/Study-Specific Procedure	Comments	
Substance Abuse History and Treatment	Complete history of previous & current illicit drug use, addictions, and treatments for any addictions (pharmacologic as well as non-pharmacologic) obtained during Screening Visit	
Psychiatric History (MINI)	Mini International Neuropsychiatric Interview, Version 6.0 (MINI) at Screening Visit	
Physical Examination and Abbreviated ROS		
Vital Signs		
Implant Insertion	Initial implantation and implant dose increase if protocol-specified criteria were met	
Implant Site Examination/Treatment Compliance	Implant site visually inspected. OL SL BPN arm to bring SL BPN at every visit (including urine tox) for counting	
Withdrawal Symptoms and Cravings	Subjective Opioid Withdrawal Scale (SOWS), Clinical Opioid Withdrawal Scale (COWS), Opioid Craving Visual Analog Scale	
Illicit Drug Use Self-Report	Patients were to be questioned about illicit drug use. The drug name, number of days used, amount used per day, average cost per day, and whether the subject 'got high' was to be documented.	
Clinical Global Impression – Self	Patients were to rate their current severity of opioid related problems and their improvement in symptoms of opioid dependence from baseline, using a 7-point Likert-type scale.	
Clinical Global Impression – Observer	The treating physician and study personnel were to rate the patient's severity of opioid dependence covering 8 specific problem areas, using a 7-point Likert-type scale, as well as global severity of opioid dependence over the last week and the patient's degree of global improvement since baseline using a 7-point Likert-type scale.	
Beck Depression Inventory (BDI-II)	Self-report, multiple choice questionnaire used to assess the severity of depressive symptoms comprising 21 questions. Final score totaled to indicate the overall level of depressive symptoms	
Psychosocial Counseling		
Electrocardiogram (ECG)		
Clinical Laboratory Evaluations	Hematology	Hematocrit, Hemoglobin, red blood cells (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RBC Morphology, white blood cells (WBC) with differential, and platelets
	Chemistry (including liver profile)	Urea nitrogen, calcium, bicarbonate, chloride, creatinine, glucose, magnesium, potassium, sodium, albumin, alkaline phosphatase, amylase, AST (SGOT), ALT (SGPT), total bilirubin, total cholesterol, gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), lipase, total protein
	Coagulation Profile	Prothrombin time (PT), INR
	Pregnancy Test	Serum or urine; females of childbearing potential only
	Urine Toxicology	Illicit opioids (including prescription analgesics, excluding BPN and its metabolites), amphetamines, antidepressants, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, methaqualone, phencyclidine, phenothiazine, propoxyphene
	Other	Plasma BPN and NorBPN levels, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV)

Evaluation/Study-Specific Procedure	Comments
	The following instruction on urine toxicology sample and pharmacokinetic sample collection was provided: <u>Urine Toxicology</u>: The temperature of a urine sample within 4 minutes of voiding should fall within the range of range of 32.2 to 37.7 degrees Celsius (90 to 100 degrees Fahrenheit). If test results are outside these ranges, the subject will be asked to immediately provide another urine sample. If this second sample is outside of the temperature range, the sample will be counted as 'missing', and should not be sent for analysis (any such samples must be documented in the subject's records). <u>Pharmacokinetic sampling</u>: Plasma for buprenorphine and norbuprenorphine quantification will be collected as described in the schedule of assessments.
Supplemental SL BPN	
Implant Removal	
Adverse Events	- AEs occurring between ICF signing and 39 days after study drug treatment was discontinued were required to be documented in the CRF. - AEs that have been designated as study drug related, and all serious AEs, were to be followed until resolution or stabilization. - AEs that were reported by the patient at times other than specified in Schedule of Events should also have been recorded.
Pregnancy	Subjects who became pregnant were to have study treatment discontinued and be removed from the study as soon as possible. Pregnancies were to be followed until the birth of the child or the termination of the pregnancy.
Concomitant Medications / Procedures	
Telephone Contact	- Subjects were to be contacted by telephone 1 week ($\pm$ 2 days) after the removal of implants <i>and 25 days ($\pm$ 2 days) following the Week 26 Follow-Up Visit</i> to capture any AEs that occurred since removal <i>and/or within 30 days following the point at which the buprenorphine plasma levels resulting from study treatment are expected to be negligible.</i> - <i>If a significant AE was described by the subject and was judged by the Investigator as being possibly related to study treatment, the subject was to visit study site for an unscheduled follow-up assessment (separate from the Week 26 Follow-Up Visit).</i> - Neither of these Telephone Contacts was required for subjects who enrolled in the extension study.

Table 6 Schedule of Events

Event	Screening		Baseline ¹	Dosing	Post-Implant ²	Treatment ³		End of Treatment	Follow-Up		
	Screening	During Induction ⁴ (Up to 16 days)				Urine Collection Visits ⁵ Weeks 1-24	1, 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20		24	25	26
Informed Consent ⁶	•										
Eligibility Criteria Review ⁷	•		•								
Randomization ⁷			•								
Medical and Medications History / Substance Abuse History and Treatments	•										
MINI, v 6.0	•										
Physical Examination ⁸	•										
Abbreviated Review of Systems			•				Week 16	•			
Vital Signs	•	•	• ⁹	• ¹⁰	•		•	•		•	
Implant Site Examination / Treatment Compliance ¹¹					•		•	•		•	
Dispense Treatment Identification Card				•							

Event	Screening		Baseline ¹	Dosing	Post-Implant ²	Treatment ³		End of Treatment	Follow-Up		
	Screening	During Induction ⁴ (Up to 16 days)				Urine Collection Visits ⁵ Weeks 1-24	1, 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20		24	25	26
Withdrawal Symptoms and Craving (SOWS, COWS, Opioid Craving VAS) ¹²	•	•	•				Weeks 1, 4, 8, 12, 16 and 20	•		•	
Illicit Drug Use Self-Report	•	•	•				•	•		•	
CGI – Self / Observer	•						Week 16	•			
BD-II	•		•				Weeks 1, 4, 8, 12, 16 and 20	•			
Psychosocial Counseling ¹³							See Drug Counseling Manual				
ECG	•						Week 4	•			
Pregnancy Test ¹⁴ (for females of childbearing potential only)	•		•				Weeks 4, 8, 12, 16, 20	•			
Chemistry, Hematology and Coagulation Profile	•		•				Weeks 4 and 16	•			
Urine Toxicology	• ¹⁵			•		3 days/week (Weeks 1–24)					

Clinical Review
 Rachel Skeete, MD, MHS
 NDA 204442
 Probuphine® (buprenorphine implant)

Event	Screening		Baseline ¹	Dosing	Post-Implant ²	Treatment ³		End of Treatment	Follow-Up		
	Screening	During Induction ⁴ (Up to 16 days)				Urine Collection Visits ⁵ Weeks 1-24	1, 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20		24	25	26
Plasma BPN/norBPN levels			• ¹⁶	• ¹⁶			Weeks 1, 4, 8, 12, 16 and 20	•			
HBV, HCV, HIV ¹⁷	•										
Induction (SL BPN) ^{18, 19}		•	•								
Probuphine® or placebo Implants (Groups A and B)				Insertion				Removal			
Implant Insertion Procedure Assessment				•							
Implant Removal Procedure Assessment								•			
SL BPN 12-16 mg/day (Group C)				Daily Dosing							
ONE Implant Dose Increase (Groups A and B) or SL BPN Dose Increase (Group C) ²⁰							• ²⁰				
Supplemental SL BPN ^{21, 22}				If needed, protocol-defined							

Event	Screening		Baseline ¹	Dosing	Post-Implant ²	Treatment ³		End of Treatment	Follow-Up		
	Screening	During Induction ⁴ (Up to 16 days)				Urine Collection Visits ⁵ Weeks 1-24	1, 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20		24	25	26
Adverse Events ^{23, 24}		•	•	•	•		•	•	•	•	•
Concomitant Medications / Procedures		•	•	•	•		•	•		•	
Wound Care Information Sheet ²⁵				•				•			
Telephone Contact ²⁶									•		•

1. Baseline procedures/evaluations may begin once the subject has completed at least 3 consecutive days at the fixed dose of Induction SL BPN, and should be completed a day prior to the Dosing Visit.
2. The Post-Implant Visit must be 1 day after the Dosing Visit.
3. The Week 1 Visit should occur 7 ($\pm$ 2) days after the Dosing Visit. All subsequent Treatment Visits should be conducted within a window of $\pm$ 2 days.
4. At least one visit will occur during the Induction period. Subjects must receive a fixed dose of 12–16 mg/day SL BPN for at least 3 consecutive days immediately prior to randomization.
5. Urine Collection Visits will be conducted 3 days per week for weeks 1–24. A total of 72 urine samples will be collected through End of Treatment. If a subject misses 9 consecutive urine collections after the Dosing Visit, the subject will be considered non-compliant and will be withdrawn from the study.
6. Subjects must voluntarily provide written informed consent prior to any study-related procedures being performed.
7. Prior to initiating Induction for this study, All Inclusion and Exclusion criteria must be met. Prior to Randomization, Randomization criteria must be met. Screening assessments that will be greater than 4 weeks old at the time of Dosing Visit may need to be repeated prior to the Dosing Visit, as directed by the Medical Monitor.
8. A complete physical exam of all major body systems will be performed at the screening visit.
9. Vital signs (temperature, blood pressure, pulse rate, and respiration rate) along with pupil diameter and weight will be measured; height is measured at the Baseline Visit only.
10. Vital signs (temperature, blood pressure, pulse rate, and respiration rate) will be measured just prior to implantation, and then 15 minutes and 30 minutes after implantation.
11. The implant site will be visually inspected. If there is any evidence of removal or attempted removal of the implants, the subject will be withdrawn from the study and all implants will be removed.
12. If a subject reports craving or withdrawal symptoms at a visit where the SOWS, COWS and Opioid Craving VAS are not scheduled, the measures may be administered and entered as "unscheduled" assessments.
13. If a subject misses 6 consecutive counseling sessions after the Dosing Visit, the subject will be considered non-compliant and will be withdrawn from the study. Additional counseling can be provided as clinically indicated; however it may constitute a treatment failure under certain circumstances (see Section 6.5.1).
14. A serum pregnancy test will be performed at the Screening Visit and the End of Treatment Visit. An "in-office" urine pregnancy test will be required at Baseline PRIOR to Randomization, and then every 4 weeks thereafter (for women of childbearing potential). A urine pregnancy test should be conducted at the Screening Visit, in addition to the sample sent for analysis by the central laboratory, if induction is to begin prior to receipt of lab results.
15. An in-office urine toxicology kit should be used at the Screening Visit and the results reviewed prior to starting induction.
16. ONE trough PK sample should be obtained approximately 24 hours following the previous dose of SL BPN; this may be accomplished at the Baseline or Dosing visit. For dose increases, the trough may be obtained the morning prior to the insertion of the 5th implant or the initiation of the new SL BPN dose. The PK sample should occur as close to 24 hours (or more) following the previous dose of SL BPN, supplemental or otherwise, as possible.
17. It is the Investigator's responsibility to understand and comply with all laws and regulations that apply to HIV, HBV, and HCV and testing of blood. HBV, HCV and HIV testing is required unless a site's IRB prohibits such testing.
18. Pregnancy results (for women of childbearing potential) and Urine Toxicology results must be reviewed prior to initiating Induction.
19. Induction SL BPN should be discontinued 12–36 hours prior to implantation. Small (2.4 mg) doses may be administered during the 12 hours prior to the procedure, at the Investigator's discretion, to manage subjects in acute withdrawal.
20. Subjects in Group A or B may receive 1 additional implant > 2 weeks after the initial Dosing Visit under protocol-defined criteria. Subjects in Group C may receive 1 dose increase, to a maximum of 16 mg QD, immediately upon meeting the dose increase criteria. Subjects will repeat the following visits: Dosing Visit, Post-Implant Visit (not attended by Group C) and Week 1 Visit; thereafter, they will resume the original visit schedule in order to complete 24 weeks on-treatment.
21. Subjects may receive supplemental SL BPN (Suboxone®) at any time after randomization under protocol-defined criteria. Supplemental SL BPN will be administered under observation at the clinic except for "take-home" doses. Peak BPN blood levels with Probuphine are achieved within the first day following insertion of the implants. Investigators are therefore advised to be very cautious when prescribing supplemental SL BPN during that time.
22. Supplemental SL BPN should not be taken less than 24 hours prior to scheduled BPN/norBPN plasma collection
23. AEs that are reported by the subject at times during the study other than during the visits as specified above (i.e., at any clinic visit) must be recorded.
24. Subjects will be monitored for at least 30 minutes after implantation for AEs.
25. A Wound Care Information Sheet will be given to the subject after each insertion/removal procedure.
26. Subjects will be contacted by telephone 1 week ($\pm$ 2 days) after the removal of implants and/or termination of SL BPN, and again 25 days ($\pm$ 2 days) following the Week 26 Follow-Up Visit, in order to capture any AEs that occurred.

Source: PRO-806-A3, Protocol PRO-806 Amendment #3

PRO-806 Study Procedures: Subject Early Withdrawal Criteria

Protocol specified criteria for early withdrawal from the study included:

- subject request
- subject non-compliance defined as refusal or inability to adhere to the study protocol:
 - if a subject missed 9 consecutive urine collections after the Dosing visit (Baseline in Study PRO-805), the subject was considered non-compliant and was withdrawn from the study
 - if a subject missed 6 consecutive counseling sessions after the Dosing visit (Baseline in Study PRO-805), the subject was considered non-compliant and was withdrawn from the study
 - any other instances of refusal or inability to adhere to the study protocol, as determined by the PI
- treatment failure, defined as having either of the following supplemental buprenorphine any time after a protocol-specified implant or daily SL buprenorphine dose increase or counseling needs:
 - $\geq$ 3 days/wk of supplemental SL buprenorphine for 2 consecutive wks
 - $\geq$ 8 days of supplemental SL buprenorphine over 4 consecutive wks
 - > 1 additional day per week of counseling for 4 consecutive weeks (i.e., > 3 sessions per week during Weeks 1–12 and > 2 sessions/ week during Weeks 13–24)

- *Subjects in the OL SL buprenorphine arm who were already at the maximum dose (16 mg) were considered treatment failures the first time they met these criteria*
 - 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
 - Subject refusal to receive a dose increase (implant or SL buprenorphine) after meeting protocol-defined criteria (*Not in PRO-805 list, but mentioned elsewhere in protocol.*)
 - intercurrent illness or circumstances (e.g., “incarceration ≥ 7 days”) that would, in the judgment of the investigator, affect assessments of clinical status to a significant extent, require discontinuation of drug, or both
 - requirement for continual use of opioid analgesics >7 days or general anesthesia for surgery
 - at the request of Titan, regulatory agencies, or the Institutional Review Board (IRB)
 - loss to follow-up

Patients who met the above criteria were to be seen for an End of Treatment Visit, for implant removal and clinical evaluations as outlined for that visit.

PRO-806 Study Procedures: Safety Considerations

Data Safety Monitoring Board

A Data Safety Monitoring Committee (DSMB) was to be established to safeguard the interests and safety of the study participants.

Concomitant Medications

- Opioid Analgesics – If continual use required for > 7 days, implants were removed and the subject withdrawn from study. Same in cases where general anesthesia was required for surgery.
- Cytochrome P450 3A4 inhibitors and inducers
 - Subjects excluded if on CYP3A4 inhibitors. Medical monitor was to be consulted if these inhibitors were required during study. Examples of CYP3A4 inhibitors included azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), and HIV protease inhibitors (e.g., ritonavir, indinavir, and saquinavir)
 - Use of CYP3A4 inducers, such as phenobarbital, carbamazepine, phenytoin and rifampicin, were to be avoided. Medical monitor was to be consulted prior to starting any patients on any of these agents.
- Sedatives – use of other narcotic analgesics, sedative-hypnotics, benzodiazepines, phenothiazines, other tranquilizers, or other CNS depressants was to be minimized during Probuphine or SL buprenorphine treatment. Medical monitor consultation required if these sedatives were required during study.

Treatment Identification Card

Patients were to receive a wallet card indicating that they were receiving buprenorphine as part of the study. The card was to be presented to health care providers by the subject in the event of an emergency, or requirement for medications such as opioid analgesics.

Wound Care Information Sheet

Subjects assigned to Probuphine or Placebo implants were to receive written instructions explaining how to care for the surgical site after implant insertion and/or removal.

Implant Site Examination

The implant site was to be visually inspected at each visit for evidence of erythema, edema, itching, pain, infection, bleeding, abnormal healing, and any other abnormalities. If there was any evidence of removal of the implants by the subject (or if the subject confirmed the removal of some or all of the implants), the subject was to be withdrawn from study. If there was evidence of attempted removal, the subject was to be withdrawn from the study and all implants were to be removed. If, upon removal, the Implanting Physician had difficulty locating the implants, they were advised that ultrasound could be used to facilitate their localization. Due to the non-biodegradable nature of the Probuphine and placebo implants, it was considered vital that no patient be lost to follow-up to ensure that proper implant removal and Follow-Up Visits were completed.

Titan noted that initiatives had been implemented to reduce the incidence of broken implants (at the removal procedure), including enhanced training, improved surgical equipment, and revisions to the procedure instructions. Titan has also instituted the Probuphine Clinical Training and Certification program to ensure that clinicians who perform the implant insertion and removal procedures met competency standards.

Possible Impairment

Patients were to receive instruction to avoid operating heavy machinery *during induction and after implant insertion* and to exercise caution in activities requiring alertness, such as driving a car *during the induction period and* during the first few days after implant insertion, or until such time that they were reasonably certain that their ability to engage in such activities was not adversely affected.

Drug Accountability and Compliance

The protocol specified the following guidance regarding drug accountability and compliance:

Detailed drug accountability records for Probuphine, placebo, and sublingual supplies must be maintained by the Investigator or a qualified designee, including the dates shipments are received, the lot numbers and quantities of material received, the amount dispensed and the dates they were dispensed, the running inventory, and the unused quantities returned to Titan's drug supply vendor at the end of the trial. The Investigator or designee must maintain an inventory record of all SL buprenorphine dispensed to subjects for the purpose of induction, treatment (for Group C subjects) and supplemental use.

PRO-806 Statistical Considerations

Titan outlined the following statistical methods for the protocol.

Sample Size Justification

The primary analysis to evaluate the efficacy of Probuphine versus placebo over the 24 weeks of treatment utilized a stratified Wilcoxon rank sum (van Elteren) test comparing the cumulative distribution functions of the percentages (%) of urine samples negative for illicit opioids between groups A and B at 24 weeks. The test was to be stratified by gender and an exact p-value was to be calculated. In order to detect a shift of 20% between the placebo and Probuphine arms using a 2-sided alpha of 0.05 and 80% power, approximately 150 patients were required. This was to take into account the 2:1 randomization, normal distributions without stratification with a common standard deviation of 30% as a conservative powering model, and an attrition rate of approximately 40%.

Subjects were randomized in a 2:1:2 ratio. Randomization was to be performed centrally in blocks within strata (gender). In PRO-805, randomization was by gender *and* site. An imbalanced randomization was chosen in order to increase exposure to Probuphine and decrease the number of patients receiving placebo implants.

Analysis Populations

The following analysis populations were defined:

- Intention-to-Treat (ITT) – all subjects who were randomized and received an implant or received SL BPN as part of SL BPN treatment assignment. Analyses based on this population grouped patients according to the treatment they were randomized to receive, regardless of actual treatment received, and is the primary analysis population.
- Efficacy Evaluable (EE) – all subjects who were treated with implants or received SL BPN as part of SL BPN treatment assignment and remained on study for at least 4 weeks
- Safety – all subjects who were treated with implants or received SL BPN as part of SL BPN treatment assignment

Analysis Methodology

General Conventions:

- Missed urine samples were considered positive.
- After a subject was withdrawn from study (e.g., treatment failure), their urine samples from that point onward were considered positive.
- All tests were to be conducted at $\alpha = 0.05$, 2-sided, unless otherwise specified.
- Subjective and objective withdrawal symptoms and opioid craving scores were analyzed by a repeated measures model including terms for gender and (pooled) site (PRO-806)

Efficacy Analysis:

The null hypotheses for the primary and secondary efficacy variables were to be tested using a fixed sequence testing procedure.

- Primary Analysis: The primary analysis was to determine if the cumulative distribution of % urine samples negative at week 24 (during weeks 1 to 24) in the Probuphine implant group (Group A) is significantly greater than that in the placebo implant group (Group B). This primary efficacy analysis was to be conducted on the ITT population. It was to compare the cumulative distribution functions of % negative urines at 24 weeks between Group B and Group A using a stratified Wilcoxon rank sum (Van Elteren) test using gender as a stratification factor. An exact p-value was to be calculated. This analysis was to be supported by presentation of the cumulative distribution functions by treatment group. Thrice weekly urine samples were to be taken during Weeks 1–24. The denominator for percentage *negative* urine samples for the primary endpoint would be all

possible urine samples that could have been collected since implantation through month 6 (Week 24 of the study), which would be 72 urine samples per patient (i.e., missed visits/samples were considered positive, and after a patient was withdrawn from study, their urine samples from that point onward were considered positive).

- Key Secondary Analyses

The key secondary analysis to evaluate the efficacy of Probuphine versus placebo from treatment weeks 1–16 and 17–24 utilized a stratified Wilcoxon rank sum (Van Elteren) test to compare the cumulative distribution functions of the percentages of thrice-weekly urine samples negative for illicit opioids between groups A and B over Weeks 1–16 and 17–24. The test was also to be stratified by gender, and an exact p-value was to be calculated. The same parameters for powering from the primary analysis were expected to apply to this key secondary analysis.

The Applicant indicated that an additional key secondary analysis would be conducted to demonstrate noninferiority of Probuphine implants (Group A) to daily 12–16 mg SL BPN (Group C) over Weeks 1–24 of treatment. However, (b) (4) an open label sublingual buprenorphine arm when a non-inferiority margin has not been established are not appropriate and not discussed further in this review.

- Other Secondary Analyses

Other secondary analyses included:

- Proportion of Study Completers
- Mean Percent Urines Negative for Illicit Opioids
- Symptoms of Opioid Withdrawal and Cravings
- Patient and Investigator Assessed Clinical Global Impressions Scale (CGI)
- Analysis of Abstinence
- Pharmacokinetic analyses

The following endpoints were considered exploratory:

- Self-report of illicit drug use
- Supplemental SL BPN use
- Beck Depression Inventory II (BDI-II)
- Treatment Failures
- Concordance of illicit drug use self-report and urine toxicology

- Safety Analysis: Adverse event, pregnancy, physical examination and abbreviated review of systems, vital sign, subject disposition and reason for study termination, concomitant medications, and laboratory evaluation summaries were to be provided based on analyses of safety data.

PRO-806 Key Protocol Amendments:

PRO-806 study initiated April 22, 2010; completed May 12, 2011.

Amendment #1 (February 17, 2010)

- Stratification by site removed
- Addition of possible repeat screening assessments for results greater than 4 weeks prior to Dosing Visit.
- Added recommendation for subjects to discontinue any NSAIDs or aspirin-containing medications 1 week prior to Dosing Visit.
- Added recommendation for subjects to bathe the day of Dosing Visit.
- Added statement regarding possible post-study treatment referral:

“At the end of the study, when clinically indicated and at the discretion of the Principal Investigator, referral for ongoing addiction treatment will be provided.”

Amendment #2 (June 11, 2010)

- Second post-treatment telephone contact 25 days ($\pm$ 2 days) following the Week 26 Follow-Up Visit added.
- Updated Individual Drug Counseling Manual.
- Text was added allowing the selection of an alternate site for the implant dose increase if clinically necessary.
- Clarification added to allow for Group C (SL BPN) subjects to receive a dose increase within the first 2 weeks following the Dosing Visit.
- Text was added clarifying that subjects will not be permitted to receive a dose increase subsequent to a dose reduction.
- Added text stipulating that subjects should not operate heavy machinery or engage in other high-risk activities such as driving during the induction phase of the study.

Amendment #3 (September 28, 2010)

- Removed requirement that any additional unscheduled assessments performed during induction be recorded in the CRF.
- Additional guidance on recording of adverse events, whereby withdrawal symptoms will be captured using specified assessments and not recorded with other adverse events.

Study Outcome:

Subject Characteristics:

A total of 480 subjects were screened and 287 were enrolled with 114 randomized to treatment with Probuphine, 54 randomized to treatment with placebo, and 119 randomized to treatment with open label sublingual buprenorphine (SL BPN) treatment.

Enrollment By Center:

PRO-806 was conducted in the US and randomized patients at 20 sites. Enrollment was distributed among centers as shown in the table below.

Site №	Institution Name and Site Investigators	Enrollment
01	SSTAR: Stanley Street Treatment & Resources Fall River, Massachusetts PI: Bailey, Genie L., MD Holmes, Katherine, MD	N = 11 patients • Probuphine: n = 3 • Placebo: n = 4 • SL BPN: n = 4
03	Behavioral Pharmacology Research Unit Behavioral Biology Research Center Johns Hopkins University School of Medicine/Bayview Campus Baltimore, MD PI: Bigelow, George, PhD Dunn, Kelly	N = 10 patients • Probuphine: n = 2 • Placebo: n = 3 • SL BPN: n = 5

Site №	Institution Name and Site Investigators	Enrollment
	Gandotra, Neeraj, MD Harrison, Joseph A. Lowery, Connie A. Nanda, Leticia, NP Savage, Shirley Umbricht, Annie, MD Wu, Yuzon	
04	New York VA Medical Center New York, New York PI: Casadonte, Paul, MD Kulaga, Agatha, MSW Rotrosen, John, MD Saunders, John D., MD Thakkar, Vatsal	N = 7 patients • Probuphine: n = 2 • Placebo: n = 2 • SL BPN: n = 3
05	Providence Behavioral Health Services Everett, Washington PI: Dickinson, William, DO Abbott, Stephanie, PharmD De Jong, Randall, ARNP Patz, John, DO	N = 6 patients • Probuphine: n = 1 • Placebo: n = 0 • SL BPN: n = 5
06	Fidelity Clinical Research Lauderhill, Florida PI: Flaherty, David H., DO (replacing Ventre) Chavoustie, Steven E., MD Gutierrez, Maria I., RMA, CMA Martin, Paul Nguyen, Lisa M., PsyD Perez, Darlene, PsyD Sancetta, Ronald, MD, LLC, FACOG Shepherd, Shaina L., PsyD Sobhan, Faujia Z., MD Spears, Antonio, OA Watson, Kadian Formerly: PI: Ventre, Peter P., MD Baptiste, Susan Chavoustie, Steven E., MD Flaherty, David H., DO Gutierrez, Maria I., RMA, CMA Martin, Paul Montero, Judith, PsyD Nguyen, Lisa M., PsyD Perez, Darlene, PsyD Sancetta, Ronald, MD Shepherd, Shaina L., PsyD Spears, Antonio, OA Watson, Kadian	N = 16 patients • Probuphine: n = 8 • Placebo: n = 3 • SL BPN: n = 5
	North County Clinical Research	

Site No	Institution Name and Site Investigators	Enrollment
07	Oceanside, California PI: Isacescu, Valentin, MD Berger, Fred, MD Lindamood, Timothy, MD Mays, C. Hugh, PhD Sheth, Manish, MD, PhD Snyder, Ole W., MD	N = 35 patients • Probuphine: n = 18 • Placebo: n = 6 • SL BPN: n = 11
08	Synergy Clinical Research National City, California PI: Ishaque, Saleem, MD Bari, Mohammed A., MD Dolnak, Douglas R., DO Jenkin, Frederick D., DO Snyder, Ole W., MD Vassilenko, Ekaterina, MD	N = 22 patients • Probuphine: n = 11 • Placebo: n = 2 • SL BPN: n = 9
09	University of Pennsylvania Treatment Research Center Philadelphia, Pennsylvania PI: Kampman, Kyle M., MD Beitler, Brenda J., MSN, APRN, BC Biddle, Janice F., MSN, CRNP Clark, Cynthia W., MSN, CRNP, APRN, BC Hendrickson, Margo E., MSS, LCSW, CCDP Kaempf, Gail, MSN, CRNP Koutroulakis, Alexis, MSW, LCSW Kranzler, Henry, MD Mahoney, Elizabeth, MA Oslin, David W., MD Varillo, Kristi M., MS Williams, Karah Wilson, Elizabeth, LSW Yu, Elmer	N = 17 patients • Probuphine: n = 6 • Placebo: n = 3 • SL BPN: n = 8
10	Precise Research Centers Flowood, Mississippi PI: Kwentus, Joseph A., MD Albert, Michael H., MD Rack, Sarah K., MD	N = 6 patients • Probuphine: n = 0 • Placebo: n = 1 • SL BPN: n = 5
11	UCLA Integrated Substance Abuse Programs Los Angeles, CA PI: Ling, Walter, MD Dickerson, Daniel, DO Miotto, Karen, MD Mooney, Larissa, MD Torrington, Matthew, MD Yaghmaie, Farzin, MD, MA	N = 12 patients • Probuphine: n = 4 • Placebo: n = 2 • SL BPN: n = 6
12	Psych Care Consultants Research St. Louis, Missouri	N = 15 patients • Probuphine: n = 9

Site No	Institution Name and Site Investigators	Enrollment
	PI: Malik, Azfar M., MD Goswami, Ravinder Joshi, Keshav Peick, Ann Malik, Shazia	• Placebo: n = 1 • SL BPN: n = 5
13	Duke University Medical Center Durham, North Carolina PI: Patkar, Ashwin A., MD Marks, David, MD Scarborough, John	N = 21 patients • Probuphine: n = 7 • Placebo: n = 4 • SL BPN: n = 10
14	St. Luke's Roosevelt Hospital Center Behavioral Sciences Research Unit, 11 th Floor New York, New York PI: Rosenthal, Richard N., MD Ajwani, Neena, BA, LMSW Balan, Sabish, MD Cummings, Allegra, MD Gomez, JoAnn Haller, Deborah, PhD Kolak, Pascal, MS, MPA, PharmD Nampiarampil, Geetha, MD Posner, Daniel, MD Sharif, Zafar, MD	N = 7 patients • Probuphine: n = 2 • Placebo: n = 3 • SL BPN: n = 2
17	Scientific Clinical Research North Miami, Florida PI: Segal, Scott D., MD Gomez, Alexander, MD Chavoustie, Steven E., MD Gomez, Edwin A., MD Gutierrez, Maria I., RMA, CMA Mary, James J. Perez, Geraldine Rodriguez, Gustavo, BA Sancetta, Ronald, MD Shepherd, Shaina L., PsyD Tireman, Erin L., MS	N = 19 patients • Probuphine: n = 6 • Placebo: n = 3 • SL BPN: n = 10
18	Operation PAR, Inc. Largo, Florida 33771 PI: Sheehan, Michael F., MD Calderon, Jose L., MD Glover, Matthew U., MD Goldman, Anthony P., MD Munger, Carole W., ARNP	N = 8 patients • Probuphine: n = 3 • Placebo: n = 3 • SL BPN: n = 2
19	East Indiana Treatment Center Lawrenceburg, Indiana PI: Somoza, Eugene, MD, PhD Bill, Jeffrey, MD	N = 27 patients • Probuphine: n = 13 • Placebo: n = 5 • SL BPN: n = 9

Site No	Institution Name and Site Investigators	Enrollment
	Bohman, Timothy Faul, Robert, MD Harris, Debra, MD Januszki, Stephanie, PA Kothegal, Hari, MD Lomas, Ben, MD Maggio, Michael, MD Winhusen, Theresa, PhD	
20	Amit Vijapura, MD and Associates Jacksonville, Florida PI: Vijapura, Amit, MD Gonzalez, Heath, CRC Hunt, John, MD Jacobs, William, Jr. Pai, Kamalesh K., MD Shah, Hemant, MD Ward, Lorene F., CRC	N = 17 patients • Probuphine: n = 6 • Placebo: n = 4 • SL BPN: n = 7
21	Carolina Clinical Trials, Inc. Charleston, South Carolina PI: Cifuentes, Eduardo, MD Boatwright, Harry W., MD Fiedler, Jennifer M. Herrera, Claudia Holt, Courtney C. King, Ashley S., BS Lopez, Steven G., MD Pepper, Kiva Rodriguez, Gustavo, BA Slawson, Karen T., MA, LPC Zurlo, Sandi, LPN	N = 18 patients • Probuphine: n = 8 • Placebo: n = 6 • SL BPN: n = 4
22	Friends Research Institute, Inc. Torrance, California PI: Kumar, Nishant, DO (replacing Dickerson) Torrington, Matthew, MD Formerly: PI: Dickerson, Daniel L., DO Corp, Stephanie, DO Kumar, Nishant, DO Torrington, Matthew, MD	N = 22 patients • Probuphine: n = 10 • Placebo: n = 4 • SL BPN: n = 8
23	University of Vermont Department of Psychiatry Burlington, Vermont PI: Sigmon, Stacey C., PhD. Bahrenburg, Betsy, RN Brooklyn, John R. Brown, Bruce Marshall, Abigail C.	N = 5 patients • Probuphine: n = 1 • Placebo: n = 1 • SL BPN: n = 3

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Rachel Skeete, MD, MHS
NDA 204442
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Site No	Institution Name and Site Investigators	Enrollment
	Dombek, Michael Ferland, Kathy Hayward, Robert, MD Jenkins, Lorian Kinlin, Nancy, RN Patrick, Mollie Saulsgiver, Kathryn Scanlin, Matthew Schmidt, Susan Smith, Lisa Wegner, Elisabeth, MD Young, Jennifer	

Patient Disposition:

Patient disposition is shown in Table 12 in section 6 below.

PRO-806 patient disposition information is also summarized for the individual PRO-806 trial in greater detail in the following table.

Table 7 Disposition of Randomized Subjects PRO-806

	Probuphine (n=114)	Placebo (n=54)	SL BPN (n=119)	Total (N=287)
Total number of subjects				
Intent-to-treat population ^a	114	54	119	287
Safety population ^b	114	54	119	287
Efficacy-evaluable population ^c	107	43	109	259
Total number of safety population subjects, No. (%)				
Completed study	73 (64.0)	14 (25.9)	76 (63.9)	163 (56.8)
Discontinued	41 (36.0)	40 (74.1)	43 (36.1)	124 (43.2)
Reasons for discontinuation, n (%)^d				
Subject request	5 (12.2)	9 (22.5)	4 (9.3)	18 (14.5)
Non-compliance	10 (24.4)	9 (22.5)	8 (18.6)	27 (21.8)
Missed 6 consecutive counseling sessions	1 (2.4)	1 (2.5)	1 (2.3)	3 (2.4)
Missed 9 consecutive urine collections after baseline	8 (19.5)	6 (15.0)	5 (11.6)	19 (15.3)
Other instances as determined by PI	1 (2.4)	2 (5.0)	2 (4.7)	5 (4.0)
Treatment failure	6 (14.6)	9 (22.5)	0	15 (12.1)
Unacceptable or intolerable treatment-related AE	0	0	1 (2.3)	1 (0.8)
Pregnancy	0	0	1 (2.3)	1 (0.8)
Use of other treatments for opioid dependence	0	2 (5.0)	2 (4.7)	4 (3.2)
Use of any other investigational treatment	0	0	0	0
Subject refusal to receive a dose increase	1 (2.4)	2 (5.0)	0	3 (2.4)

Intercurrent illness or circumstance that affected assessments of clinical status or required discontinuation of drug or both	8 (19.5)	4 (10.0)	8 (18.6)	20 (16.1)
Incarcerated ^e	4 (9.8)	2 (5.0)	5 (11.6)	11 (8.9)
Discontinued due to AE (not related to the study treatment) ^e	1 (2.4)	1 (2.5)	2 (4.7)	4 (3.2)
Unable to adhere to the protocol schedule based on self report or investigator assessment ^e	2 (4.9)	1 (2.5)	1 (2.3)	4 (3.2)
PI felt subject was not benefiting from the treatment ^e	1 (2.4)	0	0	1 (0.8)
Requirement for continual use of opioid analgesics >7 days or general anesthesia for surgery	2 (4.9)	0	0	2 (1.6)
Sponsor, IRB, or regulatory authority decision	0	0	0	0
Lost to follow-up	9 (22.0)	3 (7.5)	17 (39.5)	29 (23.4)
Other ^f	0	2 (5.0)	2 (4.7)	4 (3.2)

Abbreviations: BPN, buprenorphine; IRB, institutional review board; PI, principal investigator; SL, sublingual.

^a The intent-to-treat population was defined as all subjects who were randomized and received an implant (Groups A and B) or received SL BPN as part of SL BPN treatment assignment (Group C).

^b The safety population included all subjects who were treated with implants or who received SL BPN as part of SL BPN treatment assignment.

^c The efficacy-evaluable population was defined as all subjects who were treated with implants (Groups A and B) or received SL BPN as part of SL BPN treatment assignment (Group C) and remained on study for at least 4 weeks of efficacy evaluation.

^d Percentage for each reason was based on the total number of subjects who withdrew early.

^e Numbers and percentages in each group have been hand-calculated based on information provided directly from the sites.

^f Two subjects were discontinued because they enrolled at 2 different investigative sites. The subjects were discontinued from both sites and are each presented in Listing 16.2.12 twice; the reason for discontinuation from the first site (604) is given as “at the request of Titan” and the reason for discontinuation at the second site (614) is given as “subject was enrolled at another investigative site previously.” The subjects were both randomly assigned to receive SL BPN at site 604 and were both randomly assigned to receive placebo at site 614.

Source: PRO-806 Study Report, p. 81–2

Common reasons for early withdrawal were treatment failure, non-compliance, subject request, and loss to follow-up.

Rescue medication use was the key factor in determining treatment failure. Recall that patients were to be discontinued from the study, per protocol, if they required rescue medication exceeding certain parameters, or missed more than a specified number of visits. The number of patients reaching the criteria for “treatment failure” (exceeding rescue medication limits) was higher in Study 806 than in Study 805, presumably because the patients had to meet several criteria simultaneously in order to be eligible for rescue medication in Study 806, while in Study 805 the criteria for rescue were less

stringent. Not surprisingly, the number of patients on placebo who required rescue medication exceeding the protocol-specified limits, who were therefore discontinued from the protocol, exceeded the number in the Probuphine group. This has some potential to bias results because all urine samples collected after discontinuation were adjudicated as positive.

In this instance, loss to follow-up is a safety consideration because patients on Probuphine needed to return to have the implants removed, so those lost to follow-up may still have the implants in place. The consequences, if any, of Probuphine implants remaining in place indefinitely, are unknown.

Demographics:

Patient demographics and baseline characteristics are presented in the following tables and also shown in Table 11 in section 6 below.

Table 8 Patient Demographics PRO-806

	Probuphine (n=114)	Placebo (n=54)	SL BPN (n=119)	Total (N=287)
Sex, No. (%)				
Male	72 (63.2)	31 (57.4)	72 (60.5)	175 (61.0)
Female	42 (36.8)	23 (42.6)	47 (39.5)	112 (39.0)
Race, No. (%)				
White	95 (83.3)	45 (83.3)	97 (81.5)	237 (82.6)
Black	14 (12.3)	7 (13.0)	16 (13.4)	37 (12.9)
Asian	0	1 (1.9)	1 (0.8)	2 (0.7)
American Indian or Alaskan Native	3 (2.6)	0	0	3 (1.0)
Other	2 (1.8)	1 (1.9)	5 (4.2)	8 (2.8)
Ethnicity, No. (%)				
Hispanic or Latino	24 (21.1)	11 (20.4)	17 (14.3)	52 (18.1)
Not Hispanic or Latino	90 (78.9)	43 (79.6)	102 (85.7)	235 (81.9)
Age, years				
n	114	54	119	287
Median	36.0	33.0	32.0	33.0
Mean (SE)	36.4 (1.03)	35.2 (1.40)	35.3 (1.00)	35.7 (0.64)
CI (mean)	34.3, 38.4	32.4, 38.0	33.3, 37.3	34.5, 37.0
Range (min, max)	19, 60	19, 59	18, 60	18, 60
Abbreviations: BPN, buprenorphine; CI, confidence interval; max, maximum; min, minimum; SL, sublingual. Note: Age was calculated as follows: If on the date of informed consent the subject had had their birthday that year, Age = current year – birth year; if the subject had not had their birthday that year, Age = current year – birth year – 1.				

Source: PRO-806 Study Report, p. 87

Table 9 Patient Baseline Characteristics PRO-806

	Probuphine (n=114) n (%)	Placebo (n=54) n (%)	SL BPN (n=119) n (%)	Total (N=287) n (%)
Meets DSM-IV-TR criteria for opioid dependence				
Yes	114 (100)	54 (100)	119 (100)	287 (100)
No	0	0	0	0
First diagnosed in 2005-2010	85 (74.6)	42 (77.8)	82 (68.9)	209 (72.8)
First diagnosed in 1999-2004	13 (11.4)	6 (11.1)	16 (13.4)	35 (12.2)
First diagnosed in 1993-1998	6 (5.3)	4 (7.4)	7 (5.9)	17 (5.9)
First diagnosed in 1987-1992	4 (3.5)	2 (3.7)	8 (6.7)	14 (4.9)
First diagnosed in 1981-1986	1 (0.9)	0	3 (2.5)	4 (1.4)
First diagnosed in 1975-1980	1 (0.9)	0	2 (1.7)	3 (1.0)
First diagnosed in 1969-1974	1 (0.9)	0	1 (0.8)	2 (0.7)
First diagnosed in 1963-1968	1 (0.9)	0	0	1 (0.3)
First diagnosed date missing	2 (1.8)	0	0	2 (0.7)
Current primary opioid of abuse				
Heroin	76 (66.7)	28 (51.9)	75 (63.0)	179 (62.4)
Prescription opioid pain reliever	38 (33.3)	26 (48.1)	43 (36.1)	107 (37.3)
Other	0	0	1 (0.8)	1 (0.3)
Previously treated for opioid abuse				
Yes	63 (55.3)	31 (57.4)	68 (57.1)	162 (56.4)
No	51 (44.7)	23 (42.6)	51 (42.9)	125 (43.6)
Missing	0	0	0	0
Abbreviations: BPN, buprenorphine; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders IV text revision; SL, sublingual.				

Source: PRO-806 Study Report, p. 89

Overall, the groups were similar across demographic variables. Generally, the enrolled subjects were White, non-Hispanic/Latino males in their early to late 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.

Dosing Information:

Exposure to implant and sublingual buprenorphine data are summarized in the following table:

	Probuphine (n=114)	Placebo (n=54)	SL BPN (n=119)	Total (N=287)
Duration of exposure (weeks) from randomization to end of treatment				
n	114	54	119	287
Mean (SE)	26.9 (0.90)	18.4 (1.96)	20.7 (0.79)	22.8 (0.64)
Median	25.0	15.5	25.0	25.0
Range (min, max)	4, 60	1, 56	1, 65	1, 65
Total SL BPN dose (mg) before randomization				
n	114	54	119	287
Mean (SE)	143.4 (5.26)	138.3 (9.04)	145.1 (5.11)	143.1 (3.42)
Median	132.0	124.0	140.0	132.0
Range (min, max)	44, 306	44, 432	42, 282	42, 432
Average daily dose (SL BPN mg)				
n	N/A	N/A	119	119
Mean (SD)	–	–	12.8 (0.33)	12.8 (0.33)
Median	–	–	13.8	13.8
Range (min, max)	–	–	1, 19	1, 19
Total dose (SL BPN mg)				
n	N/A	N/A	119	119
Mean (SD)	–	–	1848.8 (81.41)	1848.8 (81.41)
Median	–	–	2016.0	2016.0
Range (min, max)	–	–	60, 2944	60, 2944

Abbreviations: BPN, buprenorphine; max, maximum; min, minimum; SL, sublingual.
 Note: Denominators for percentages were N, the total number of subjects overall. Duration of exposure (weeks) was calculated as: date of last dose – date of first dose + 1.

All patients in the Probuphine or placebo implant arms received four implants initially. Twenty-five Probuphine subjects and 21 placebo subjects received a one implant dose increase to a fifth implant.

PRO-806 Major Protocol Violations

The following major protocol violations were noted:

Protocol Violation	Probuphine	Placebo	SL BPN
Screen Failure – benzo dependence		(b) (6)	
Missing or Out of Range VAS scores (VAS ≤ 20 for randomization)	• (b) (6) (21 mm) • (b) (6) (no)	• (b) (6) (no baseline VAS reported)	• (b) (6) (68 mm) • (b) (6) (56)

Protocol Violation	Probuphine	Placebo	SL BPN
	VAS measured for eligibility)	• (b) (6) (30 mm) • (b) (6) (45 mm) • (b) (6) (34 mm)	• (b) (6) (23 mm)
COWS score out of range		• (b) (6)	
Disallowed Medications	• (b) (6) • • •	• (b) (6)	• (b) (6)
Dose increases excluding them from per protocol population	•	• (b) (6)	
Treatment failure criteria met, but not initially withdrawn	•		
Implant dose increase without meeting dose criteria		• (b) (6)	

The distribution of protocol violations, both number and type, was similar across the treatment arms, and not anticipated to materially impact interpretation of the efficacy findings. Disallowed medications were more common in the Probuphine arm. This could impact interpretation of efficacy findings if the disallowed medications were for opioid dependence treatment or withdrawal, but use of disallowed medications occurred infrequently, even among the Probuphine-treated patients.

***Efficacy Results are reported and discussed in Section 6, below.
 Safety Results are discussed in Section 7, below.***

Detailed descriptions of Studies PRO-807 (open-label extension to PRO-805) and PRO-811 (open-label extension to PRO-805), are included in Appendix 9.4.

6 Review of Efficacy

Efficacy Summary

Two 24-week Phase 3 safety and efficacy studies were completed to evaluate the efficacy of Probuphine for the maintenance treatment of opioid dependence. In these studies, opioid-dependent patients who had not received treatment for opioid dependence within the previous 90 days, first underwent a sublingual buprenorphine induction over a period of 10–16 days, during which they had to be stabilized on 12–16 mg of sublingual buprenorphine for at least 3 consecutive days. Sublingual buprenorphine was discontinued and Probuphine or placebo implants were inserted into

the inner upper arm of the patients during an in-office procedure. Implants were indwelling for six months, and were removed in a subsequent in-office procedure. (One dose increase to add one additional implant was permissible when certain protocol-specified conditions based on use of rescue medication were met. Study treatment was administered in conjunction with standardized, manual-based psychosocial support. All patients were allowed to receive sublingual buprenorphine when certain protocol-defined criteria were met.

The primary efficacy analysis compared the cumulative distribution function (CDF) of the percentage of urine samples negative for opioids in the two treatment groups. Urine samples were collected three times per week. 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, which over the 24 week period amounted to 72 urine samples. Subjects were also asked about their use of illicit opioids approximately every two weeks. If a subject reported opioid use for the past two weeks, any negative urine tests were considered positive for those two weeks. A significant difference was noted between the response profile for placebo and Probuphine in favor of Probuphine for both studies. However, there were no subjects submitting all opioid-negative urines. The largest differences were seen for percentages of negative urines of 30% or better. In other words, 45% of patients treated with Probuphine submitted $\geq 30\%$ opioid-negative urine samples compared with 27% of the subjects on placebo in the first study. As mentioned, no patients submitted 100% opioid-negative urine samples, and 1% and 2% of the subjects on Probuphine submitted $\geq 95\%$ and $\geq 90\%$ opioid-negative urine samples vs. none on placebo. In short, the statistically-significant findings are driven by differences seen among patients who are submitting opioid-negative urine samples approximately one-third of the time, across a period of 24 weeks. A similar pattern was observed in the second study. While efficacy based on the primary endpoint was established in the first trial and replicated in the second trial, it remains unclear if these findings translate to any clinically-meaningful benefit for the patient.

Certain sections in the NDA template within the Review of Efficacy section are not applicable to this review and have been deleted from the Review of Efficacy section of the template for the purposes of this review. Deleted sections from the template include the following:

- Section 6.1.6 Other Endpoints
- Section 6.1.10 Additional Efficacy Issues/Analyses

6.1 Indication

The Applicant proposes the following language – taken from draft labeling – as the indication for Probuphine:

“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 proposed indication, however, does not fully explicate the conditions under which study patients, who were new entrants to opioid dependence treatment, were allowed to receive the implants. In turn, it does not fully convey the criteria that must be met in order for appropriate patients to receive Probuphine in the clinical setting.

In the Phase 3 clinical trials, patients had to successfully undergo induction with sublingual buprenorphine to a target dose of 12–16 mg for at least three consecutive days prior to implantation and to have completed induction within 10 – 16 days of the start of induction. Accordingly, a more appropriate wording of the indication would be maintenance treatment of opioid dependence, following induction and titration to a stable dose of sublingual buprenorphine. The language indicating that Probuphine should be used as part of a complete treatment program to include counseling and psychosocial support should remain.

6.1.1 Methods

Efficacy data derive from studies PRO-805 and PRO-806 described above (Section 5.3). The Statistics Reviewer, David Petullo, MS, repeated the Applicant’s analyses to determine whether the Applicant’s findings could be reproduced if the same datasets and analytic procedures were employed. Given that the primary analysis was a responder analysis that, on face, is not easily interpretable from the standpoint of derived clinical benefit, additional analyses were performed by the Statistics Reviewer to compare findings from the Probuphine and placebo arms based on endpoints that may more readily correspond with a meaningful clinical benefit. The PRO-806 trial included an open-label buprenorphine arm. The open-label design renders it inappropriate for comparative efficacy claims. For the purposes of this review, however, exploratory comparisons were made between the Probuphine and sublingual buprenorphine arms.

6.1.2 Demographics

Selected demographic and baseline characteristics for the participants in Study PRO-805 are summarized in the following table.

Table 10 PRO-805 Patient Demographic and Baseline Characteristics

Variable/Category	Probuphine N=108	Placebo N=55
Age (years)		
Mean (SE)	36 (1.1)	39 (1.6)
Range	19 – 62	20 – 61
Sex – n (%)		
Male	72 (67)	40 (73)
Female	36 (33)	15 (27)
Race – n (%)		
White	82 (76)	40 (73)
Black	14 (13)	6 (11)
Asian	-	1 (2)
American Indian or Alaskan Native	5 (5)	-
Native Hawaiian or Other Pacific Islander	1 (1)	-
Other	6 (6)	8 (15)
Ethnicity – n (%)		
Hispanic or Latino	12 (11)	12 (22)
Not Hispanic or Latino	96 (89)	43 (78)
Duration of Opioid Dependence (years) Study Initiation / Completion Dates: April 2, 2007 / June 19, 2008		
First Diagnosed in 2002–2007	78 (72)	40 (73)
First Diagnosed in 1996–2001	17 (16)	4 (7)
First Diagnosed in 1990–1995	8 (7)	6 (11)
First Diagnosed in 1984–1989	1 (1)	1 (2)
First Diagnosed in 1978–1983	1 (1)	3 (6)
First Diagnosed in 1972–1977	1 (1)	1 (2)
First Diagnosed in 1966–1971	2 (2)	-
Previously Treated for Substance Abuse/Dependence – n (%)		
Yes	73 (87)	36 (90)
No	11 (13)	4 (10)
Missing	24	15
Current Primary Opioid of Abuse		
Heroin	69 (64)	34 (62)
Prescription Opioid	39 (36)	21 (38)

Source: Adapted from Integrated Summary of Safety, Table 20 pp 72 – 73 & PRO-805 Final Study Report, Table 5 p. 55.

Selected demographic and baseline characteristics for the participants in Study PRO-806 are summarized in the following table.

Table 11 PRO-806 Patient Demographic and Baseline Characteristics

Variable/Category	Probuphine N=114	Placebo N=54	OL SL BPN N=119
Age (years)			
Mean (SE)	36 (1.0)	35 (1.4)	35 (1.0)
Range	19 – 60	19 – 59	18 – 60
Sex – n (%)			
Male	72 (63)	31 (57)	72 (61)
Female	42 (37)	23 (43)	47 (40)
Race – n (%)			
White	95 (83)	45 (83)	97 (82)
Black	14 (12)	7 (13)	16 (13)
Asian	-	1 (2)	1 (1)
American Indian or Alaskan Native	3 (3)	-	-
Other	2 (2)	1 (2)	5 (4)
Ethnicity – n (%)			
Hispanic or Latino	24 (21)	11 (20)	17 (14)
Not Hispanic or Latino	90 (79)	43 (80)	102 (86)
Duration of Opioid Dependence (years) Study Initiation / Completion Dates: Apr 22, 2010 / May 12, 2011			
First diagnosed in 2005–2010	85 (75)	42 (78)	82 (69)
First diagnosed in 1999–2004	13 (11)	6 (11)	16 (13)
First diagnosed in 1993–1998	6 (5)	4 (7)	7(6)
First diagnosed in 1987–1992	4 (4)	2 (4)	8 (7)
First diagnosed in 1981–1986	1 (1)	-	3 (3)
First diagnosed in 1975–1980	1 (1)	-	2 (2)
First diagnosed in 1969–1974	1 (1)	-	1 (1)
First diagnosed in 1963–1968	1 (1)	-	-
First diagnosed date missing	2 (2)	-	-
Previously Treated for Opioid Abuse – n (%)			
Yes	63 (55)	31 (57)	68 (57)
No	51 (45)	23 (43)	51 (43)
Current Primary Opioid of Abuse – n (%)			
Heroin	76 (67)	28 (52)	75 (63)
Prescription Opioid	38 (33)	26 (48)	43 (36)

Abbreviations: BPN=buprenorphine; OL=open-label; SE=standard error; SL = sublingual

Source: Adapted from Integrated Summary of Safety, Table 20 pp 72 – 73 & PRO-806 Final Study Report, Table 11-2 p. 89.

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.

Baseline characteristics were fairly well balanced across the treatment arms, except for a slightly higher proportion of subjects in the Probuphine arm reporting heroin use as

their primary opioid of abuse in PRO-806. This is not, however, anticipated to bias results in favor of Probuphine.

6.1.3 Subject Disposition

Subject disposition for the Probuphine and placebo arms in the pooled double-blind studies is summarized in the following table.

Table 12 Disposition of Subjects in the Double-Blind Studies PRO-805 and PRO-806

Disposition	Double-Blind Studies				
	Study PRO-805		Study PRO-806		
	Probuphine N=108 n (%)	Placebo N=55 n (%)	Probuphine N=114 n (%)	Placebo N=54 n (%)	SLBPN N=119 n(%)
Subject Completed Study	71 (65.7)	17 (30.9)	73 (64.0)	14 (25.9)	76 (63.9)
Subject Withdrew Early	37 (34.3)	38 (69.1)	41 (36.0)	40 (74.1)	43 (36.1)
Most Common Reasons for Early Withdrawal					
Subject Request	8 (7.4)	9 (16.4)	5 (4.4)	9 (16.7)	4 (3.4)
Subject Non-Compliance	12(11.1)	7 (12.7)	10 (8.8)	9 (16.7)	8 (6.7)
Treatment Failure	0 (0.0)	17 (30.9)	6 (5.3)	9 (16.7)	0 (0.0)
Unacceptable or intolerable treatment-related adverse event	4 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
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)
Lost to Follow-Up	10 (9.3)	4 (7.3)	9 (7.9)	3 (5.6)	17 (14.3)

Note: Percentages for each reason are based on the total number of subjects in the population.

Source: Adapted from Integrated Summary of Efficacy, p. 48

Most of the subjects who discontinued early were in the placebo arm of the trials, and placebo-treated patients discontinued approximately twice as often as the subjects in the placebo arm. Among those in the placebo arm, the most common reason for early discontinuation was treatment failure. “Treatment failure” was defined in the protocol as those subjects who, at any time after the implant dose increase, required ≥ 3 days per week of supplemental SL buprenorphine for 2 consecutive weeks or ≥ 8 days of

supplemental SL buprenorphine over 4 consecutive weeks. Neither urine toxicology findings nor the self-reported opioid use data were taken into account when defining a treatment failure. Treatment failures, thus, occurred among the subset of subjects who received a dose increase, i.e., an implant dose increase to five total implants in the case of the implant treatment arms or a sublingual buprenorphine dose increase in patients in the OL SL buprenorphine arm. Implant dose increases were received by 47 subjects in the Probuphine arm (21%) and about half the subjects in the placebo arm (n=53, 49%) across the double-blind studies. As noted in Section 5 above, the criteria for permitting SL buprenorphine rescue differed between Studies 805 and 806, explaining the lower rate of “treatment failure” in the placebo groups in the two studies.

The other common reason for early withdrawal that addresses efficacy was noncompliance. Subject non-compliance was defined as refusal or inability to adhere to the study protocol:

- if a subject missed 9 consecutive urine collections after the baseline visit
 - urine samples were collected thrice weekly
- if a subject missed 6 consecutive counseling sessions after the baseline visit
 - counseling sessions took place twice weekly during the first 12 weeks, and once weekly during the next 12 weeks
- any other instances of refusal or inability to adhere to the study protocol, as determined by the PI)

In PRO-805 and PRO-806, patient disposition based on categories of noncompliance was as follows:

	PRO-805		PRO-806		
	Probuphine N = 108 n (%)	Placebo N = 55 n (%)	Probuphine (n=114) n (%)	Placebo (n=54) n (%)	SL BPN (n=119) n (%)
Patient Non-Compliance	12 (11.1)	7 (12.7)	10 (8.8)	9 (16.7)	8 (6.7)
9 consecutive urine samples missed	7 (6.5)	4 (7.2)	8 (7.0)	6 (11.1)	5 (4.2)
6 consecutive counseling sessions missed	2 (1.9)	1 (1.8)	1 (0.9)	1 (1.9)	1 (0.8)
Refusal or inability to adhere to study protocol / Other instances per PI	3 (2.8)	2 (3.6)	1 (0.9)	2 (3.7)	2 (1.7)

Within the categories of noncompliance, the reasons for discontinuation are similar among the treatment arms in PRO-805. In contrast, in PRO-806, placebo withdrawals are more common across all the categories, and primarily in the missed urine visits categories. This may be the result of the stricter requirements for sublingual

buprenorphine in the PRO-806 study. Since rescue medication had to be picked up at the clinic or pharmacy and administered at the clinic under observation, it is possible that there was more of an incentive to attend the clinic visits where urine samples were collected and counseling sessions in PRO-805 because of the lower threshold for receiving supplemental sublingual buprenorphine.

The Applicant indicates that the overall pattern of subject disposition was similar at the individual study level with the following minor exceptions:

- A higher proportion of subjects in the placebo group were discontinued due to treatment failure in Study PRO-805 (30.9% [17 subjects]) than in Study PRO-806 (16.7% [nine subjects]); conversely, whereas no Probuphine subjects experienced treatment failure in Study PRO-805, 5.3% (six subjects) in this group were discontinued due to treatment failure in Study PRO-806.
- The majority of subjects discontinued due to intercurrent illness or other circumstances were in Study PRO-806 (eight of the nine discontinued Probuphine and all four of the discontinued placebo subjects). Half of these discontinuations in each treatment group were related to subject incarceration.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy analysis was a comparison of the cumulative distribution function (CDF) of the percentage of urine samples negative for opioids, over different study periods, in the Probuphine and placebo treatment groups achieved by using a stratified Wilcoxon rank sum (van Elteren) test with (pooled) site and gender as stratification variables. ([Pooled] site was not a stratification variable for the primary efficacy analysis in PRO-806). PRO-805 and PRO-806 were the two Phase 3 controlled clinical trials intended to establish and replicate the efficacy of Probuphine for the treatment of opioid dependence. The studies are discussed individually, beginning with the analysis of the primary efficacy endpoint in PRO-805, followed by the analysis of the primary efficacy endpoint in PRO-806.

PRO-805: Cumulative distribution of percent negative urines

For PRO-805, the primary efficacy variable was the CDF of the percentage of urine samples that were negative for opioids for Weeks 1 through 16, using the intent-to-treat or ITT population.

PRO-805 was the first Phase 3 trial in the clinical development program. When Titan entered Phase 3 of the Probuphine clinical development program, the Applicant still had some uncertainty about the total duration of therapy with the Probuphine implants. While the Applicant was operating under the premise that the implant provided buprenorphine for a total of six months, they acknowledged that it was possible that it

only delivered active drug for four. As such, when they proceeded with the PRO-805 clinical trial, the strategy taken was to use a four-month window for the primary analysis and to subsequently also evaluate the six-month time period. The second Phase 3 study to replicate findings would be of six month duration if it worked for that whole time period during the initial study and a four-month duration if it worked for the lesser of the time periods. Since Titan judged that the implant lasts for six months, the fourth month evaluations are no longer of relevance. The primary endpoint of interest was the CDF of the percentage of negative urines for Weeks 1–24, incorporating self-report data.

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.⁸ Positive urine samples underwent confirmatory testing. A sample found to be negative for opioids in the initial screen or confirmatory assay was defined as negative for purposes of data analysis.

Missing urine samples were handled as follows for the purposes of the Applicant's analysis.

- If a subject was withdrawn from the study, urine samples from that point onward were considered positive.
- If a valid urine sample was not provided by a subject, the sample was considered missing and therefore positive.
- If a valid urine sample was obtained from the subject but was deemed non-missing and non-analyzable, then the sample was removed from the analysis.
- If urine sample data were missing for any other reason, the urine sample was considered positive.

The decision to incorporate self-report data came later in the development program. At the outset of the development program, and upon the resumption of this development program, which had been halted for a time due to financial reasons, the primary endpoint was to be adjudicated based on urine toxicology data alone. However, once

⁸ Tested drugs for urine toxicology included the following:

- Amphetamines: d-Amphetamine, d-Methamphetamine, Ecstasy
- Barbiturates: Amobarbital, Butabarbital, Butalbital, Pentobarbital, Phenobarbital, Secobarbital
- Benzodiazepines: Alprazolam + metabolites, Diazepam, Nitrazepam + metabolites, Flunitrazepam + metabolites, Oxazepam, Temazepam, Clonazepam + metabolites, N-desmethyldiazepam, Flurazepam + metabolites, Lorazepam
- Δ 9-tetrahydrocannabinol
- Cocaine + metabolite benzoylecgonine
- Methadone + metabolite EDDP (2-ethylidene- 1,5-dimethyl-3,3-diphenylpyrrolidine)
- Methaqualone
- **Opiates: Codeine, Dihydrocodeine, Hydrocodone, Hydromorphone, Morphine, Oxycodone, Oxymorphone, Meperidine/Normeperidine, 6-Acetyl Morphine: 6-AM**
- Phencyclidine
- Phenothiazines: Chlorpromazine, Trifluoroperazine, Thioridazine/Mesoridazine metabolites
- Propoxyphene, Norpropoxyphene
- Tricyclic antidepressants: Amitriptyline, Desipramine, Doxepin + metabolites, Imipramine, Nortriptyline

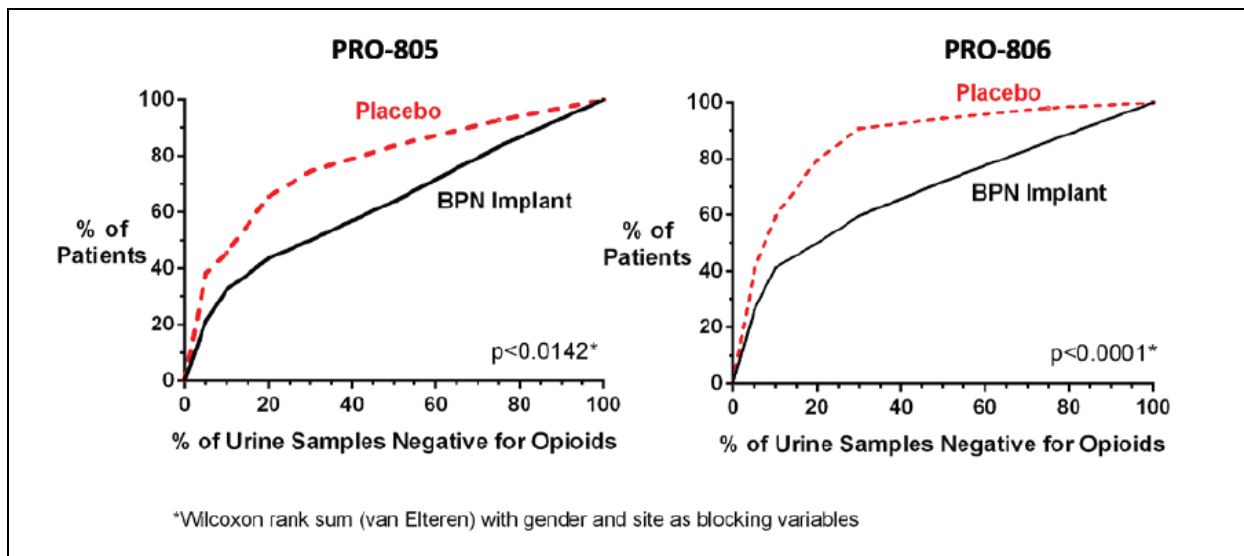
preliminary data from the initial Phase 3 study and extension study were available, it appeared that subjects in the Probuphine arm were reporting illicit drug use more frequently. Notably, this was *all* illicit drugs, not merely opioids. Given the likelihood of the self-report data to be factual when the patient admits to using illicit drugs, and the potential for false-negative urine samples, it seemed prudent to use all available sources of data to provide the most accurate picture of the clinical response with this product. Thus, the opioid use self-report data (for illegal “street” opioids and prescription opioids for which the subject did not have a prescription) were used in the data analyses.

In the Phase 3 double-blind studies, an Illicit Drug use Self-Report was conducted approximately every 2 weeks. It explored drug use questions including drug name, number of days used, daily use, cost per day, and queried about whether the person ‘got high’. For the purposes of the analysis, imputation was performed by the Applicant as follows:

For each post-baseline illicit opioid use self-report, the corresponding urine toxicity data (by date) in the interval of the previous self-report + 1 day (or first dose date + 1 day for the first self-report) and the current self-report was required to have at least one positive urine toxicity assessment for opioids for each day of self-reported opioid use. If there were not enough positive samples to equal the number of days of opioid use indicated on the self-report, negative urine samples were changed to positive until the number of positive urines for the period was equal to the number of days of self-reported illicit opioid use, or until all samples obtained during the period were changed to positive. Missing self-report illicit opioid use data were not imputed. 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.

The Applicant’s graphs are presented in the following two figures.

Figure 2 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

The graphs produced by the Applicant and shown above, display the percent of patients who had a given proportion of negative samples or fewer. For this reason, Titan's cumulative distribution functions rise from zero at the left to 100% at the right.

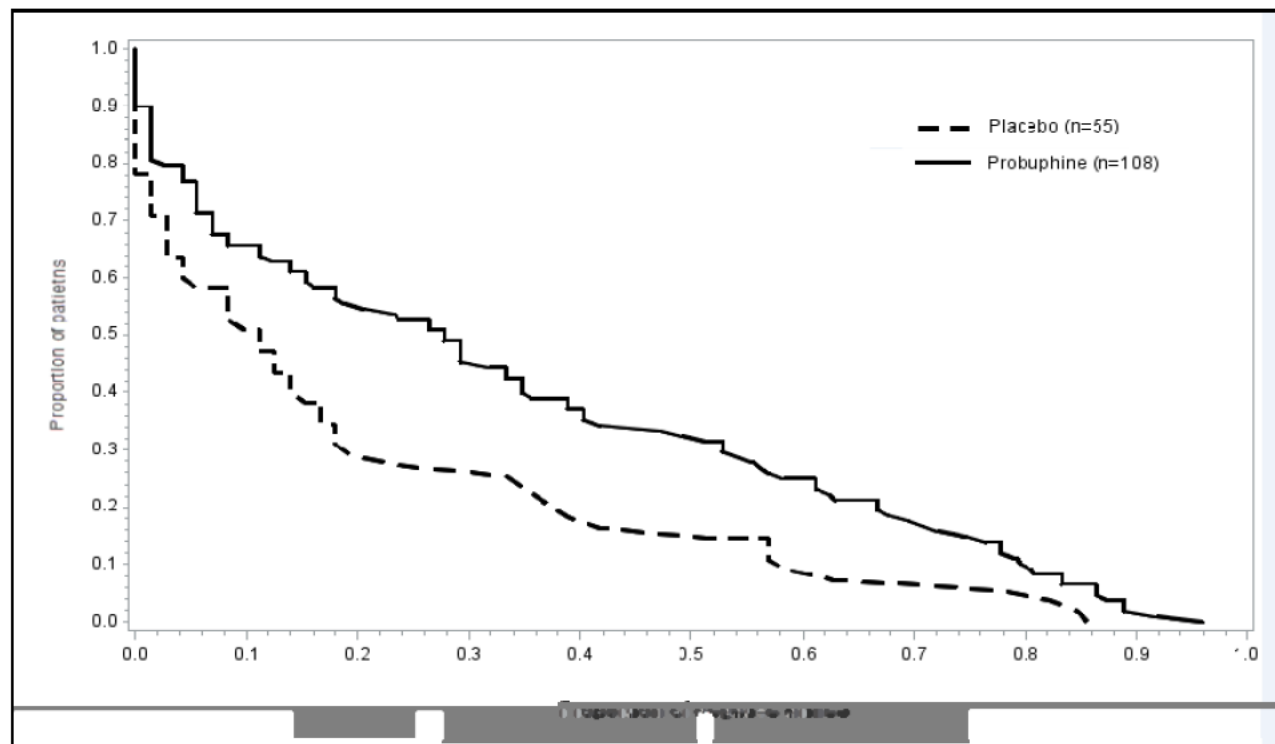
The Statistical Reviewer, David Petullo, M.S., repeated the analyses performed by the Applicant. The figures generated by the Statistics Reviewer differ from those generated by the Applicant. In the analyses performed by the Statistics Reviewer, the graphs show a more intuitive representation of data, that is, the proportion of patients who provided a given proportion of negative samples or better. Accordingly, when David Petullo performed the reanalysis, he provided graphs that denote the number of subjects with negative urines at a certain percentage or greater.

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?"

Figure 3 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.

Figure 3 CDF of the Percentage of Urine Samples Negative for Opioids in Weeks 1 – 24 with Incorporation of Subject Illicit Opioid Self-Report, Study PRO-805 (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.

Table 13 Percentage of negative urines for subjects in Study PRO-805

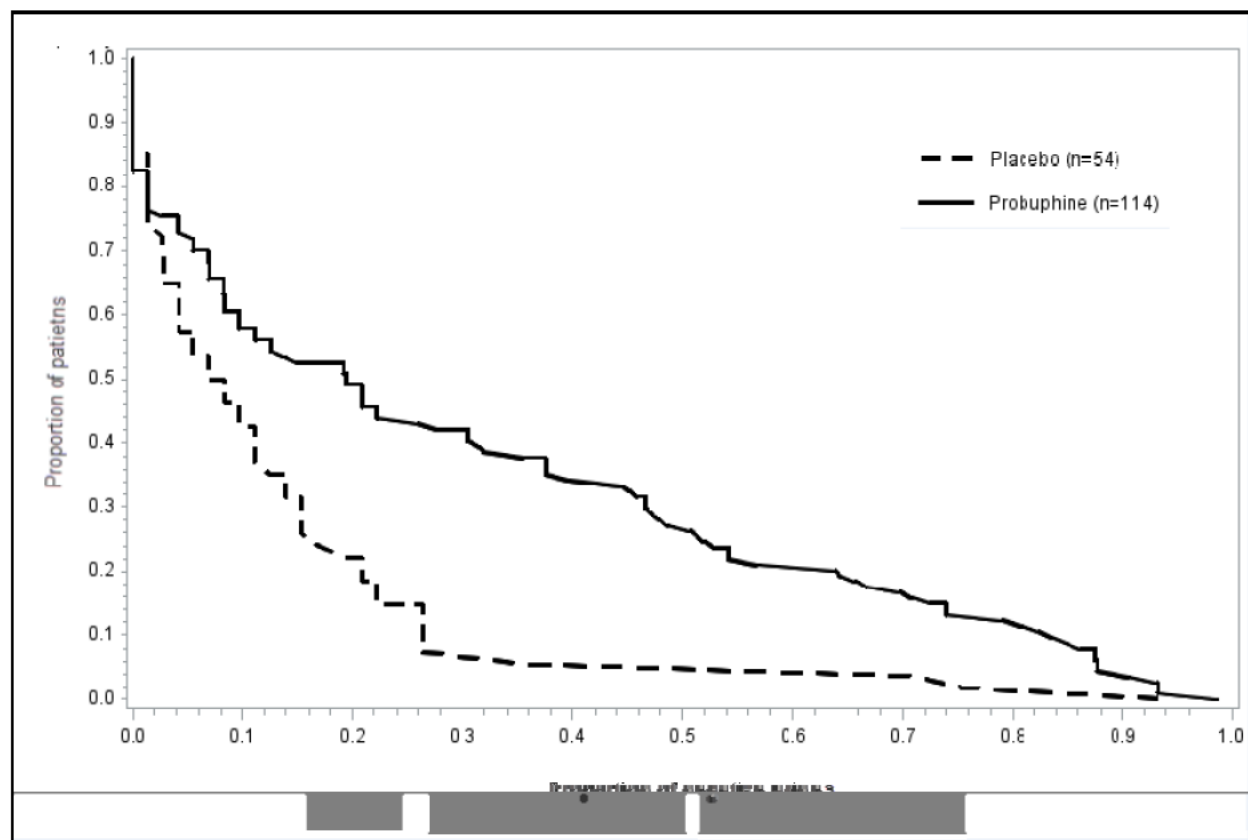
Study	% Negative Urines	% of subjects	
		Probuphine	Placebo
PRO-805	≥ 30	45	27
	≥ 50	32	16
	≥ 75	15	7
	≥ 80	10	5
	≥ 85	6	2
	≥ 90	2	-
	≥ 95	1	-
	100	-	-

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.

PRO-806: Cumulative distribution of percent negative urines

Figure 4 displays the CDF of percent negative urine samples for Weeks 1–24 for Study PRO-806 with self-reported use incorporated. Again, these curves generated by the Statistics Reviewer display the proportion of patients who provided a given proportion of negative samples or better, and fall from 0% at the left to 100% at the right.

Figure 4 CDF of the Percentage of Urine Samples Negative for Opioids in Weeks 1 – 24 with Incorporation of Subject Illicit Opioid Self-Report, Study PRO-806 (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 for Study PRO-806 in the following table.

Table 14 Percentage of negative urines for subjects in Study PRO-806

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.

Primary Efficacy Analysis Incorporating a Grace Period

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, and in turn, performed analyses of the CDF of the percentage of negative urine results for opioids with imputation for subject illicit opioid self-report over Weeks 5–24 and over Weeks 9–24. Based on these analyses, the Applicant 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 (p-value of 0.0024 and 0.0008, respectively). It is noteworthy, though, that no patients achieved complete abstinence when these grace periods of four and eight weeks were considered.

As noted earlier, the Applicant performed analyses of the primary endpoint for Weeks 17 – 24, in the context of the uncertainties surrounding the total duration of the treatment cycle with each Probuphine treatment cycle. Although the intent of these analyses was to examine varying treatment durations, for the purposes of the Agency review, these analyses were reproduced with the intent of allowing an even longer grace period and providing even more leniency with respect to allowing for engagement in treatment in order to assess for better outcomes. The last eight weeks of treatment

were examined under the assumption that if the drug was not effective for 6 months, the CDFs for percent negative urines during Weeks 17–24 would look worse than the CDFs for Weeks 1–24. Conversely, if the curves looked better, it could suggest that given time, patients improve. CDFs of percent negative urines for the last 8 weeks of treatment (Weeks 17–24) for PRO-805 are presented in Figure 5 and then in tabular format in Table 15.

PRO-805: Allowing for a 16-week grace period (Weeks 17 – 24)

Figure 5 CDF of percent negative urines for Weeks 17-24 in Study PRO-805

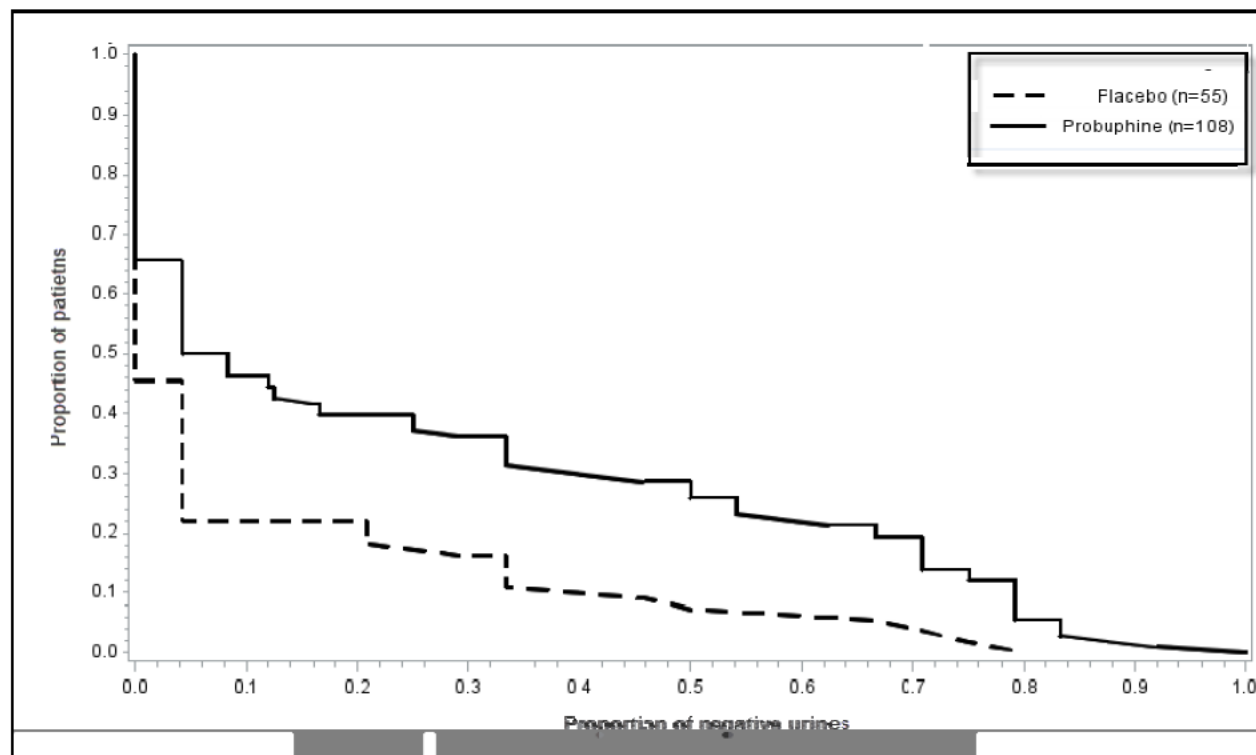


Table 15 Percent negative urines Weeks 17–24, PRO-805

Study	% Negative Urines	% of subjects	
		Probuphine	Placebo
PRO-805	≥ 30	36	16
	≥ 50	29	9
	≥ 75	14	4
	≥ 80	6	2
	≥ 85	3	-
	≥ 90	2	-
	≥ 95	1	-
	100	1	-

The distribution of negative urine screens for Weeks 17–24 did not differ from the distribution of the data for Weeks 1–24. It should be noted that there was one patient in the Probuphine arm that achieved complete abstinence when Weeks 1–16 were excluded from the analysis. At the same time, however, even with a grace period of 16 weeks, it is only a single patient that achieved abstinence.

PRO-806: Allowing for a 16-week grace period (Weeks 17 – 24)

CDF of percent negative urines for the last 8 weeks of treatment (Weeks 17–24) for PRO-806 are presented in Figure 6 and then in tabular format in Table 16.

Figure 6 CDF of percent negative urines for Weeks 17-24 in Study PRO-806

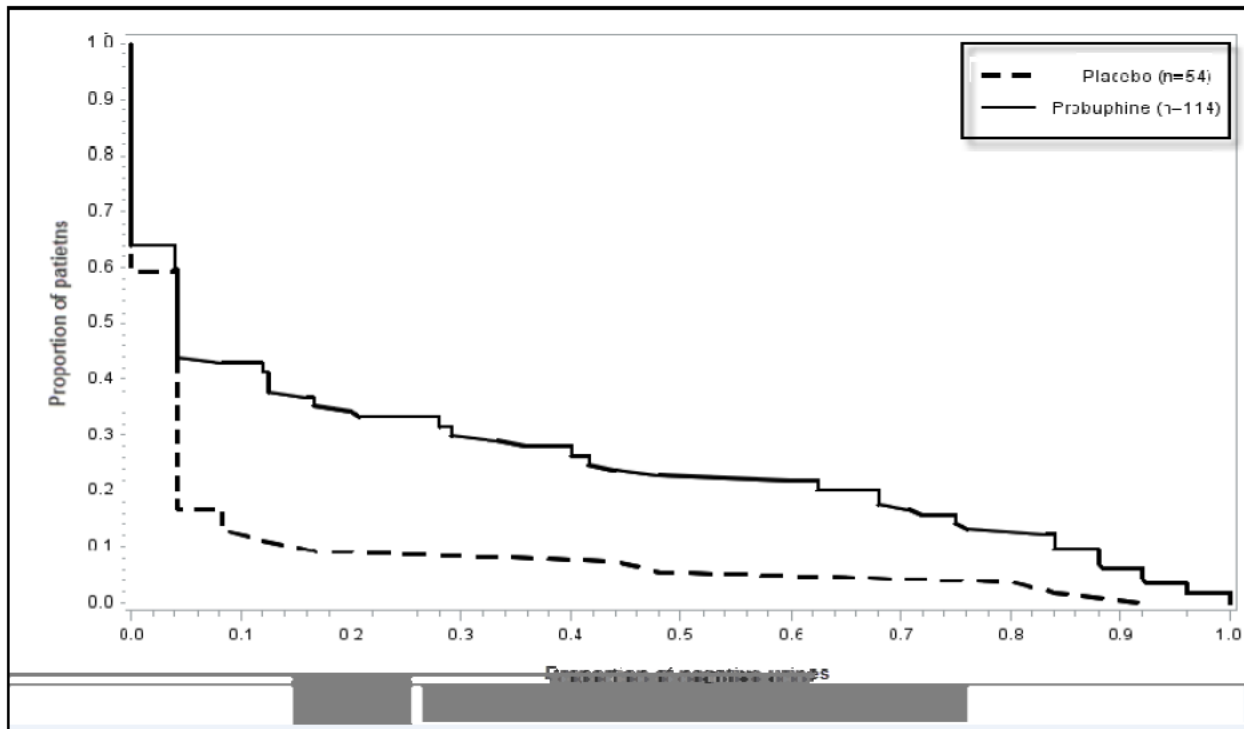


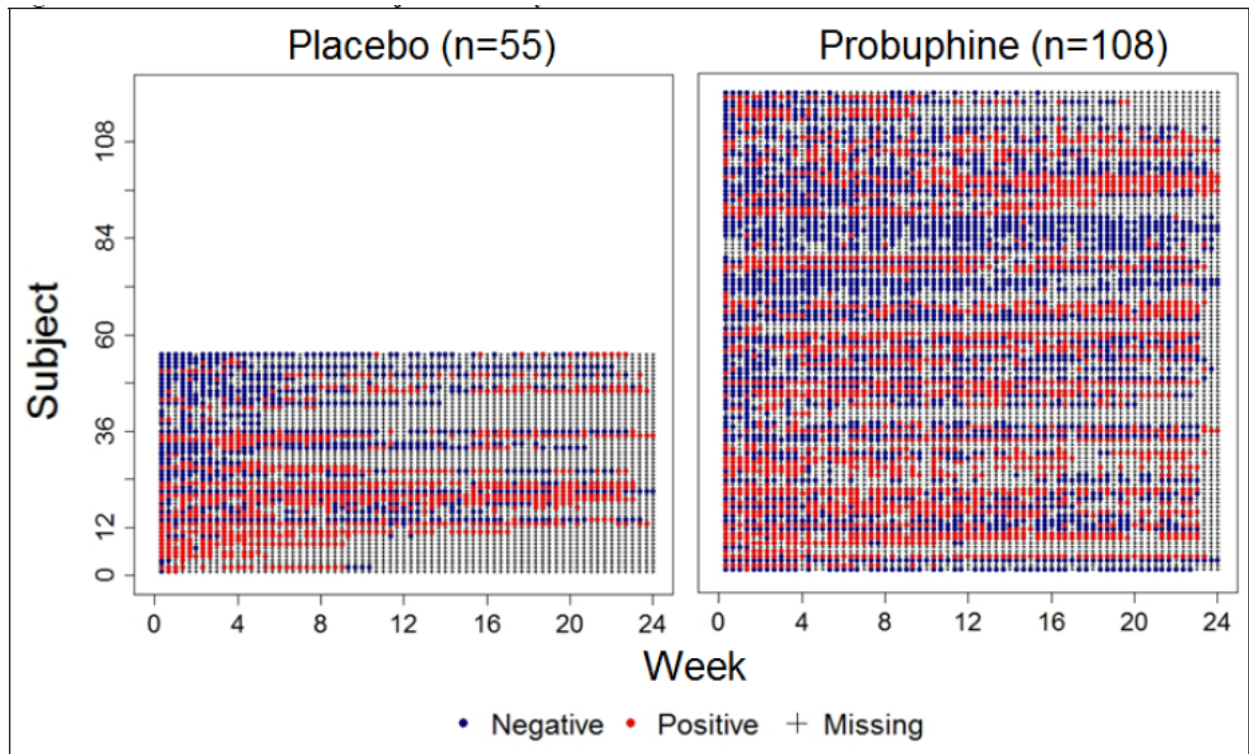
Table 16 **Percent negative urines Weeks 17–24, PRO-806**

Study	% Negative Urines	% of subjects	
		Probuphine	Placebo
PRO-806	≥ 30	30	9
	≥ 50	23	6
	≥ 75	16	6
	≥ 80	13	6
	≥ 85	10	2
	≥ 90	6	2
	≥ 95	4	-
	100	2	-

The cumulative distribution function and the tabular summary demonstrate that at each given level of the percentage of negative urines (e.g., ≥30% or ≥80%), patients on Probuphine in Study PRO-806 were more likely to submit opioid-negative urines. However, again, as in PRO-805, it should be noted that there were two patients in the Probuphine arm that achieved complete abstinence when Weeks 1–16 were excluded from the analysis. At the same time, however, even with a grace period of 16 weeks, only two patients on Probuphine achieved abstinence, while no patients on placebo were observed to ever achieve abstinence across any of the analyses.

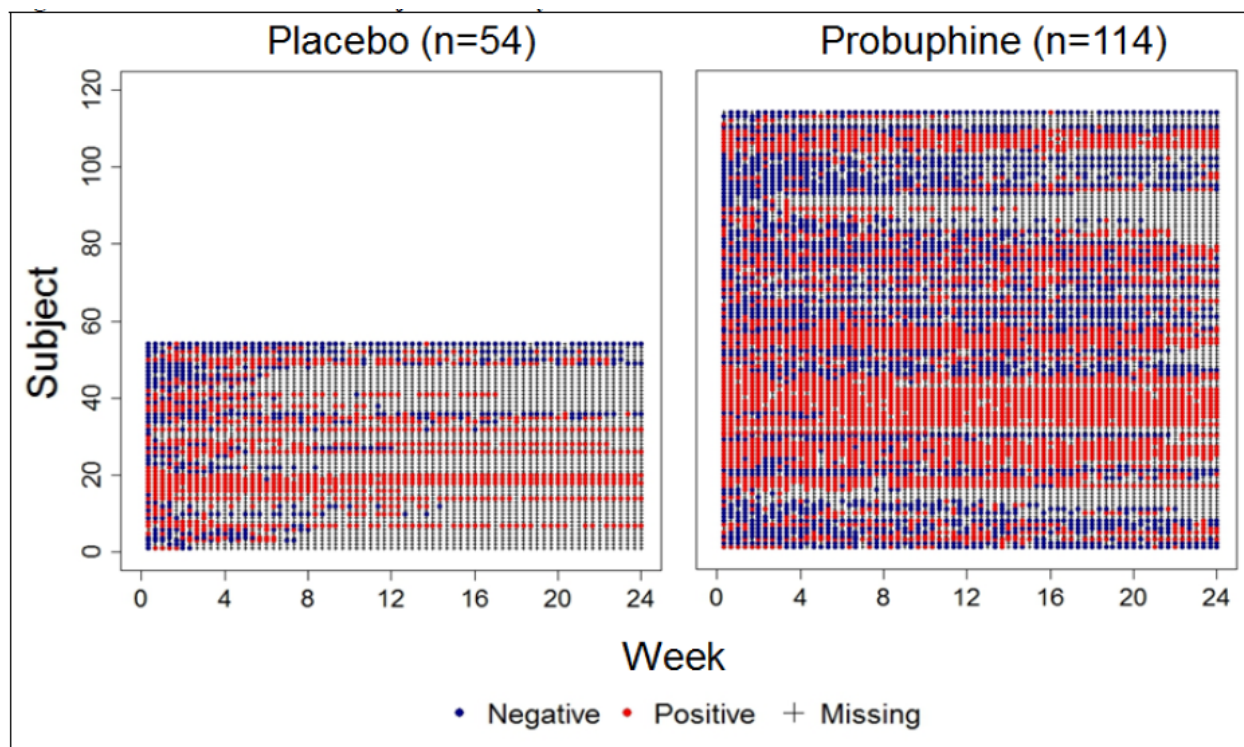
The Statistics Reviewer also performed subject-level analyses of the primary efficacy data by study. These subject-level analyses are shown below. In these presentations, each individual subject is represented along the y-axis. On the x-axis are the time points during which urine samples were collected. (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 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.

Figure 7 PRO-805 Subject-level Urine Sample Results



Source: Statistics Review

Figure 8 PRO-806 Subject-level Urine Sample Results



Source: Statistics Review

The subject-level analyses demonstrate that although there are a subset of patients submitting opioid-negative urines most of the time during the 24-week ascertainment window, the majority of subjects are submitting opioid-positive urines for most of the time that they are on treatment, and even at the end of the treatment after they received treatment for six months or were approaching six months of treatment. The results were similar for the open-label sublingual buprenorphine arm, although these comparisons are made with an open-label arm which affords no opportunity for minimizing bias though blinding.

Based on the various analyses of the primary endpoint and the analyses evaluating various levels of abstinence, Probuphine appears to demonstrate some benefit over placebo with respect to drug use behavior. However, the effect appears minimal and there were complete abstainers on treatment only when a grace period of 16 weeks was allowed. At the same time, in no analyses were there abstainers in the placebo arms. It is unclear whether these differences in favor of Probuphine translate to clinically-meaningful changes in drug use behavior that would ultimately lead to the quality of life improvements anticipated with treatment of underlying opioid addiction.

6.1.5 Analysis of Secondary Endpoints(s)

In addition to the examination of the CDF over various timeframes, with the key timeframes having been discussed above, other secondary endpoints included:

- Retention in treatment
- Self-reported illicit drug use (opioids and non-opioids)
- Supplemental SL buprenorphine use
- Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), and Visual Analog Scale (VAS) for cravings
- Clinical Global Impressions scores, for self and observer (CGI-self, CGI-observer).

Retention in Treatment

Retention in treatment in this setting can serve as an indicator of the length of time that a patient was engaged in psychosocial treatment. Along with the pharmacologic treatment, or facilitated by the pharmacologic treatment, the psychosocial treatment program is intended to aid the patient in altering their drug use behavior.

Retention in treatment was assessed through analyses of study completion rates and time-to-event analyses addressing time to discontinuation.

The following table summarizes the completion rates for PRO-805 and PRO-806 individually.

	Probuphine	Placebo
Study PRO-805		
Number of subjects enrolled	108	55
Number of subjects discontinuing	37	38
Median time to discontinuation (days) ^b	32.1	16.7
Percentage Completing Study	65.7%	30.9%
Study PRO-806		
Number of subjects enrolled	114	54
Number of subjects discontinuing	41	40
Median time to discontinuation (days) ^b	27.3	10.3
Percentage Completing Study	64.0%	25.9%

Source: Adapted from Summary of Clinical Efficacy, Table 10, p. 52

In all the analyses of completion rates across PRO-805 and PRO-806, patients in the Probuphine arm fare better than their counterparts in the placebo arm with respect to study retention.

These findings related to study retention must be interpreted in light of the trial design for these studies. It was specified in the protocol that if someone needed more than a threshold level of buprenorphine rescue, they were removed from the study. Patients on placebo are more likely to require rescue medication, so this may have inflated some of the study completer findings favoring Probuphine.

Although subjects on Probuphine in the studies remained *on study* longer than their placebo counterparts, it is still unclear that this would translate to remaining longer *in treatment* in clinical practice. In other words, it is still unclear that patients on Probuphine would actually realize the benefits that are considered associated with retention in treatment.

Patients on Probuphine in the clinical trials had some incentives for complying with regular clinic visits over the six months. For example, there was the prospect of receiving rescue medication at any time. The supplemental buprenorphine use data that will be displayed later in this review demonstrate that they continued to receive rescue medication sporadically throughout the entire treatment period.

It should be kept in mind that 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 attend counseling visits or check ups with their treatment provider and in fact, may actually 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. In light of these factors, it remains uncertain that the benefits of “retention in treatment” will necessarily accrue to patients on Probuphine in practice.

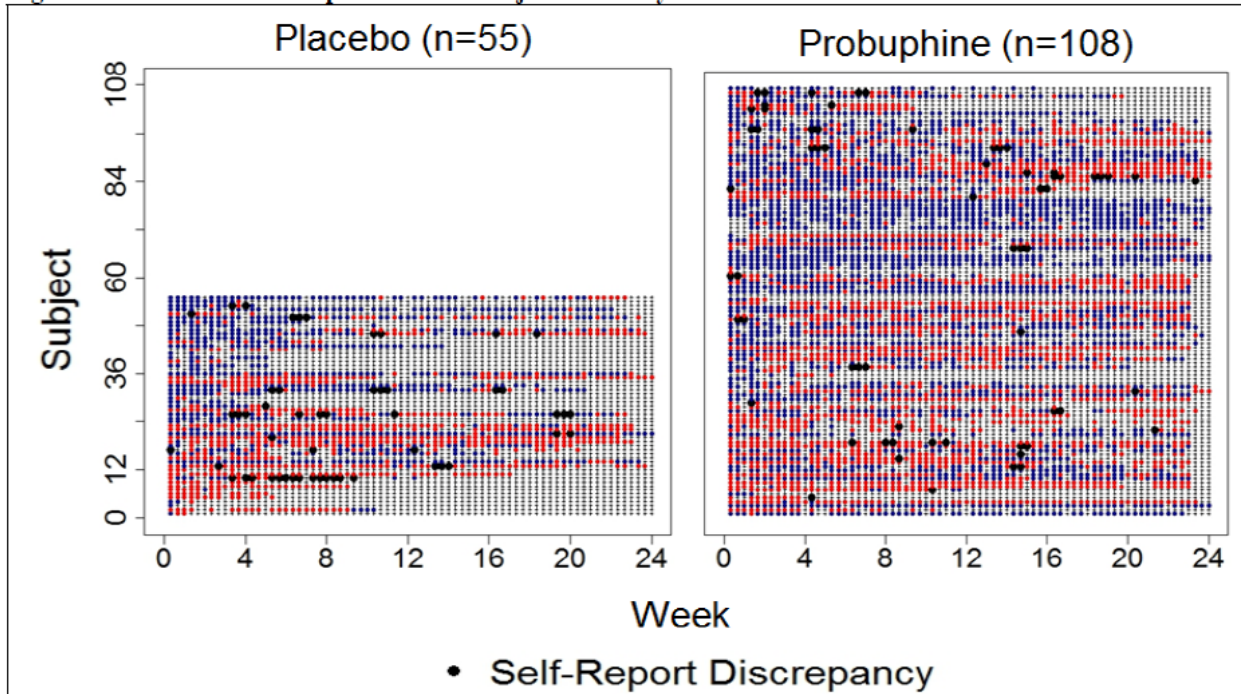
Self-reported Opioid Use

Self-reported opioid use data are used to complement and supplement urine toxicology findings to provide a more complete picture of response to therapy by employing all available data sources. Self-reported illicit opioid use data were taken into account when the primary efficacy analyses were performed. Furthermore, the Statistics Reviewer, David Petullo, performed the analyses with and without incorporation of self-report data, in order to determine how these data may have influenced the findings. When the analyses with and without incorporation of self-report data were compared, it was noted that the findings were fairly similar, and accordingly, the self-report data and urine toxicology data were not often discordant, suggesting that there were not many false negative urine toxicology samples.

The following graphs are provided to illustrate the influence of self-report data on the subject-level findings. These graphs superimpose a black dot over the original subject-

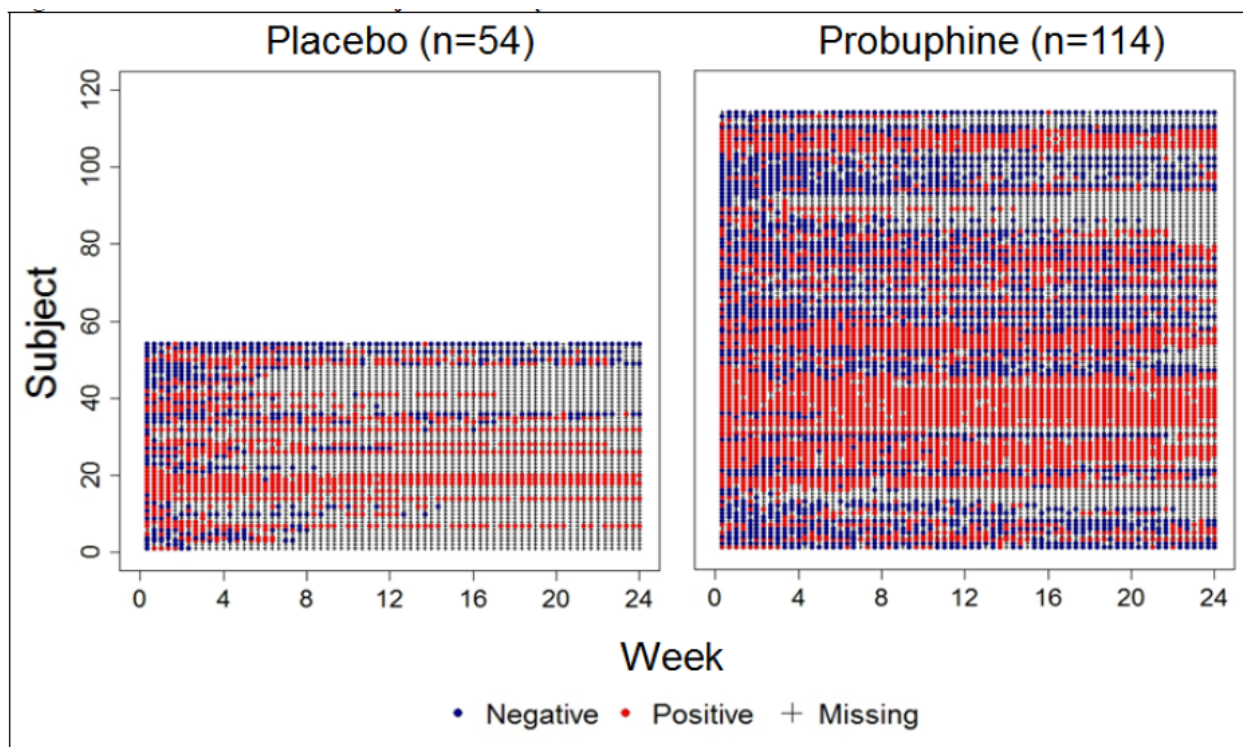
level urine data presentations to indicate a discrepancy between the urine sample findings and self-report.

Figure 9 Influence of self-report data for subjects in Study PRO-805



Source: Statistics Review

Figure 10 Urine test results for subjects in Study PRO-806



Supplemental Sublingual Buprenorphine Use

Subjects were allowed, per protocol, to receive supplemental (rescue) sublingual (SL) buprenorphine (all studies) and/or one additional implant, as clinically indicated, if they met certain protocol-specified criteria for insufficient control of opioid withdrawal symptoms and cravings or at the investigator's discretion.

In Studies PRO-805 and PRO-806, pre-specified criteria for supplemental SL buprenorphine were:

- Withdrawal symptoms with a score of >12 on the COWS
- Cravings with a score of >20 mm on the opioid-cravings VAS
- Subject request for supplemental SL buprenorphine deemed appropriate by the investigator

In PRO-805, subjects needed to meet one or more of the above criteria. In Study PRO-806, subjects had to meet all three criteria.

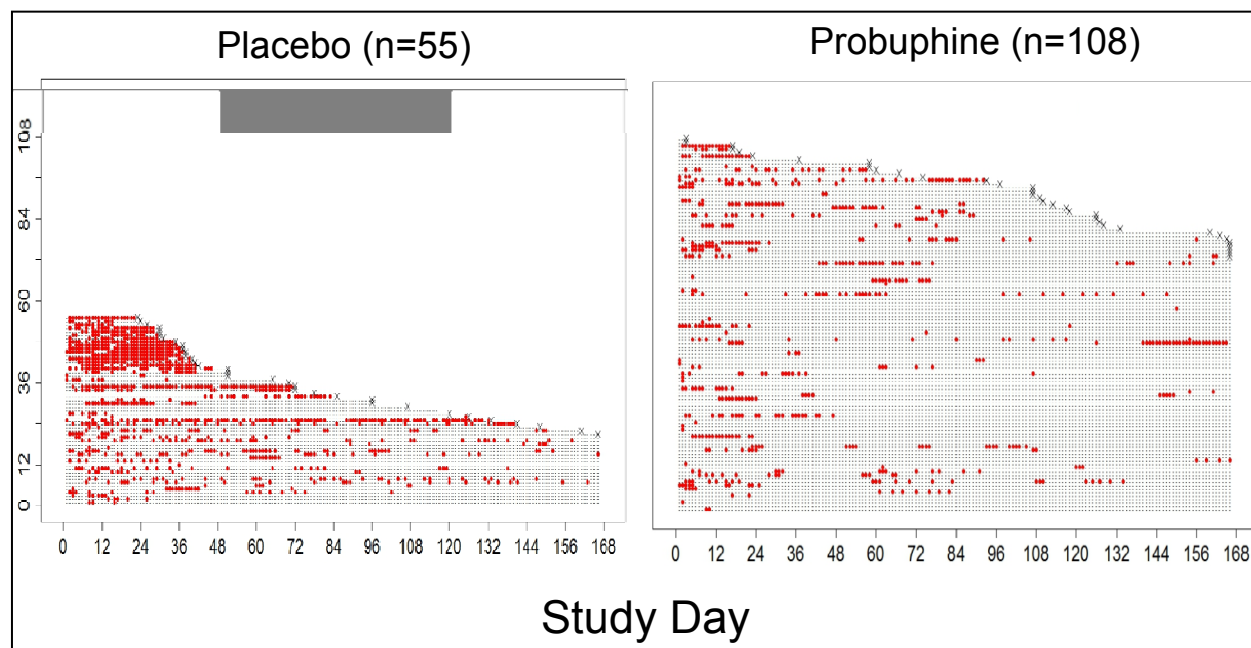
Subjects with the following SL buprenorphine requirements were required to receive one additional implant:

- ≥ 3 days per week of supplemental SL buprenorphine for 2 consecutive weeks
- ≥ 8 days of supplemental SL buprenorphine over 4 consecutive weeks

Supplemental SL buprenorphine use in Studies PRO-805 and PRO-806 and requirement for a fifth implant are summarized in the following table.

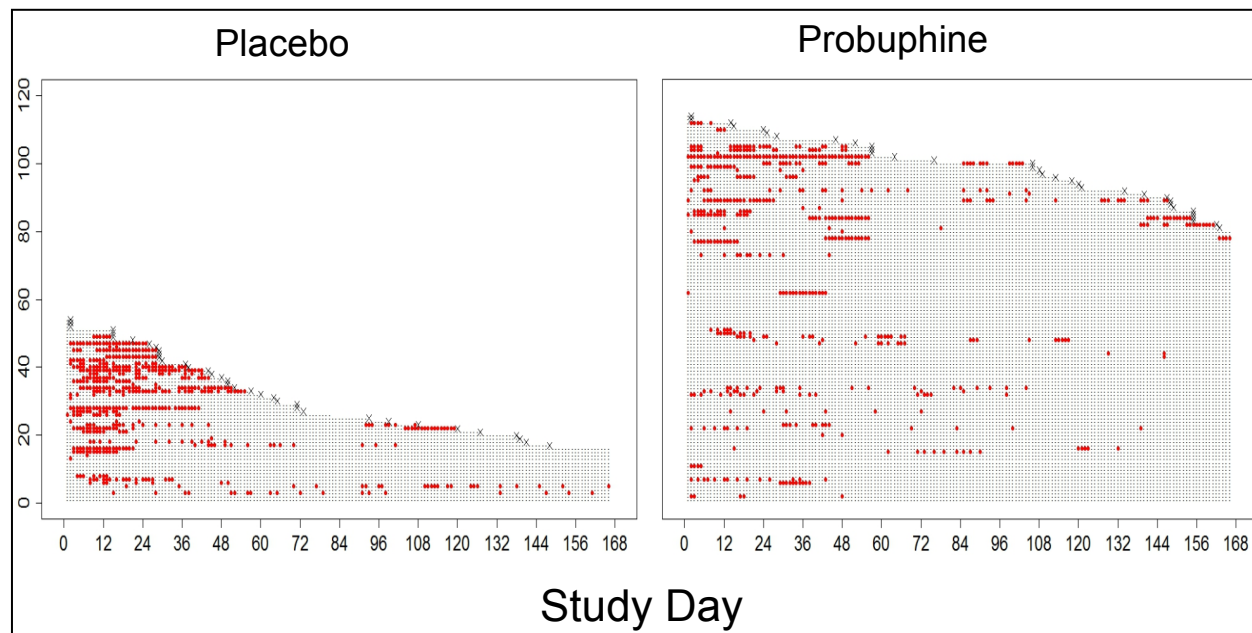
Study	Treatment Group	Number (%) Subjects Requiring Supplemental SL Buprenorphine	Number (%) Subjects Requiring Fifth Implant
PRO-805	Probuphine	67 (62.0)	22 (20.4)
	Placebo	50 (90.9)	32 (58.2)
PRO-806	Probuphine	45 (39.5)	25 (21.9)
	Placebo	36 (66.7)	21 (38.9)
	SL buprenorphine	7 (5.9)	Not allowed

The Statistics Reviewer performed additional analyses of the supplemental sublingual buprenorphine use at the subject level. The results of these analyses for Study PRO-805 are displayed 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.



Source: Statistics Reviewer-generated graphical displays

The results of these analyses for Study PRO-806 are displayed below.



Source: Statistics Reviewer-generated graphical displays

In both studies, the proportion of subjects requiring supplemental buprenorphine in the Probuphine arm was considerably smaller than the proportion in the placebo arm. The same can be said for the subjects requiring a fifth implant. The subject-level analyses show that subjects on Placebo seem to use rescue medication more frequently early on and then discontinue, whereas subjects on Probuphine seem to use more sporadically and stay in the study longer. Because patients had to take the supplemental buprenorphine under observation, the threshold for providing rescue was high, and may actually underestimate the amount of rescue patients may request or need in practice. The PRO-805 findings compared to the PRO-806 findings provide some evidence to that effect, in that when subjects had to meet all three criteria to receive rescue medication, use had already diminished compared to PRO-805. It is not likely that a similar bar will be set in clinical practice for provision of rescue medication. Moreover, clinicians will not be blind to their patient's urine toxicology results, and are likely to provide supplemental doses to any patient who continues with unrelenting illicit drug use.

Finally, although it is not appropriate to make any efficacy assessments based on comparisons of the blinded arms to the open-label sublingual buprenorphine arm, it is of note that such a small proportion of subjects required supplemental sublingual buprenorphine. This is consistent with the clinical pharmacology findings that Probuphine delivers a steady state dose which is one-third of the steady-state plasma levels (and one-half of the trough level) delivered by buprenorphine sublingual tablets at a dose of 16 mg/day.

The Applicant performed a further analysis of supplemental SL buprenorphine use by the number of implants received during the study.

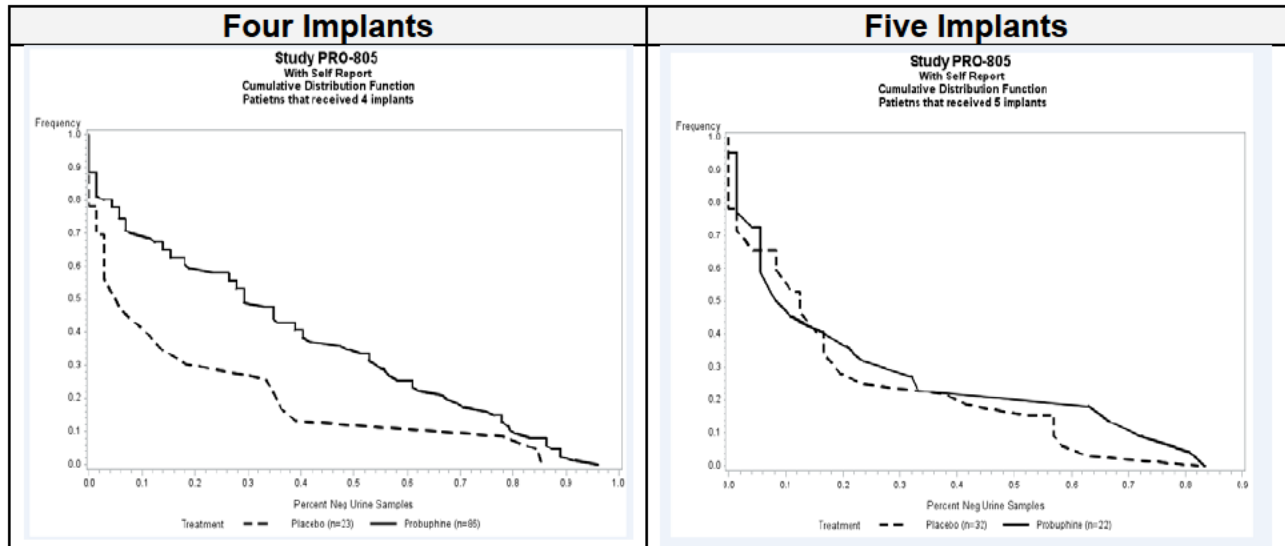
Table 17 Summary of Mean Supplemental SL Buprenorphine Use, Studies PRO-805 & PRO-806 (ITT Population)

	Subjects Receiving 4 Implants		Subjects Receiving 5 Implants, Before Implant		Subjects Receiving 5 Implants, After Implant	
	Probuphine	Placebo	Probuphine	Placebo	Probuphine	Placebo
Double-Blind Studies						
Total number of subjects	175	56	47	53	47	53
Number (%) of subjects requiring supplemental SL buprenorphine	65 (37.1)	33 (58.9)	47 (100.0)	53 (100.0)	26 (55.3)	42 (79.2)
Days Used/Week	0.23	0.88	2.03	3.54	0.46	2.16
mg Used/Week	2.61	10.40	23.11	37.72	6.06	25.04

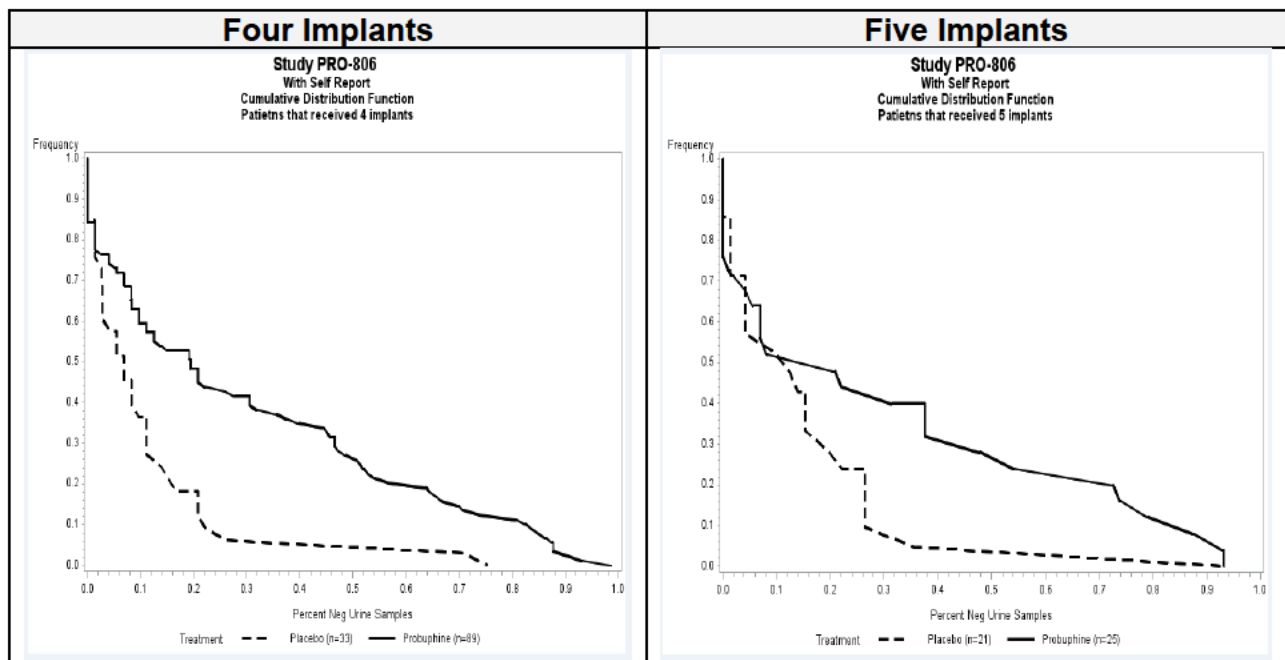
Source: Summary of Clinical Efficacy, p. 58 (Only data from the double-blind studies were included in this reproduced table).

These summary data suggest that there may be little added benefit from receiving the fifth implant, and that Probuphine’s utility may be restricted to the subset of patients who do not exhibit the supplemental buprenorphine needs that were protocol-specified criteria for receiving a fifth implant. CDF plots of the percentage of negative urines that were generated by Statistics Reviewer David Petullo, stratifying by number of implants would appear to support this notion in the case of PRO-805. However, for PRO-806, there is a suggestion that there may be some benefit to the fifth implant, though overall, on inspection of the sets of curves for study PRO-806, subjects with four implants appear to have received the greater benefit.

PRO-805



PRO-806



Opioid Withdrawal Symptoms and Craving Assessments (SOWS, COWS, VAS)

The Applicant assessed opioid withdrawal symptoms and craving assessments using the Subjective Opiate Withdrawal Scale, the Clinical Opiate Withdrawal Scale, and a

Visual Analog Scale (VAS) for “cravings.” It should be noted that the concept of craving is not a well-understood or validated concept and differs in meaning across individuals. The instruments used have also not been developed or evaluated in accordance with the principles laid out in the Agency’s guidance for Patient-Reported Outcome measures. Therefore, the utility of these data are uncertain and they are not being reviewed here for the purposes of efficacy evaluation. The sponsor’s results are shown below for completeness.

For these measures, the data were analyzed by repeated measures ANCOVA including treatment, week, treatment by week, gender, and (pooled) site as categorical factors, baseline as a covariate, and subject as a random effect. An auto-regressive correlation (AR1) structure was used. Negative LS means values indicate lower scores in the Probuphine group compared to the placebo group.

The results of these analyses are summarized in the following table:

Table 18 Analyses Comparing Probuphine to Placebo for Opioid Withdrawal Symptoms (SOWS, COWS), Studies PRO-805 & PRO-806, Pooled (ITT Population)

Timepoint^a	SOWS^b	COWS^b
Average total score over Weeks 1-24	-3.62 (-5.13, -2.11) <0.0001	-1.82 (-2.40, -1.24) <0.0001
Week 1	-5.25 (-7.15, -3.34) <0.0001	-3.13 (-3.91, -2.34) <0.0001
Week 4	-3.38 (-5.46, -1.30) 0.0015	-2.20 (-3.08, -1.33) <0.0001
Week 16	-3.47 (-6.16, -0.77) 0.0117	-1.15 (-2.30, -0.00) 0.0497
Week 24/EOT	-4.24 (-6.18, -2.30) <0.0001	-1.91 (-2.71, -1.11) <0.0001
Follow-up Week 26	-1.29 (-3.40, 0.82) 0.2316	-0.90 (-1.78, -0.01) 0.0466

COWS = Clinical Opiate Withdrawal Scale; EOT = end of treatment, the visit at which the implants were removed; SOWS = Subjective Opiate Withdrawal Scale.

^a Missing values were imputed using Last-Observation-Carried-Forward (LOCF) mechanism.

^b Values displayed are LS mean differences between the treatment groups, confidence intervals, and P-values from a repeated measures analysis of covariance including treatment, week, treatment by week, gender and (pooled) site as categorical factors, baseline as a covariate, and subject as a random effect. An auto-regressive correlation (AR1) structure was used. Negative LS means values indicate lower scores in the Probuphine group compared to the placebo group.

Source: Summary of Clinical Efficacy, p. 55 (Findings from the VAS and references to the VAS have been removed from the duplication of the table).

Clinical Global Improvement Assessments

For this measure, the Applicant conducted a responder analysis on the pooled and study-level CGI-self and CGI-observer data for Week 16 and Week 24 (end of treatment, the visit at which implants were removed). CGI-self and CGI-observer response definitions as determined by the Applicant are as follows:

- CGI-self responders: subjects providing responses of “No problems” or “Borderline problems.”
- CGI-observer responders: subjects providing responses of “No symptoms” or “Borderline symptoms.”

The amount of missing data at the Week 16 time point (as much as 75% of values are missing for the placebo arm) makes it difficult to assess the findings. At the end-of-treatment visit, 56% of Probuphine-treated patients in Study 805 were responders based on self-assessment, vs 36% of placebo-treated patients. In Study 806, the two arms were more similar, at 41% vs 37%. In summary, the supportive findings from analyses of the secondary endpoints, seem to be consistent with some beneficial effects of Probuphine with respect to remaining on study, and decreased need for supplemental SL buprenorphine, the formulation that has been prone to misuse and diversion.

6.1.7 Subpopulations

The primary efficacy endpoint was examined in various subpopulations as defined by the Applicant:

- Gender
- Age (18-35; 36-65)
- Race (White; Black; Other)
- BMI (≤ 25 kg/m²; > 25 kg/m²)
- Primary opioid of abuse (heroin; prescription opioid pain reliever)

Table 19 Summary of CDFs of Percentage of Negative Results for Opioids by Subpopulation, with Imputation for Subject Illicit Opioid Self-Report, Studies PRO-805 & PRO-806 (ITT Population)

Subpopulation	Probuphine N	Placebo N	P-value ^a
Sex			
Female	78	38	0.0410
Male	144	71	<0.0001
Age Group			
18-35 years	115	55	0.0023
36-65 years	107	54	0.0001
Race			
White	177	85	0.0005
Black	28	13	0.0236
Other	17	11	0.0417
BMI			
BMI ≤25 kg/m ²	114	62	<0.0001
BMI >25 kg/m ²	108	47	0.1438
Subpopulation	Probuphine N	Placebo N	P-value
Primary Opioid of Abuse			
Heroin	145	62	<0.0001
Prescription opioid pain reliever/Other	77	47	0.0051

BMI = body mass index.

Note: Urine toxicology data did not include buprenorphine or its metabolites. Self-reported data was incorporated as follows: For each post-baseline illicit opioid use self-report, the corresponding urine toxicity data (by date) in the interval of the previous self-report + 1 day (or first dose date + 1 day for the first self-report) and the current self-report must have at least one positive urine toxicity assessment for opioids for each day of self-reported use. If there were not enough positive samples to equal the number of days of illicit opioid use indicated on the self-report, negative urine samples were changed to positive until the number of opioid positive urines for the period was equal to the number of days of self-reported use, or until all samples obtained during the period were changed to positive. Missing self-report illicit opioid use data was not imputed.

^a Based on a stratified Wilcoxon rank sum (van Elteren) test with gender and (pooled) site included as blocking variables.

Source: Summary of Clinical Efficacy, p. 64

Analyses of the primary endpoint in subpopulations defined by gender, age, race, and primary opioid of abuse demonstrated no major differences based on comparisons of relevant categories within these demographic and baseline classifications. Conversely, when body mass index (BMI) comparisons are made, there appears to be a difference with respect to the efficacy endpoint based on a dichotomous grouping of subjects with a BMI no more than 25 and those with a BMI higher than 25. While this information

must be evaluated in light of the multiple comparisons, it is noteworthy that efficacy appears limited in persons with a higher BMI. With Probuphine, there is still uncertainty as to whether the plasma buprenorphine levels are sufficient to effectively manage opioid addiction, especially given the markedly lower plasma levels of buprenorphine with Probuphine as compared with the reference sublingual products. It is conceivable that this variation based on BMI is reflective of differential exposure and potentially adequate buprenorphine exposure in persons with lower BMI.

The Applicant makes a similar case. According to the Applicant, overall, Probuphine subjects with a BMI ≤ 25 tended to have higher plasma buprenorphine and norbuprenorphine concentrations than the BMI > 25 group. The differences between the two groups overall increased with time on study. By Week 24, the BMI ≤ 25 group had 35.4% higher mean plasma buprenorphine levels than the BMI > 25 group (0.696 ng/mL vs. 0.514 ng/mL) and 70.9% higher mean plasma norbuprenorphine levels than the BMI > 25 group (0.340 ng/mL vs. 0.199 ng/mL).

The Applicant further explains that the pattern of higher plasma buprenorphine levels in the Probuphine BMI ≤ 25 group was also seen among females as compared with males receiving Probuphine. For example, at Week 24, females had a mean plasma buprenorphine level of 0.724 ng/mL, as compared to 0.548 ng/mL for males (a 32.1% difference); for norbuprenorphine the values at Week 24 were 0.358 ng/mL and 0.227 ng/mL for females and males, respectively (a 57.7% difference). This similarity in plasma drug/metabolite patterns among the Probuphine BMI and gender groups is consistent with the higher relative proportion of males in the Probuphine BMI > 25 group compared to the placebo BMI categories. In sum, Probuphine individuals with higher BMI values, most of whom were male, appear to have experienced lower plasma buprenorphine and norbuprenorphine concentrations than Probuphine individuals with lower BMI values.

The Applicant concluded that taken together, the subpopulation efficacy analyses discussed here indicate that the effects of Probuphine treatment relative to placebo are the same in the overall population as in the subpopulations examined, with the exception of individuals with higher BMI values. Subjects with BMI > 25 kg/m² (and possibly males in particular in this BMI category) may require more buprenorphine than individuals with a lower BMI and thus may benefit from reminders to request supplemental SL buprenorphine if needed to significantly reduce opioid use.

It is worth considering whether Probuphine use should be limited to patients with a BMI that is no more than 25, or limiting its use to persons with a normal BMI⁹ until further dose exploration is undertaken. It is conceivable that in its present state, Probuphine may be most effective in patients with a normal BMI who have no need for a fifth implant.

⁹ The NHLBI defines BMI categories as follows: Underweight = < 18.5 ; Normal weight = 18.5–24.9; Overweight = 25–29.9; Obesity = BMI of 30 or greater.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Summary of Dose-Response Information

The dosing recommendations for Probuphine are for the insertion of four Probuphine implants into the subdermal space of the inner upper arm following induction with sublingual buprenorphine, where the patient is to achieve a stable target dose of 12–16 mg/day for three consecutive days prior to implantation. A subject may receive a fifth implant depending on sublingual buprenorphine requirements; the fifth implant is to be implanted after 2 weeks of the initial implantation. Six months after the initial insertion of the first four implants, the implants are to be removed.

The first clinical study of Probuphine, Study TTP-400-02-01, examined the PK and limited efficacy measures of two vs. four implants in subjects previously maintained for extended periods of time on 8 or 16 mg/day SL buprenorphine, respectively. The Applicant used the results from this study as the basis for selecting four implants as the starting dose in all subsequent studies. A subset of subjects in these later studies went on to receive a fifth implant. PK data suggest that these individuals had higher plasma buprenorphine concentrations on average than subjects who received only the initial four implants. The Division has concern that Titan only identified a minimum effective dose for Probuphine, as no higher doses were explored, and expressed this concern to the Titan.

Titan, however, emphasizes that their studies allowed for sublingual supplemental buprenorphine, and draft labeling provides for use of supplemental sublingual buprenorphine. Per Titan, it is important to note that the dosage regimen employed in the double-blind and open-label extension studies allowed for supplemental (rescue) SL buprenorphine and/or a fifth implant within protocol-specified restrictions. As such, they explain, dosing in these studies was fundamentally allowed to titrate to effect. That Probuphine (but not placebo) subjects receiving a fifth implant used much less supplemental SL buprenorphine after receiving the fifth implant than before indicates that provision of a fifth implant is important for successful titration to an efficacious dose for some individuals. For these reasons, the proposed (draft) label text provides for use of supplemental SL buprenorphine and/or a fifth Probuphine implant for individuals experiencing insufficient efficacy after receiving the recommended starting dose of four Probuphine implants. Titan, however, does not make clear that the proportion of subjects with a fifth implant requiring sublingual buprenorphine was still higher than the proportion who received only the fourth implant. The primary advantage of this implantable formulation was to reduce the need for sublingual buprenorphine administration. However, in its current form, the dosage recommendations call for sublingual buprenorphine for titration. Probuphine received a priority review designation primarily because of its potential for decreasing misuse and diversion of sublingual buprenorphine. Accordingly, it would seem that reliance on supplemental buprenorphine for enhanced efficacy of the product is not an appropriate objective.

Titan goes on to provide further dose-response information from Study TTP-400-02-01 and summarizes the key dose-response information as follows:

- Plasma buprenorphine concentrations at “steady state” were roughly two-fold higher in subjects receiving four implants as compared to those receiving two implants (0.37 ng/mL vs. 0.72 ng/mL).
- Efficacy measures such as opioid withdrawal symptoms and cravings, as measured by the SOWS, OOWS (comparable to the COWS), and VAS scores, were all low in both groups.
- Illicit opioid use as measured by self-report and urine testing was lower in the 2-implant group; the higher usage in the 4-implant group was likely primarily driven by one subject in this group who experienced moderate cravings (VAS score 14.4 out of 100) who used illicit opioids throughout the study.
- The number of subjects using rescue SL buprenorphine was similar in the 2-implant group (n=3) and the 4-implant group (n=2); however, the average number of days of use (10 vs. 2) and amount of rescue SL buprenorphine used (6.4 mg/day vs. 2.3 mg/day) were greater in the 2-implant group than the 4-implant group.

Notably, opioid blockade was never factored into the dose-response assessments.

Titan also asserts that the cross-study PK analyses support the dosing recommendations. According to the Applicant, cross-study PK analyses in the overall population receiving four implants indicate that this dose provides a sustained steady-state daily exposure of roughly 0.5 – 1 ng/mL, similar to that observed in Study TTP-400-02-01. This steady-state exposure was seen in each study, and is somewhat lower (the clinical pharmacology review found it to be half) than trough levels obtained at steady state with SL BPN 16 mg/day (approximately 1.5 ng/mL Study PRO-810) or 12 to 16 mg/day (approximately 1 to 2 ng/mL in Study PRO-806).

The Applicant indicates that as the recommended target dose for most opioid-dependent individuals treated with SL buprenorphine is 16 mg/day SL buprenorphine (Suboxone Label), it was hypothesized that patients who were therapeutically maintained on 12 to 16 mg SL buprenorphine could be successfully switched to a starting dose of four Probuphine implants, with the possibility of a single-implant dose increase to a maximum of five implants. The Applicant considers that the overall Phase 3 program was overall successful in testing this hypothesis.

Among the Phase 3 double-blind Probuphine population, approximately 21% needed a fifth implant and approximately 50% required supplemental SL buprenorphine at least once during the study. Patients maintained on 16 mg/day SL buprenorphine, including 7 (5.9%) of the SL buprenorphine subjects in Study PRO-806, likewise occasionally needed rescue medication for breakthrough “cravings.” It is worth reiterating that ongoing illicit drug use was not considered in the provision of rescue medication or

implant titration and that investigators were blind to the urine toxicology results; in clinical practice, doses are adjusted upward or treatment is otherwise modified if the patient persists in regular illicit drug use. The proportion of subjects requiring a fifth implant or rescue SL buprenorphine was higher in the placebo group than Probuphine groups in both Study PRO-805 and PRO-806.

Although placebo subjects required more SL buprenorphine support than did Probuphine subjects, a substantial proportion of all subjects required supplemental SL buprenorphine at least once during any given study, including all Probuphine subjects requiring a fifth implant. (It should be noted that the requirement for a fifth implant was based on supplemental sublingual buprenorphine needs; therefore, all subjects requiring a fifth implant necessarily had to have needed SL buprenorphine to get the implant). Because blood draws were not consistently timed relative to a subject's last, most recent dose of SL buprenorphine, the plasma concentration data for any given subject could have been drawn anywhere on the SL buprenorphine elimination curve; it was judged by the Applicant that the data are best analyzed as group values. For this reason, Titan viewed it as difficult to draw any conclusions for specific subjects as potential relationships between plasma Probuphine levels (or other demographic parameters) and those subjects' requirements for supplemental SL buprenorphine or a fifth implant. That said, Titan asserts that the fact that supplemental SL buprenorphine use among Probuphine subjects receiving a fifth implant dropped precipitously after insertion of the fifth implant suggests that the additional buprenorphine supplied by the fifth implant had replaced the buprenorphine previously supplied by the SL buprenorphine formulation. This precipitous drop that the Applicant claims is relative to 100%, since all subjects who received a fifth implant received SL buprenorphine. As noted above, following insertion of the fifth implant, those requiring any SL buprenorphine still represented a higher proportion than that seen in the group that received only four implants.

The final point that the Applicant makes with respect to the summary of dose-response information is that the efficacy and safety data indicate overall that transitioning subjects from 12 – 16 mg/day SL buprenorphine to four 80-mg Probuphine implants was not associated with any meaningful increase in opioid withdrawal symptoms or cravings, such as might be expected if subtherapeutic buprenorphine levels were experienced during the transition (a similar pattern was observed after implant insertion in the open-label Studies PRO-807 and PRO-811, notes Titan). By contrast, Titan asserts, transitioning subjects in the double-blind studies from SL buprenorphine at induction to placebo implants was associated at Week 1, as expected, with relatively greater increased opioid withdrawal symptoms and cravings as shown in (the table below). Mean change-from-baseline data in SOWS, COWS, and VAS assessments at Week 1 after implant insertion illustrate this point in the following table. (Note that the interpretation of the VAS scores in this case, is of uncertain utility, as the concept of craving is ill-defined).

Table 20 Summary of SOWS, COWS, and VAS Change-from-Baseline Data at Week 1, Studies PRO-805 & PRO-806, (ITT Population)

Assessment	Study PRO-805		Study PRO-806		Pooled Studies PRO-805/PRO-806	
	Probuphine	Placebo	Probuphine	Placebo	Probuphine	Placebo
SOWS	-1.27	3.02*	1.25	9.15†	0.01	5.87†
COWS	0.00	1.81**	0.73	5.52†	0.37	3.56†
VAS	2.20	9.65 ns ^a	6.45	27.77†	4.38	18.08†

COWS = Clinical Opiate Withdrawal Scale; ns = not significant; SOWS = Subjective Opiate Withdrawal Scale; VAS = Visual Analog Scale.

^a LS-means comparison between Probuphine and placebo groups P=0.0511. Otherwise: * = P<0.05; ** = P<0.01; † = P<0.0001.

Source: Summary of Clinical Efficacy, page 70.

Titan, in summarizing the above information, states that for the reasons discussed, the proposed label for Probuphine calls for an initial dose of four Probuphine implants but also allows for insertion of a fifth implant two weeks or more after initial implantation and/or administration of SL buprenorphine for individuals experiencing insufficient control of opioid withdrawal symptoms and cravings. Provision of a fifth implant is expected to reduce the requirement for supplemental SL buprenorphine significantly. No untoward safety signals were observed in subjects given a fifth implant in the Probuphine development program apart from issues related to the additional implant procedure.

It may be noted that the dose of buprenorphine necessary to treat symptoms of withdrawal is much lower than the dose necessary to block the effects of exogenous opioids. The dose of sublingual buprenorphine recommended in labeling is based on the blocking dose, in order to provide both the reinforcing agonist effects and to provide disincentive to continue illicit opioid use. The data suggest that Probuphine may provide a dose sufficient to palliate the symptoms of withdrawal and potentially the subjective urge to use illicit opioids, but it does not seem to provide a dose that blocks exogenous opioids, as evidenced by many patients who persisted in regular drug use while on Probuphine.

Dose Titrations or Modifications

Subjects in each clinical study were allowed to receive limited supplemental rescue SL buprenorphine if they met one or more of the following pre-specified criteria in PRO-805 and PRO-807, and all three in PRO-806 and PRO-811, or at the investigator's discretion:

- Opioid withdrawal symptoms with a score of greater than 12 on the COWS
- Cravings with a score of greater than 20 mm on the opioid craving VAS

- Subject request for supplemental SL buprenorphine deemed appropriate by the investigator

Additionally, for all studies except Study PRO-810, subjects who required ≥ 3 days per week of supplemental SL buprenorphine for 2 consecutive weeks or ≥ 8 days of supplemental SL buprenorphine over 4 consecutive weeks were allowed one additional implant. Subjects were allowed to refuse the recommended additional implant, but were discontinued from the study in those circumstances. This occurred in 1 Probuphine and 2 placebo cases across the 6 studies, all in Study PRO-806.

The decision to allow a subject to receive supplemental SL buprenorphine or a fifth implant was made on the basis of clinical signs and symptoms of opioid withdrawal or cravings, not on the basis of plasma buprenorphine levels or ongoing opioid-positive urine samples.

Overall, the Applicant found no consistent temporal pattern over which subjects required supplemental buprenorphine support. Instead, based on informal interviews with subjects, supplemental buprenorphine use was generally required during intermittent periods of personal stress and anxiety. SL buprenorphine use declined in Probuphine subjects receiving a fifth implant, consistent with delivery of additional buprenorphine from the additional implant.

In summary, Titan asserts that a dosage regimen wherein individuals initially receive four implants, with the possibility of receiving supplemental SL buprenorphine and/or one additional implant for a maximum of five implants, is appropriate for effective maintenance treatment of opioid dependence in adult male and female individuals.

Dosing Interval Information

The formulation provides a consistent, stable release of buprenorphine for the entire proposed 6-month implant period. Ex vivo analyses of drug content in implants after removal at the 6-month timepoint from Study PRO-805 indicate that on average approximately 40% of the original drug load remains in the removed implants. Based on this information, the Applicant contends that the fact that the implants have not been completely exhausted of their buprenorphine load by the 6-month timepoint suggests that it will be possible to deviate slightly from the 6-month reimplantation schedule if, for example, scheduling conflicts delay an individual's reimplantation visit by a few weeks after the 6-month timepoint.

The Applicant affirms that the formulation is resistant to certain manipulations. According to Titan, the formulation is also resistant to manipulations such as physical damage (implant breakage) or direct application of heat, based on the results from a dog PK study comparing buprenorphine PK in the presence vs. absence of heat application indicates that this manipulation has no effect on buprenorphine release from

the Probuphine implant. Thus, individuals are unlikely to be able to cause dose-dumping or otherwise accelerate drug release to the point where the implants will become exhausted before the 6-month timepoint. Despite the resistance to manipulation cited by the Applicant, the CMC reviewer did indicate that breakage of implants could result in variability in exposure because of the increased surface area for exposure resulting from implant breakage and cracks.

Probuphine, as judged by Titan, is also overall well tolerated through the implant period without any new safety issues other than those associated with the implant insertion and removal procedures relative to other marketed buprenorphine products. Taken together, Titan finds that these data indicate that a 6-month implant period is appropriate to assure sustained safe and effective maintenance treatment of opioid dependence in the adult population.

Subpopulation-Specific Dose-Response Findings

Hepatic or Renal Impairment: In light of the lower buprenorphine plasma concentrations observed with Probuphine relative to SL buprenorphine, studies of subjects with hepatic or renal impairment are not needed for Probuphine.

Pediatric Populations: The Division agreed with Titan's proposal to seek a waiver for studies in pediatric subjects (b) (4) years of age, and to request to defer studies in pediatric subjects (b) (4) years of age until after product approval, but the Applicant was informed that the adequacy of this proposal would ultimately be determined by the Pediatric Review Committee (PeRC) during the NDA review. Based on the Applicant's pediatric submission, the Division considers a full waiver to be more appropriate. Upon review of the full waiver request, the PeRC concurred with the Division that a full waiver is appropriate.

Demographic and Other Baseline Characteristics: The available clinical data have been analyzed for the primary integrated efficacy endpoint by various subpopulations. These analyses indicate that, except for BMI, the treatment effect with respect to the CDF over Weeks 1 through 24 was statistically significant and similar in each subpopulation. Refer to Section 6.17 of this review for further discussion of these findings.

Dosage Recommendations

Based on all the information discussed in this section, the Applicant has proposed dosage recommendations. In summary, Titan indicates that the data summarized in this section suggest that Probuphine efficacy is similar or superior for subjects receiving four implants as compared with two implants. Furthermore, comparative PK analyses indicate that buprenorphine exposure is (a) approximately two-fold higher among subjects receiving four implants as compared to two implants and (b) somewhat lower than trough levels associated with steady-state SL buprenorphine dosing at 12 to 16

mg/day, a typical efficacious dose range for SL buprenorphine. In the comparative bioavailability study, it was demonstrated that Probuphine delivers a steady state dose which is one-third of the steady-state plasma levels (and one-half of the trough level) delivered by buprenorphine sublingual tablets at a dose of 16 mg/day. The Applicant argues that treatment with four or five Probuphine implants was shown to be non-inferior to 12 to 16 mg daily SL buprenorphine. However, an open-label sublingual arm is not appropriate for a non-inferiority evaluation, and an appropriate non-inferiority margin was not established. (The Applicant has been informed that non-inferiority claims under these circumstances would not be appropriate). Finally, the need for supplemental SL buprenorphine decreases dramatically following insertion of a fifth implant to Probuphine subjects experiencing insufficient control of opioid withdrawal symptoms and cravings with the initial four-implant dose. Titan contends that these findings, in the context of the overall safety profile associated with Probuphine, support the proposed (draft) labeling dosage recommendation text, which calls for an initial dose of four implants potentially augmented by a fifth implant two weeks or more after initial implantation as clinically indicated, to achieve adequate control of the symptoms of opioid dependence.

Upon review of the efficacy data, the dosage information should stipulate that subjects must undergo induction with SL buprenorphine and be stabilized on a target dose of 12 to 16 mg/day that is to be maintained for at least three consecutive days prior to implantation. There is a six-month duration for the implantation period per implantation, beginning with four implants. Based on review of the data, it is questionable whether the fifth implant provides much additional benefit, and should be included particularly in light of the need to undergo a second procedure for insertion of the fifth implant.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Long-term Exposure Population

The long-term exposure population includes 156 subjects who completed a full 6-month treatment period across the double-blind studies and in Study TTP-400-02-01. There were 83 subjects who had who completed approximately one year of treatment in the Probuphine arm; these subjects were on Probuphine in the double-blind studies and the extension studies.

Long-term Drug Delivery and Efficacy Profiles

After subdermal implantation of Probuphine, the buprenorphine plasma concentration profile shows an initial peak concentration on the first day, followed by a gradual decrease in plasma concentration over 4 weeks to a more constant, low plasma level that is then maintained for the duration of the 6-month treatment. The Applicant refers to this latter phase of sustained buprenorphine release as the "steady-state" phase.

Titan makes four points regarding the temporal profile of buprenorphine release in the clinical studies:

- The time-concentration profile after insertion of Probuphine implants was consistent across all six clinical studies.
- Treatment with Probuphine implants was associated with efficacy relative to placebo on a variety of primary and secondary efficacy endpoints.
- In the double-blind studies, Probuphine efficacy on a variety of primary and efficacy endpoints demonstrated statistical and clinical superiority to placebo. Efficacy was maintained throughout the treatment period. Most (approximately 65%) of the Probuphine subjects remained on-study for the full 24-week period.
- Patients receiving an additional 24-week implant period had buprenorphine exposures that were similar to those experienced in the initial double-blind 24-week implant cycle. The majority of subjects, including 78% of subjects previously treated with Probuphine, that entered the extension studies remained on-study for the full 24-week study period.

Titan further explains that there appear to be neither formulation issues such as failure of buprenorphine delivery, pharmacodynamic effects such as tolerance, nor dramatic changes in absorption, distribution, metabolism, or excretion that would interfere with sustained efficacy. Titan also maintains that the subset of subjects requiring a fifth Probuphine implant appear, on the basis of decreased SL buprenorphine use after the fifth implant is inserted, to likewise experience adequate efficacy for the remainder of their designated implant period. Titan states that subjects also tolerated serial implant insertion and removal procedures with a low incidence of adverse events associated with the surgeries.

The subject-level analyses of urine toxicology data did not indicate that patients are successfully treated early in the treatment cycle and then experience a waning of the treatment effect toward the end of the treatment cycle, which would suggest that more frequent implants were needed. Furthermore, analyses using various grace periods did not demonstrate that treatment effect wanes over time.

Experience after Implant Removal

Subjects' experiences following discontinuation (i.e., post-implant removal) were assessed in each clinical study by contacting subjects by phone for a check-in 1 to 5 weeks after implant removal and by conducting an in-person follow-up visit 2 weeks post-removal (4 weeks in Study PRO-811). Titan indicates that the most directly relevant assessments made during the post-removal period were regarding opioid withdrawal symptoms and "cravings" and subject illicit drug self-report.

On the COWS, SOWS, and VAS, the assessment tools intended to assess opioid withdrawal symptoms and "cravings," the treatment group differences in opioid withdrawal symptoms (SOWS, COWS) and cravings (VAS) that had developed during

the implant period, expressed as difference in LS means, had diminished (COWS) or disappeared (SOWS, VAS) by the post-treatment follow-up visit.

For each study, patterns of subject self-reported illicit drug use at the post-removal follow-up visit were slightly elevated after implant removal relative to that reported during the implant period.

Early Discontinuations

As compared with subjects in the placebo arms of the double-blind studies, subjects in the Probuphine arms remained on-study longer (completed at a higher rate). A significant contributor to this treatment group difference is the lower level of treatment failure in the Probuphine group as compared with the placebo group. In the context of open-label access to Probuphine, subjects in the extension studies completed at an even higher rate than did Probuphine subjects in the double-blind studies (approximately 78% vs. approximately 65%).

In terms of the effects of early discontinuation on study subjects, it was anticipated that any subject exiting a Probuphine clinical study would be at risk for developing opioid withdrawal symptoms and opioid cravings if not provided adequate medication-assisted treatment. Therefore, all subjects were allowed up to 1 week of SL buprenorphine support after implant removal at the principal investigator's discretion. There was no limit on medication-assisted treatment elsewhere following implant removal, and assessment of the impact of removal of study treatment was not a study outcome. Observation of subjects in the absence of treatment was therefore not a part of the investigational plan.

In sum, with respect to persistence of efficacy and/or tolerance effects, efficacy analyses were completed at varying timepoints over the course of the six-month treatment duration, and there were no salient differences observed in the efficacy findings across the different groups based on various timepoints along the six-month treatment cycle. There were no placebo-controlled comparisons beyond the initial implantation for a six-month cycle of treatment. Data in the submission do not suggest that there is an effect of tolerance to treatment with Probuphine.

7 Review of Safety

Safety Summary

For this Review of Safety, safety data from the following sources were reviewed.

Phase 3 Safety and Efficacy Trials:	PRO-805 & PRO-806
Phase 3 Extension Trials:	PRO-807 & PRO-811
Clinical Pharmacology Studies:	TTP-400-02-01 & PRO-810

The Applicant's submission included pooled safety data from the Phase 3 safety and efficacy studies, which was supplemented by data from the two follow-on extension studies to each of the primary Phase 3 safety and efficacy studies. Limited safety data were available from the clinical pharmacology studies, and were used to supplement and complement safety data provided by the major contributors to the safety database, namely the Phase 3 double-blind and extension studies.

As Probuphine is an implantable formulation of buprenorphine, the framework used for the Review of Safety centered broadly on (1) safety of Probuphine as it relates to the systemic effects of the active ingredient buprenorphine; and (2) safety of Probuphine as it relates to the implants themselves, and the insertion and removal procedures necessary for Probuphine administration.

The safety profile of buprenorphine has been fairly well-characterized, and given that Probuphine provides much lower exposure to buprenorphine than the antecedent sublingual buprenorphine formulations on which the safety profile is based, Probuphine could be expected to have a more favorable safety profile. As anticipated, review of the Probuphine safety data did not identify systemic safety concerns beyond those consistent with the established safety profile of buprenorphine.

Similarly, procedural complications were not common overall. There were few difficulties with insertion, but a greater number of removal difficulties. In short, the procedural complications associated with insertion and removal of the implants in the clinical trial database were not worrisome overall, although the rate of complications associated with removal in this small database is considered relatively high. Because the database is small, however, it should be noted that it may not allow for full characterization of these safety issues. It is believed, however, that with appropriate training and if enough procedures are performed, the implanting clinician can be come adept at the procedures and safely insert and remove the implants.

7.1 Methods

For the evaluation of safety, data from the Phase 3, double-blind, safety and efficacy trials, PRO-805 and PRO-806, were pooled, as were the data from the Phase 3, open-label, extension trials, PRO-807 and PRO-811 (PRO-805 and PRO-806 extension trials, respectively). Additionally, limited safety data were available from the clinical pharmacology studies TTP-400-02-01 and PRO-810, and were used to supplement and complement safety data provided by the major contributors to the safety database, namely the Phase 3 double-blind and extension studies. The safety information that was reviewed was primarily from the Integrated Summary of Safety (ISS). Safety information included in the individual study reports for PRO-805 and PRO-806 was referenced when additional detail beyond that included in the ISS was needed.

Probuphine is an implantable formulation of buprenorphine. The framework used for the Review of Safety centered broadly on (1) safety of Probuphine as it relates to the systemic effects of the active ingredient buprenorphine; and (2) safety of Probuphine as it relates to the implants themselves, and the insertion and removal procedures necessary for Probuphine administration.

Since the safety profile for buprenorphine is fairly well-characterized, we were focused on new or unanticipated systemic effects of buprenorphine, if any, that were specific to intrinsic properties of buprenorphine or to buprenorphine when administered via this novel delivery system. Given the established safety profile of buprenorphine, the primary focus of the safety evaluation was the safety experience related to the implants and insertion and removal procedures.

Specifically, the safety evaluation for the implants and insertion and removal procedures addressed the overall safety experience with Probuphine based on the clinical trial safety data available on Probuphine implant insertion and removal, and on local effects resulting from the indwelling implant. Secondly, the safety experience based on the operator for these procedures, that is, the implanting physicians in the clinical trials, was evaluated examining procedural outcomes of the physicians in the clinical trials and the potential relationship of these findings to clinical practice. Thirdly, because improvements were made to the device, techniques, and the training and certification program during the clinical development program, this resulting “natural experiment” was exploited in order to compare safety findings before and after these changes were introduced.

Our Obstetrics and Gynecology physician colleagues in the Division of Reproductive and Urologic Products (DRUP) were consulted to assist with evaluation of the procedural safety data given their experience with similar implantable products, namely the implantable contraceptives, and given their surgical expertise. In light of the limited procedural safety data available in the Probuphine NDA, our DRUP colleagues were also asked to provide additional insight on these safety issues based on their

experience with the implantable contraceptives, and the substantially greater number of exposures in the clinical trial and postmarketing setting for the implantable contraceptive drug products.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The following clinical trials in the Probuphine clinical development program were used to evaluate safety:

Phase 3 Safety and Efficacy Trials:	PRO-805 & PRO-806
Phase 3 Extension Trials:	PRO-807 & PRO-811
Clinical Pharmacology Studies:	TTP-400-02-01 & PRO-810

Safety data derive primarily from the Phase 3 safety and efficacy studies and extension trials, Studies PRO-805, PRO-806, PRO-807, and PRO-811. The clinical pharmacology studies, TTP-400-02-01 and PRO-810, contribute additional limited safety data and serve to supplement and complement safety data provided by the major contributors to the safety database, namely the Phase 3 double-blind and extension studies.

The clinical trials and studies used to evaluate safety are described above in Section 5.

7.1.2 Categorization of Adverse Events

Adverse event terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Studies PRO-805 and PRO-807 used MedDRA Version 10, while the later safety and efficacy trial, PRO-806, and its follow-on extension (PRO-811) used MedDRA Version 14. For the Integrated Summary of Safety, MedDRA Version 14.0 was used. Standardized MedDRA Queries¹⁰, were used in the safety evaluation of adverse events of special interest related to the systemic effects of buprenorphine.

¹⁰ The MedDRA Maintenance and Support Services Organization (MSSO) defines Standardised MedDRA Queries (SMQs) as: "groupings of terms from one or more MedDRA System Organ Classes (SOCs) that relate to a defined medical condition or area of interest. They are intended to aid in case identification. The included terms may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory, and other physiologic test data, etc., related to the medical condition or area of interest.

SMQs were developed to facilitate retrieval of MedDRA-coded data as a first step in investigating drug safety issues in pharmacovigilance and clinical development."
From the MedDRA MSSO website available at: http://www.meddramsso.com/subscriber_smq.asp

According to the statistical analysis plan for the ISS, adverse events were coded by primary system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events were grouped as implant site adverse events and non-implant site adverse events.

Categorization of implant site adverse events varied by study. In Study PRO-805 and Study PRO-807, the case report form (CRF) presented a check list of 6 possible implant site treatment-emergent adverse events (TEAEs), as well as “Other implant site TEAE” and “non-implant site TEAEs.” Only “Other implant site TEAEs” and “non-implant site TEAEs” had free-text recorded. In the original [Complete Study Reports](#), the implant TEAEs were not coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

For the ISS, all terms were coded using MedDRA; however, the Applicant chose to make the determination of whether or not an event was an implant site TEAE based solely on the designation from the individual study CRF check box.

In Study PRO-806 and Study PRO-811, there was a CRF check box to designate TEAEs as implant site-related. All TEAEs had free text descriptions that were coded; again, the Applicant chose to make a determination of implant/non-implant status based on the CRF check box.

The Applicant’s methods for categorizing the adverse events appear adequate overall. The differences in implant site adverse event data collection, coding, and categorization across the studies could potentially make it difficult to correctly ascribe adverse events as being implant-related or non-implant-related. This is not anticipated to greatly impact the review of implant site adverse events because the implant site adverse events of interest in this case are generally those related to insertion and removal complications; these data were made available separately (in response to an Information Request). For the non-implant and implant site adverse events in general, it is possible that some of these events may be incorrectly classified as implant- or non-implant- related; however, because the local and systemic effects are fairly distinct, this is only likely to have an impact for certain adverse events that are commonly associated with buprenorphine exposure and procedures, e.g., pain.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data from the Phase 3 safety and efficacy trials and extensions were pooled in three ways. The three data pooling strategies involved:

- (1) pooling across the double-blind studies – *Pooled Double-Blind Studies*
- (2) pooling across the open-label studies – *Pooled Open-Label Studies*

- (3) pooling across all subjects with any Probuphine exposure in the trials, i.e., data from subjects in the Probuphine arm were pooled across all double-blind and open-label studies – *All Probuphine Group*

Subjects in the Pooled Double-Blind Studies and Pooled Open-Label Studies are presented by the treatment that they received in the double-blind studies (PRO-805 or PRO-806). For most analyses, subjects assigned to daily sublingual buprenorphine (abbreviated as SL BPN at times in this review) in the PRO-806 Study were grouped with the placebo subjects. In the pooled data for implant site TEAEs, treatment groups include subjects in the Probuphine groups and subjects in the placebo implant groups. Subjects in the SL buprenorphine group are excluded as they did not have an implant.

The Applicant summarized their rationale for grouping subjects assigned to daily sublingual buprenorphine with those assigned to placebo subjects as follows:

Since PRO-806 is the only study with a daily SL buprenorphine treatment group, direct comparisons between Probuphine and SL buprenorphine are best performed with Study PRO-806. It should be noted that all subjects in all studies took SL buprenorphine during induction and could have been offered SL buprenorphine by the PI as rescue medication during treatment if the subjects met certain protocol-specified criteria.

In the evaluation of pooled data for all TEAEs and non-implant site TEAEs, the treatment groups included the Probuphine groups and a combined placebo/SL buprenorphine group. The rationale for combining the placebo and SL buprenorphine groups in the statistical analysis was that such a high percentage of subjects in the placebo group received SL buprenorphine rescue medication that there ultimately was only a difference of degrees of exposure to buprenorphine between the SL buprenorphine group and the placebo group for safety issues.

For the analysis of data pooled from the double-blind and open-label studies (*All Probuphine Group*), TEAEs are presented as a single group representing data from Probuphine subjects in both double-blind studies combined with data from all subjects in the open-label studies. Thus, this group (*All Probuphine Group*) includes all subjects treated at any time with Probuphine in double-blind and/or open-label studies. A subject that has a TEAE occurring in both studies (double-blind and open-label) is counted as one subject having a TEAE in the *All Probuphine Group*.

Note that for the double-blind studies, there are instances where pooling of daily SL buprenorphine subjects with placebo subjects would not be appropriate or a more thorough examination of these 2 groups in a separate manner would be warranted. Double-blind analyses where the daily SL buprenorphine subjects are presented separately from the placebo subjects include:

- Dispositions
- Exposure: Daily SL buprenorphine subjects did not have implants, thus their exposure analysis does not have them pooled with placebo subjects.

- Special Interest Adverse Events: These events include implant site events, thus they are presented both with placebo/SL buprenorphine pooled and separately.
- PK analyses: The placebo subjects received SL buprenorphine on a sporadic, as-needed basis, whereas the daily SL buprenorphine group had a defined regimen, in addition to as-needed exposure.
- QT prolongations: As these events could have been dose-dependent in the placebo and SL buprenorphine groups, they are presented both with placebo/SL buprenorphine pooled and separately.

Additionally, SL buprenorphine subjects were excluded from the following analyses since they did not have implants and were not at risk:

- Any analyses presenting the results by the number of implants
- Implant site TEAEs

The Applicant's procedures for pooling data across studies and presenting the findings are generally acceptable. Where appropriate for this safety review, the placebo and sublingual buprenorphine arms were analyzed separately when evaluating effects of systemic buprenorphine exposure. Procedure-related adverse events were primarily evaluated by aggregating data across the Probuphine and placebo treatment arms, as subjects in each arm were subjected to the same insertion and removal procedures. Implant site adverse events were evaluated separately to assess local toxicity given that both the Probuphine implants (buprenorphine + ethylene vinyl acetate [EVA]) and placebo implants (EVA only) have been demonstrated to produce local irritancy, with the buprenorphine in the Probuphine implants producing additional local irritant effects beyond that of the EVA alone.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.1.1 Exposure

7.2.1.1.1 Pooled Double-Blind and Pooled Open-Label Studies

The Probuphine safety database includes 450 opioid-dependent subjects who participated in the pooled double-blind studies. Among these subjects are:

- 222 subjects treated with Probuphine;
- 109 subjects treated with placebo; and
- 119 subjects treated with sublingual buprenorphine

In the pooled, open-label studies, there were 147 subjects who received open-label Probuphine treatment in these studies.

Across the Pooled Double-Blind and Pooled Open-Label Studies, the Applicant's submission includes safety data from a total of 262 unique patients who were treated with Probuphine, of whom 201 received one course of treatment (24 weeks) and 82 received a second course of treatment (a total of 48 weeks).

7.2.1.1.2 Clinical Pharmacology Studies

Limited safety data were contributed by the two additional pharmacokinetic (PK) studies, Study TTP-400-02-01 and Study PRO-810. In Study TTP-400-02-01, 12 heroin-dependent subjects were exposed to two or four Probuphine implants. In Study PRO-810, nine opioid-dependent subjects had exposure to four Probuphine implants. (In PRO-810 implants were intended to be indwelling for 24 weeks. The study, however, was terminated after 8 weeks (due to financial constraints)).

7.2.1.1.3 Cumulative Probuphine Exposure

Table 21 summarizes the cumulative exposure to Probuphine in opioid-dependent subjects who participated in the Phase 3 pooled double-blind and open-label studies, and the clinical pharmacology studies.

Table 21 Cumulative Exposure to Probuphine in Opioid-Dependent Subjects

	Any Exposure	Months					
		≥1	≥3	≥6	≥9	≥12	
Double-Blind and Extension Studies							
PRO-805/PRO-807	108	102	96	75	42	38	
PRO-806/PRO-811	114	112	108	92	53	47	
Open-Label Extension Study							
PRO-807/Placebo → Probuphine	12	12	11	10	n/a	n/a	
PRO-811/Placebo → Probuphine	8	8	7	7	n/a	n/a	
PRO-811/SL BPN → Probuphine	20	18	16	13	n/a	n/a	
Clinical Pharmacology Studies							
TTP-400-02-01	12	12	12	12	n/a	n/a	
PRO-810	9	8	0	0	n/a	n/a	
Total	283	272	250	209	95	85	

Abbreviations: SL = sublingual; BPN = buprenorphine

Source: Adapted from Cumulative Exposure to Probuphine Table submitted in Titan Response to Clinical Queries Provided by Email, Dated March 8, 2013.

7.2.1.2 Demographic and Baseline Characteristics

Demographic and other baseline characteristics for opioid-dependent subjects in the population who participated in the pooled double-blind and open-label studies are summarized in the following table.

	Double-Blind Studies					Open-Label Studies	
	Study PRO-805 N=163		Study PRO-806 N=287			Study PRO-807 N=62	Study PRO-811 N=85
	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 (%)
Gender							
Male	72 (66.7)	40 (72.7)	72 (63.2)	31 (57.4)	72 (60.5)	44 (71.0)	56 (65.9)
Female	36 (33.3)	15 (27.3)	42 (36.8)	23 (42.6)	47 (39.5)	18 (29.0)	29 (34.1)
Race							
White	82 (75.9)	40 (72.7)	95 (83.3)	45 (83.3)	97 (81.5)	48 (77.4)	72 (84.7)
Black	14 (13.0)	6 (10.9)	14 (12.3)	7 (13.0)	16 (13.4)	5 (8.1)	11 (12.9)
Asian	0 (0.0)	1 (1.8)	0 (0.0)	1 (1.9)	1 (0.8)	0 (0.0)	0 (0.0)
American Indian or Alaskan Native	5 (4.6)	0 (0.0)	3 (2.6)	0 (0.0)	0 (0.0)	2 (3.2)	1 (1.2)
Native Hawaiian or Other Pacific Islander	1 (0.9)	0 (0.0)	N/A	N/A	N/A	0 (0.0)	0 (0.0)
Other	6 (5.6)	8 (14.5)	2 (1.8)	1 (1.9)	5 (4.2)	7 (11.3)	1 (1.2)
Ethnicity							
Hispanic or Latino	12 (11.1)	12 (21.8)	24 (21.1)	11 (20.4)	17 (14.3)	9 (14.5)	19 (22.4)
Not Hispanic or Latino	96 (88.9)	43 (78.2)	90 (78.9)	43 (79.6)	102 (85.7)	53 (85.5)	66 (77.6)
Age (years)							
N	108	55	114	54	119	62	85
Median	33.0	39.0	36.0	33.0	32.0	37.0	37.0
Mean (SE)	35.8 (1.06)	39.3 (1.58)	36.4 (1.03)	35.2 (1.40)	35.3 (1.00)	38.6 (1.44)	37.5 (1.29)
Range	(19, 62)	(20, 61)	(19, 60)	(19, 59)	(18, 60)	(20, 62)	(19, 61)

Source: Integrated Summary of Safety

In addition to the characteristics summarized in the table, primary opioid of abuse information was also available. Heroin was the primary opioid of abuse for all participants in the pooled double-blind and open-label studies (Probuphine, n =145, 65%, placebo/SL BPN, n=137, 60% in the pooled double-blind studies; Probuphine → Probuphine, n=66, 62%, placebo/SL BPN → Probuphine, n=29, 73% in the pooled open-label studies). Among the US opioid-dependent population, the primary opioid of abuse is prescription opioid analgesics. Although the clinical trial population differs from the US opioid abuse and dependence population in this regard, the safety database offers an opportunity to evaluate hepatic safety data in a population likely to have a high prevalence of viral hepatitis.

7.2.2 Explorations for Dose Response

All patients who were assigned to treatment arms receiving implants in the Phase 3 studies received four or five implants. All subjects initially received 4 implants of either Probuphine or placebo (double-blinded), or open-label sublingual buprenorphine at a dose of 12–16 mg once daily (QD) in the double-blind period of Study PRO-806. Subjects assigned to an implant group could receive a 1-implant dose increase (arriving at 5 implants total) if protocol dose increase criteria were met as described in the protocol summaries in Section 5 of this review.

In the open-label extension period, all subjects initially received 4 Probuphine implants with the ability to receive a dose increase to a 5th implant if protocol dose increase criteria were met. Supplemental SL buprenorphine could be supplied as rescue medication to all groups in the double-blind and open-label studies as noted in the protocol summaries in Section 5 of this review.

The Applicant displayed treatment-emergent adverse events by the number of implants at the time the TEAE started. The Applicant also calculated person-years based on the actual time that subjects had 4 or 5 implants. Denominators for the 5 implant TEAEs are the total number of subjects who received a 5th implant.

7.2.3 Special Animal and/or In Vitro Testing

Local tissue effects of Probuphine and Placebo (EVA only) implants were evaluated microscopically in dogs after subcutaneous exposures of 1 month and 10 months using standard testing protocols for medical devices.

Key findings from the Nonclinical Review Team’s assessment of these data are:

- Probuphine and Placebo were each moderately irritating after 1 month and slightly irritating after 10 months (see Figure below).
- Predominant histological observations observed were generally more severe in Probuphine treated animals compared to Placebo animals.
- Severity of local toxicity decreased over time but was substantial during the early phase after implant insertion with the presence of buprenorphine in Probuphine causing increased local toxicity compared to Placebo (see Table below)

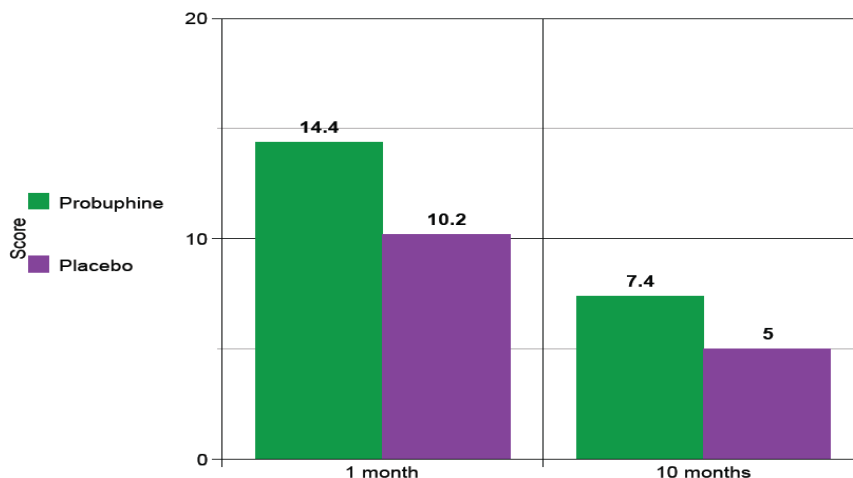
Table 22 Severity^a of Local Toxicity Based on Histological Observations in Dogs Treated with Probuphine or Placebo (EVA only) Implants for 1 or 10 months

Observation	Probuphine		Placebo	
	1 month	10 months	1 month	10 months
Increased fibrosis	1 to 4	1 to 2	1 to 3	1
Increased inflammatory cells				
Polymorphonuclear cells	1 to 3	0	1	0
Lymphocytes	1 to 3	1 to 2	1 to 3	0 to 1

Macrophages	1 to 4	0 to 3	1 to 3	0 to 1
Plasma cells	0 to 1	0 to 1	0	0 to 1

a - severity of fibrosis (0 - none, 1 – narrow band, 2 – moderately thick band, 3 – thick band, 4 – extensive band)
 - severity of inflammatory cells (0 – none, 1 – rare, 2 – 5-10 per microscopic field, 3 – heavy infiltrate, 4 – packed)
 Table prepared by Nonclinical Reviewer from implant site histology data in study PRO-NTR-0215

Figure 11 Individual Implant Local Toxicity Scores^b



b - Nonirritant (0.0-2.9), Slight Irritant (3.0-8.9)
 Moderate Irritant (9.0-15.0), Severe Irritant (≥15.1)

Source: Figure prepared by Nonclinical Reviewer from implant site histology data in study PRO-NTR-0215

7.2.4 Routine Clinical Testing

Routine clinical testing in the Probuphine clinical trials, included evaluations of treatment-emergent adverse events, (TEAEs), blood chemistry, hematology and urinalysis laboratory evaluations, urine toxicology screens, ECG evaluations, vital signs, and pupillary diameter.

Refer to the description of the clinical trials in Section 5 and in the Appendix for the timetable of clinical testing in each of the studies.

The table below summarizes the adverse event collection timeframes for each of the studies.

Protocol	Follow-up Time by Study	TEAEs Included in Pooled Data^a
PRO-805	Day of Insertion to 14 days post implant removal (30 days for SAEs)	All TEAEs were AEs that started on or after the day the implants were inserted or the day of the first post-randomization dose of SL buprenorphine for subjects in the SL buprenorphine group in Study PRO-806
PRO-806	Day of Insertion or first post-randomization dose of SL buprenorphine to 39 days post implant removal or last on-study dose of SL buprenorphine	
PRO-807	Day of Insertion to 14 days post implant removal (30 days for SAEs)	
PRO-811	Day of Insertion to 28 days post implant removal	

Source: Integrated Summary of Safety

7.2.5 Metabolic, Clearance, and Interaction Workup

The Applicant is relying on clinical pharmacology data for buprenorphine in the sublingual tablet formulation. Metabolic, Clearance and Interaction Workup information are taken from the label for Subxone sublingual tablet.

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 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 ^a n=6
C _{max} (ng/mL)	8.61 (6.900)	10.40 (13.400)	4.89 (1.110)	0.91 (0.157)	0.78 (0.128)
T _{max} ^b (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 _{0-t} ^c (ng•hr/mL)	66.25 (35.878)	62.67 (36.397)	113.13 (27.737)	19.60 (3.372)	10.23 (2.264)
AUC ₀₋₂₄ (ng•hr/mL)	66.25 (35.878)	62.67 (36.397)	75.191 (24.443)	19.60 (3.372)	10.23 (2.264)
t _{1/2} ^b (hr)	11.42 (11.04, 12.09)	7.63	--	--	--
λ _z (hr ⁻¹)	0.0604 (0.00231)	0.0908	--	--	--

λ_z = apparent elimination rate constant; AUC₀₋₂₄ = area under the plasma concentration-time curve from time 0 to 24 hours; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to t, where t is the last measurable plasma concentration; C_{max} = maximum observed plasma concentration; t_{1/2} = apparent terminal elimination half-life; T_{max} = 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).

^a Day 57 represents parameters after removal of the Probuphine implants.

^b Median (minimum, maximum) reported for T_{max} and t_{1/2}.

^c On Days -1 and -2, AUC_{0-t} represents the AUC from Day -1 or Day -2 Hour 0 through Day 1 or Day -2 Hour 12. On Day 1, AUC_{0-t} represents the AUC from Day 1 Hour 0 through Day 2 Hour 36, relative to the time of insertion.

Buprenorphine distribution, metabolism, elimination, and drug-drug interactions are described in detail in the Suboxone label:

Distribution:

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

Naloxone is approximately 45% protein bound, primarily to albumin.

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. Naloxone undergoes direct glucuronidation to naloxone-3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.

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 and naloxone has a mean elimination half-life from plasma ranging from 2 to 12 hours.

Drug-drug Interactions:

CYP3A4 Inhibitors and Inducers: Subjects receiving SUBOXONE sublingual tablet should be monitored if inhibitors of CYP3A4 such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin) or HIV protease inhibitors and may require dose-reduction of one or both agents. The interaction of buprenorphine with all CYP3A4 inducers has not been studied, therefore it is recommended that patients receiving SUBOXONE sublingual tablet be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered.

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine, has been found to be a moderate CYP2D6 inhibitor in in-vitro studies employing human liver microsomes. However, the relatively low plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic doses are not expected to raise significant drug-drug interaction concerns.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Probuphine, buprenorphine hydrochloride; ethylene vinyl acetate is an implantable, extended release formulation of buprenorphine. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid. As a partial μ -receptor agonist with low intrinsic activity at the receptor site, buprenorphine exhibits a “ceiling effect” such that its opioid agonist effects plateau at higher doses. Potential adverse events then would be those anticipated for an opioid agonist, keeping in mind the ceiling effect on opioid agonist effects. In addition to the adverse events anticipated with the active pharmaceutical ingredient, adverse events related to the insertion and removal procedures are also of importance. Thus, comprehensive evaluation involved review of adverse events observed in drugs using similar implantable formulations and insertion and removal procedures.

Expected adverse events include those relating to the systemic effects of opioid exposure, and those observed in the implantable contraceptives experience.

The Agency's previous experience with surgically-implanted 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 Probuphine 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, 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.

While implantable contraceptive methods are generally well-tolerated, procedure-related adverse events are notable for 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.

Notably, implantable contraceptive products are inserted and removed by obstetrician/gynecologists, who are surgically trained specialists. 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 implantation or removal procedures, or to manage complications.

7.3 Major Safety Results

Review of major safety results included a review of deaths, nonfatal serious adverse events, permanent treatment discontinuations, significant adverse events, and submission-specific primary safety concerns.

7.3.1 Deaths

There were no deaths that occurred among subjects on Probuphine in any trial in the clinical development program.

There was a single death in the clinical development program for Probuphine. This occurred in a patient in the sublingual buprenorphine arm of Study PRO-806. PRO-806, the second Phase 3 safety and efficacy study had three arms, a Probuphine arm, a placebo implant arm, and an open-label sublingual buprenorphine arm.

Subject 619-036 was a 29-year-old female subject with opioid dependence, whose primary opioid of abuse was heroin. Following induction with sublingual buprenorphine from (b) (6) to (b) (6), the subject continued on buprenorphine until (b) (6), when treatment was discontinued at subject request. The subject had an accidental heroin overdose on (b) (6).

7.3.2 Nonfatal Serious Adverse Events

Nonfatal serious adverse events occurred in eight subjects on Probuphine (4%), 7 subjects on placebo (6%), and six subjects on sublingual buprenorphine (5%) in the pooled double-blind studies. In the pooled open-label extension studies, these occurred among three subjects on Probuphine in the double-blind studies who continued on Probuphine in the open-label studies, and one subject who was on placebo during the controlled studies, and newly exposed to Probuphine in the open-label extension. A single subject who participated in the clinical pharmacology studies, experienced nonfatal serious adverse events.

The following table provides an overall summary of nonfatal serious adverse events by study and treatment arm. Additional details on the subjects and the events are provided in subsequent tables in this section of the review.

Pooled DB Studies – PRO805 & PRO-806		
Probuphine (4%)	Placebo (6%)	SL BPN (5%)
1. Hypotension (sepsis, BP meds)	1. Respiratory Failure (heroin withdrawal; agitation → intubation)	1. Major depression
2. COPD exacerbation & PE	2. Suicidal Ideation	2. Pyrexia (infxn)
3. Pneumococcal pneumonia	3. Tylenol overdose (per pt 50 500-mg pills)	3. Angina pectoris
4. Pneumonia	4. Pneumonia; Explant Site Cellulitis (805)	4. Pulmonary embolism
5. Umbilical hernia, obstructive	5. Limb abscess (not implant site)	5. Rib fracture
6. Tooth abscess	6. Gastroenteritis	6. Spontaneous abortion
7. Second degree burns	7. Relapse	
8. Breast cancer		
Pooled OL Extension Studies – PRO-807 & PRO-811		
Probuphine → Probuphine	Placebo → Probuphine	
1. CAD, worsening	1. Pneumonia (pneumonia in primary study also)	
2. Cellulitis antecubital fossa (methamphetamine IV)		
3. Suicidal ideation		

Clinical Pharmacology Study PRO-810

1. pancreatic cyst x 2, nausea

Several of the events were of an infectious etiology, including abscesses potentially related to intravenous drug use, which may not be unexpected in a population of injection drug users. Depression and suicidal ideation were also reported. 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. This occurred in Study PRO-805, which predates the surgical device and technique improvements, and training and certification program.

There were few serious adverse events overall, and the observed events were not of a pattern to suggest a new unexpected safety signal related to buprenorphine systemic exposure. Additional safety labeling beyond current labeling for the sublingual formulations with respect to serious adverse events does not appear warranted.

The following tables provide additional details of the serious adverse events presented in the summary table above and included in the above discussion.

Probuphine Nonfatal Serious Adverse Events – Controlled Studies

Subject ID / Age/ # implants	Induction / Target dose	SAE(s)	Narrative
PRO-805 (b) (6) 47 y/o M X implants	(b) (6) – (b) (6) 12mg	- SAE#1: COPD Exacerbation (b) (6) - SAE#2: COPD Exacerbation, Pulmonary Embolism (b) (6) - SAE#3: Pulmonary Embolism (b) (6)	- also c/o R calf pain x 2 mos - utox: (+) cocaine - utox (+) opiates & cocaine; also COPD exacerbation
(b) (6) 27 F 4 implants	(b) (6) 14 mg	2nd Degree Burns to Lower Bilateral Limbs (b) (6)	
PRO-806 (b) (6) 21 F 4 implants	(b) (6) 12 mg	Pneumonia pneumococcal (b) (6)	Additional non-serious AEs pleural effusions, empyema, pneumothorax, & dehydration
(b) (6) 39 F 4 implants	(b) (6) 12 mg	breast cancer (b) (6)	invasive ductal carcinoma of left breast

Subject ID / Age/ # implants	Induction / Target dose	SAE(s)	Narrative
(b) (6) 60 M 4 implants	(b) (6) 16 mg	Umbilical hernia, obstructive ((b) (6))	h/o ongoing diverticulum and umbilical hernia Implants removed (b) (6) for hernia surgery requiring general anesthesia.
(b) (6) 25 M 4 implants	(b) (6) 16 mg	Tooth abscess ((b) (6))	Hospitalized; 8 teeth extracted.
(b) (6) 42 F 5 implants	(b) (6) 16 mg	Pneumonia ((b) (6))	Hospitalization
(b) (6) 59 F 4 implants	(b) (6) 16 mg	Hypotension ((b) (6))	On lisinopril and atenolol (HTN before randomization, started on BP meds) Non-serious mild AE of sepsis

Placebo Nonfatal Serious Adverse Events – Controlled Studies

Subject ID / Age/ # implants	Induction / Target dose	SAE(s)	Narrative
PRO-805			
(b) (6) 34 y/o M 5 implants	(b) (6) 16 mg	Suicidal Thoughts ((b) (6))	h/o depression
(b) (6) 51 M 5 implants	(b) (6) 16 mg	- Pneumonia ((b) (6)) - Left upper extremity cellulitis ((b) (6))	- Completed study (b) (6); - hospitalized (b) (6) after presenting to investigator's office with pneumonia; left arm abscess at explant site.
(b) (6) 58 M 4 implants	(b) (6) 16 mg	Opiate dependency relapse ((b) (6))	Inpatient rehabilitation facility hospitalization
(b) (6) 40 M 4 implants	(b) (6) 16 mg	- Respiratory failure ((b) (6))	Transferred to hospital with SOB while incarcerated for heroin possession. Pt stated he was in heroin withdrawal. Ultimately intubated for agitation. Dysmetation and fever. Rhabdo without renal failure.
PRO-806			
(b) (6) 26 F 4 implants	(b) (6) 14 mg	Abscess limb ((b) (6))	Not implant site
(b) (6) 46 M	(b) (6)	Gastroenteritis ((b) (6))	Hospitalized

Subject ID / Age / # implants	Induction / Target dose	SAE(s)	Narrative
4 implants	16 mg		
(b) (6) 26 F 4 implants	(b) (6) 16 mg	Tylenol Overdose (b) (6)	Reported swallowing fifty 500-mg tablets. No hospitalization. At a site visit (b) (6), instructed to go to hospital, but refused

OL SL Buprenorphine Nonfatal Serious Adverse Events – Controlled Studies

Subject ID / Age / # implants	Induction / Target dose	SAE(s)	Narrative
PRO-806			
(b) (6) 46 M	(b) (6) 12 mg	Angina pectoris (b) (6)	- Hospitalization - Elevated BP prior to randomization and throughout study.
(b) (6) 24 M	(b) (6) 16 mg	Pyrexia (b) (6)	Hospitalized with T 102.5. CT abd/pelvis findings suggestive of enterocolitis. Diphtheroids & gram(+) rods on blood culture. IV vanc/ceftriaxone. Pt. left AMA.
(b) (6) 24 M	(b) (6) 12 mg	Rib fracture (b) (6)	Sustained in motorcycle accident.
(b) (6) 52 M	(b) (6) 16 mg	Major depression (b) (6)	- h/o depression and suicide attempt (in (b) (6)) - Voluntarily went to ER and hospitalized with complaints of auditory hallucinations and suicidal ideation. He reported hearing his own voice telling him to use heroin.
(b) (6) 26 F	(b) (6) 16 mg	Abortion spontaneous (b) (6)	hospitalized with severe vaginal bleeding
(b) (6) 46 M	(b) (6) 16 mg	Pulmonary embolism (b) (6)	No obvious predisposing factors.

Probuphine Nonfatal Serious Adverse Events – Uncontrolled Open-Label Extension Studies

Subject ID / Age/ # implants	Induction / Target dose	SAE(s)	Narrative
PRO-807			
Placebo in Double-Blind Studies → OL Probuphine			
(b) (6) 51 M 4 implants	(b) (6) 16 mg	• Pneumonia (b) (6)	• See also above re: explant site infection
PRO-811			
Probuphine in Double-Blind Studies → OL Probuphine			
(b) (6) 54 M 4 implants	(b) (6) 16 mg	• Coronary artery disease (b) (6) • (b) (6)	• Completed PRO-806 on (b) (6) • Before study drug started, hospitalized for elective angiogram. Angiography revealed > 50% blockage of one right vessel.
(b) (6) 40 M 4 implants	(b) (6) 12 mg	• Right antecubital fossa cellulitis (b) (6)	• Completed PRO-806 on Feb 17, 2011 • IV methamphetamine use on (b) (6) • On the CRF, it was mentioned that the location of the cellulitis was at the explant site.
(b) (6) 51 F 4 implants	(b) (6) 12 mg	• Suicide ideation (b) (6)	• Completed PRO-806 on Feb 8, 2011 • h/o bulimia nervosa (since (b) (6)), depression (since (b) (6)), panic disorder (since (b) (6)).

7.3.3 Dropouts and/or Discontinuations

Analyses of adverse events associated with premature discontinuation of study drug identify the type and frequency of adverse events that subjects were unable to tolerate even in a clinical trial setting, where there is perhaps more support for patients to persist on treatment while experiencing these adverse events than would be the case in a clinical practice setting. Adverse dropouts may also provide a clue to unexpected, but important, adverse reactions that may be initially ascribed to intercurrent illness.

Adverse dropouts 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 6 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.

The following table provides an overall summary of the adverse events associated with dropout by study and treatment arm. The study numerical identifier in which the adverse event occurred is included in parentheses next to each event, primarily for the assessment of implant site adverse events. For Studies 806 and 811, improvements to the applicator device, surgical technique and training and certification program were instituted for the insertion and removal procedures.

Additional details on the subjects who discontinued due to adverse events and the adverse events associated with the dropouts are provided in subsequent tables in this section of the review.

Pooled Double-Blind Studies – PRO-805 & PRO-806		
Probuphine (3%)	Placebo (2%)	SL BPN (4%)
1. Implant Site Pain/Infection (805)	1. Tylenol Overdose (806)	1. ALT/AST increased (806)
2. Implant Site Pain/Infection (805)	2. Hepatitis C (806)	2. Weight decreased (806)
3. Implant Site Pain (805)		3. Neck pain (806)
4. Hepatic Enzyme increases (805)		4. Sinus tachycardia (806)
5. LFT abnormal (806)		5. Drug dependence (806)
6. Breast Cancer (806)		
Pooled OL Extension Studies – PRO-807 & PRO-811		
1. Implant Site Hemorrhage, Infection, Edema & Erythema (807) – Probuphine → Probuphine		
2. Implant Site Infection (807) – Probuphine → Probuphine		
3. ALT increased (811) Probuphine → Probuphine		
Clinical Pharmacology Study PRO-810		
1. Adverse dropout in BA Study (810) – pancreatic cyst		

Probuphine Treatment Discontinuations – Controlled Studies

Subject ID / Age/ # implants	Induction / Target dose/ Rescue SL (where relevant)	SAE(s)	Narrative
PRO-805			
(b) (6) 52 M # implants not specified	(b) (6) Not specified Mg Supplemental SL BPN at 8 mg started Dec 21st; received doses of 4 to 8mg from (b) (6) through (b) (6)	Hepatic enzyme increased (elevated liver enzymes) (b) (6)	- h/o hepatitis C - Pre-Induction ALT 75, AST 55 - high of 1304 U/L and 1048 U/L, respectively, on (b) (6) - Concomitant medications included ibuprofen, Vicodin, and lidocaine
(b) (6) 27 M # implants not specified	(b) (6) – (b) (6)	- Implant site pain (b) (6) - Implant site infection (b) (6)	- No meds given. (b) (6) – implants removed and subject discontinued from study. - Investigator reported the subject as recovered from the AEs of implant site pain and implant site infection on (b) (6).
(b) (6) 25 F 4 Probuphine implants	(b) (6) – (b) (6)	- Implant site pain (b) (6) - Implant site infection (b) (6)	- Paracetamol, PCN, and cephalixin. - Implant site pain and infection recovered (b) (6) and (b) (6), respectively. (b) (6) – implants removed and subject discontinued from study.
(b) (6) 32 F	(b) (6) – (b) (6) 16 mg	implant site pain (b) (6)	- recovered (b) (6) - Sep 6th – implants removed and subject discontinued from study.
PRO-806			
(b) (6) 39 F 4 implants	(b) (6) – (b) (6) 12 mg No supplemental	breast cancer	(b) (6) – SAE of breast cancer – invasive ductal carcinoma of the left breast
(b) (6) 40 M 4 implants	(b) (6) – (b) (6) 12 mg No supplemental BPN	Liver function test abnormal	(b) (6) – AE of LFT abnormal. At baseline all values above ULN: ALT 73; AST 64; GGT 105; LDH 266; Peak values (b) (6) ALT 559; AST 634; GGT 280; LDH 478 (b) (6) – study drug d/ced, LFTs decreasing; Increasing again on (b) (6) after study drug withdrawn

Placebo Treatment Discontinuations – Controlled Studies

Subject ID / Age/ # implants	Induction / Target dose	SAE(s)	Narrative
PRO-806			
(b) (6) 26 F 4 implants	(b) (6) – (b) (6) 16 mg SL BPN started (b) (6) with 8 mg, and continued at this dose until (b) (6).	Tylenol Overdose (b) (6) See also SAEs	- Reported swallowing fifty 500-mg tablets. No hospitalization. - At a site visit (b) (6), instructed to go to hospital, but refused
(b) (6) 53 M 4 implants	(b) (6) – (b) (6) 16 mg	Worsening Hepatitis C (b) (6)	- History of Hepatitis C in (b) (6) - At screening, AE of Hep C, condition didn't improve and AE on the (b) (6). (b) (6) – Implants d/ced; subject withdrawn from study

OL SL Buprenorphine Treatment Discontinuations – Controlled Studies

Subject ID / Age/ # implants	Induction / Target dose	SAE(s)	Narrative
PRO-806			
(b) (6) 46 M	(b) (6) – (b) (6) 12 mg No supplemental BPN.	- Alanine aminotransferase increased (b) (6) - Aspartate aminotransferase increased (b) (6)	- Last SL BPN dose (b) (6) & AEs of ALT & AST increased. - ALT 38 AST (b) (6) - ALT 559, AST 290 (b) (6); - Drug discontinued (b) (6) when ALT 717 & AST 382, also last day of contact
(b) (6) 39 M	(b) (6) – (b) (6) 16 mg No supplemental BPN.	Drug dependence (b) (6)	- AE of drug dependence; heroin and cocaine by self-report; urine tox (+) heroin metabolites; Treatment for drug detoxification included diazepam and methadone, and he received dicycloverine hydrochloride for associated abdominal cramping. - Drug discontinued (b) (6) t
(b) (6) 43 F	(b) (6) – (b) (6) 12 mg began receiving supplemental SL BPN at a dose of 4 mg on (b) (6)	Weight decreased (b) (6)	Baseline wgt 78.91 kg (b) (6) to 64.40 kg (b) (6) (Week 10) 31 lbs. Drug withdrawn and pt discontinued on (b) (6)

	(b) (6); the dose was increased to 16 mg on (b) (6) and supplemental dosing continued at this dose until (b) (6). The subject's assigned SL BPN dose was increased to 16 mg on (b) (6).		
(b) (6) 32 F	(b) (6) – (b) (6) 12 mg No supplemental BPN	Sinus tachycardia ((b) (6))	- Last SL BPN dose taken before event onset was on (b) (6). No treatment given for the event. - ECG: non-clinically significant sinus tachycardia with left atrial enlargement; Max HR = 109 bpm; QTcB & QTcF < 450 msec - On (b) (6), treatment with study drug was discontinued - investigator reported the event outcome recovered on (b) (6)
(b) (6) 54 F	(b) (6) – (b) (6) 16 mg No supplemental BPN	neck pain ((b) (6))	- Last SL BPN dose taken before event onset was on (b) (6). - No treatment was given for the event - Drug d/ced (b) (6) - Study withdrawal (b) (6) due to non-compliance; missed 9 consecutive urine samples. - investigator reported the event outcome as recovered on (b) (6)

Probuphine Treatment Discontinuations – Uncontrolled Open-Label Extension Studies

Subject ID / Age/ # implants	Induction / Target dose	SAE(s)	Narrative
Probuphine in Double-Blind Studies → OL Probuphine			
PRO-807			
(b) (6) 21 F 4 implants	(b) (6) – (b) (6) (completed PRO-805 (b) (6))	- Implant site bleeding ((b) (6)) - implant site infection ((b) (6))	(b) (6) – 1 of 4 implants removed intact that day (b) (6) – subject d/ced treatment that day due to implant site

	12 mg No supplemental	• implant site erythema (b) (6) • implant site edema (b) (6)	AEs; remaining 3 implants removed.
(b) (6) 38 M 4 implants	(b) (6) – (b) (6) (completed PRO-805 (b) (6)) No supplemental BPN	• Implant site infection (b) (6)	• subject dced treatment (b) (6) due to event, and implants removed
PRO-811 (b) (6)	(b) (6) – (b) (6) (completed study (b) (6))	• Elevated alanine aminotransferase • (b) (6)	• History of hepatitis C • Met exclusionary ALT criteria prior to induction, but nevertheless was implanted. • (b) (6) – implants removed
(b) (6) 33 F 4 implants	(b) (6) – (b) (6) (completed study (b) (6)) 16 mg		

There were few adverse events associated with discontinuation overall. A number of these events were implant site related adverse events. Of note is that, these occurred in Studies PRO-805 and PRO-807 which predate all the improvements to the applicator, surgical technique, and training and certification program for the insertion and removal procedures. The drop in adverse events associated with discontinuation in the latter Phase 3 safety and efficacy trial may be a result of the improvements; however, the training program has never been validated. Many of the sites participated in both studies; therefore, it may also be merely a result of the implanting physicians becoming more adept at the procedures over time, and with more opportunities for repeated procedures. Whatever the basis for the decrease, the adverse events have decreased considerably between the first and second sets of Phase 3 studies.

The other group of adverse events that occurred in more than one subject and may represent an important systemic effect of Probuphine and sublingual buprenorphine are the liver function test abnormalities. These were seen across all treatment arms, and in the double-blind and open-label studies. These patients typically had underlying diagnoses of hepatitis C and/or elevated hepatic enzymes at baseline. Some subjects were on concomitant medications that could cause hepatic enzyme elevations. One subject (b) (6) did not meet Hy's Law criteria but had an elevated AST and ALT and a bilirubin approaching the total bilirubin threshold of > 2 x ULN. This patient saw a downward trend in the lab values while the Probuphine implants were still in place. Of note, this occurred in the extension study, and this patient had already been exposed to Probuphine in the primary safety and extension trial. It is conceivable that the higher buprenorphine exposures with Probuphine earlier in treatment may have played a contributory role. (b) (4)

Other adverse events associated with discontinuation occurred singly, and are not critical events that would seem to significantly alter the recognized buprenorphine safety

profile. One of these single occurrences was an event of relapse in a patient on sublingual buprenorphine that pertains to efficacy of sublingual buprenorphine rather than a safety concern.

7.3.4 Significant Adverse Events

Specific adverse events have been designated significant adverse events for the purposes of this review because they are known safety concerns with buprenorphine for which there are warnings and precautions, or because they are safety concerns that are currently undergoing evaluation.

Of the special interest AEs, unanticipated systemic findings were observed for the hepatic injury data and QT interval data in this new drug application upon review. (Safety data related to abuse potential were reviewed by the Controlled Substance Staff (CSS). The reader is referred to the CSS review for additional details about the relevant safety findings.)

Hepatic Injury

Buprenorphine has been associated with hepatitis and other hepatic events. The *Warnings and Precautions* section of current labeling for sublingual buprenorphine (as Suboxone) includes safety labeling regarding hepatitis and hepatic events as follows:

5.6 Hepatitis, Hepatic Events

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through post-marketing adverse event reports. The spectrum of abnormalities ranges 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. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Liver function tests, prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, SUBOXONE sublingual tablet may need to be carefully discontinued to prevent withdrawal signs and symptoms and a return by the patient to illicit drug use, and strict monitoring of the patient should be initiated.

Hepatitis and hepatic events are considered part of the known safety profile of buprenorphine. In evaluating the hepatic safety of Probuphine, the objective was to establish whether the hepatic safety findings from the Probuphine clinical trial database were consistent with the known safety profile of buprenorphine, and to identify new safety information, if any, for buprenorphine exposure intrinsically or as a result of buprenorphine exposure in the setting of this novel delivery system. To facilitate this

effort, the Applicant was advised to search the pooled safety database for hepatic adverse events with specific focus on “Hy’s Law”¹¹ cases.

The laboratory conventions used most commonly for identifying Hy’s Law cases are AST or ALT elevations > 3xULN along with total bilirubin elevations ≥ 2xULN. However, the Applicant used the following liver function test criteria to identify possible Hy’s Law cases:

- ALT >3X ULN (upper limit of normal) or AST >3X ULN, and
- Total bilirubin >2X ULN or >50% elevated over baseline.

Using this case definition for Hy’s Law cases, the Applicant identified Hy’s Law cases in the Probuphine arm (n=3, 1.4%) and the combined placebo/sublingual buprenorphine arm (n=6, 2.6%) of the pooled double-blind studies. An additional 5 patients on Probuphine in the open-label extension studies were identified as meeting Hy’s Law criteria.

On review of the cases identified by the Applicant as meeting Hy’s Law criteria, the majority met the definition due to transaminitis in the setting of bilirubin elevations that were more than 50% higher than the baseline values, although still (for the most part, well) within normal limits (upper limit of normal for total bilirubin, 1.2). In two cases where the bilirubin approached a two-fold ULN elevation, other plausible alternative explanations for the pattern of LFT abnormalities were identified, namely a Tylenol overdose a few days prior (one time dose of 25,000 mg) in one case, and a new diagnosis of Hep C in the other (See also SAEs and discontinuations). In summary, no Hy’s Law cases were identified, although LFT changes consistent with the labeled effects of buprenorphine were observed.

In addition to an evaluation of abnormal liver function tests, the Applicant performed a search for adverse events using hepatic injury-related SMQs and found that, apart from two placebo-treated patients with AEs coded to the term "Hepatitis C," all events were in the SOC Investigations. The findings from the search of possible hepatic injury treatment-emergent adverse events are consistent with the LFT findings.

¹¹ Hy’s Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

Excerpt from Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation available at: <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf>

The LFT abnormalities observed in the Probuphine clinical trial database for patients exposed to Probuphine in addition to sublingual buprenorphine or sublingual buprenorphine alone, were primarily marked transaminase elevations that occurred in patients with baseline LFT abnormalities, underlying viral hepatitis diagnoses, and/or use of concomitant licit or illicit substances that may have had a causal or contributory role. Buprenorphine exposure, alone, or in combination with these other potential etiologies, could be causal as well. In the end, however, the Probuphine safety database reveals no new hepatic safety concerns beyond those previously identified in the clinical trial and postmarketing setting for the marketed sublingual buprenorphine products.

QT prolongation

Prolongation of the QT/QTc interval is associated with increased susceptibility to arrhythmias, in particular, Torsades de Pointes.

A signal for QT prolongation has been identified in a study of transdermal buprenorphine used for analgesia. The extent of prolongation noted was considered to meet the threshold for regulatory concern, a value which is used to determine whether or not the effect of a drug on the QT/QTc interval in target patient populations should be studied intensively during later stages of drug development. 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.

Electrocardiogram (ECG) data from the Probuphine clinical trials were evaluated for the pooled double-blind and open-label studies. An analysis of QT interval data based on Probuphine clinical trial data was performed and summaries are provided for QT interval data using Bazett's corrections and Fridericia's corrections, based on QT/QTc interval and changes from baseline.

While there is no consensus concerning the choice of upper limit values for absolute QT/QTc interval and changes from baseline, the categories used in this data summary have been offered as guideline thresholds for analysis.

QTcB

Numbers and percentages of the patients in each category are provided by treatment arm, along with the minimum and maximum values observed for a particular category.

	Probuphine N = 222	Placebo N = 109	SL BPN N = 119
BASELINE QTcB			
> 450			
Probuphine	Placebo	SLBPN	
12 (5.4)	9 (8.3)	7 (5.9)	
454 - 614	452 - 580	456.7 - 479.1	
> 480			
Probuphine	Placebo	SLBPN	
3 (1.4)	4 (3.7)	0	
482 - 614	484 - 580		
> 500			
Probuphine	Placebo	SLBPN	
2 (0.9)	1 (0.9)	0	
569.2 - 614	580 - 580		
QTcB - MAXIMUM POSTBASELINE VALUE			
<i>Absolute Values</i>			
> 450			
Probuphine	Placebo	SLBPN	
17 (7.7)	13 (11.9)	16 (13.4)	
450.6 - 531	454.4 - 547	450.2 - 493.3	
> 480			
Probuphine	Placebo	SLBPN	
2 (0.9)	3 (2.8)	1 (0.8)	
527 - 531	484 - 547	493.3 - 493.3	
> 500			
Probuphine	Placebo	SLBPN	
2 (0.9)	2 (1.8)	0	
527 - 531	501 - 547		
<i>Change from baseline</i>			
Change from baseline > 30			
Probuphine	Placebo	SLBPN	
44 (19.8)	23 (21.1)	10 (8.4)	
32 - 124	30.8 - 119	34.1 - 95.2	

Probuphine N = 222	Placebo N = 109	SL BPN N = 119
Change from baseline > 60		
Probuphine	Placebo	SLBPN
16 (7.2)	9 (8.3)	2 (1.7)
63 - 124	62 - 119	77.1 - 95.2
Change from baseline > 100		
Probuphine	Placebo	SLBPN
5 (2.3)	2 (1.8)	0
100 - 124	117 - 119	

Prolongation of QTc > 500 ms during therapy has been a threshold of particular concern in clinical trials. However, there were both Probuphine and placebo subjects with baseline QTcB values above 500 and none in the SL arm. After baseline, all groups had more patients meeting these thresholds. But the more extreme shifts were seen among the Probuphine and placebo arms and the proportions were similar between Probuphine and placebo, and sometimes higher in the Placebo arm.

QTcF

Numbers and percentages of the patients in each category are provided by treatment arm, along with the minimum and maximum values observed for a particular category.

Probuphine N = 222	Placebo N = 109	SL BPN N = 119
BASELINE QTcF		
> 450		
Probuphine	Placebo	SLBPN
9 (4.1)	5 (4.6)	4 (3.4)
452 - 579	454 - 553	450.2 - 469
> 480		
Probuphine	Placebo	SLBPN
3 (1.4)	1 (0.9)	0
482 - 579	553 - 553	
> 500		
Probuphine	Placebo	SLBPN
2 (0.9)	1 (0.9)	0
525.5 - 579	553 - 553	

Probuphine N = 222	Placebo N = 109	SL BPN N = 119
QTcF - MAXIMUM POSTBASELINE VALUE		
<i>Absolute Values</i>		
> 450		
Probuphine 7 (3.2) 451 - 504	Placebo 6 (5.5) 455 - 522	SLBPN 6 (5.0) 450.5 - 476
> 480		
Probuphine 2 (0.9) 500 - 504	Placebo 2 (1.8) 492 - 522	SLBPN 0
> 500		
Probuphine 1 (0.5) 504 - 504	Placebo 1 (0.9) 522 - 522	SLBPN 0
<i>Change from baseline</i>		
Change from baseline > 30		
Probuphine 33 (14.9) 30.4 - 101	Placebo 15 (13.8) 33 - 95	SLBPN 8 (6.7) 30.1 - 74.4
Change from baseline > 60		
Probuphine 10 (4.5) 68 - 101	Placebo 7 (6.4) 61 - 95	SLBPN 2 (1.7) 61.7 - 74.4
Change from baseline > 100		
Probuphine 1 (0.5) 101 - 101	Placebo 0	SLBPN 0

Because Bazett's correction overcorrects at elevated heart rates and under corrects at heart rates below 60 beats per minute (bpm), Fridericia's correction is considered more accurate than Bazett's correction in subjects with such altered heart rates. QTcF findings across the treatment arms were similar to that seen with the QTcB data. With the more accurate QTcF correction, there were fewer cases overall meeting these thresholds.

QT interval prolongation was observed across all treatment arms in the clinical trial database, suggesting that this is not a phenomenon specific to Probuphine.

The potential for doses of buprenorphine used for the treatment of opioid dependence to prolong the QT interval is to be evaluated in formal thorough QT studies. Because the signal was identified when several formulations of buprenorphine were already on the market, sponsors of new buprenorphine products have been informed that they will be permitted to complete the TQT studies as post-marketing requirements.

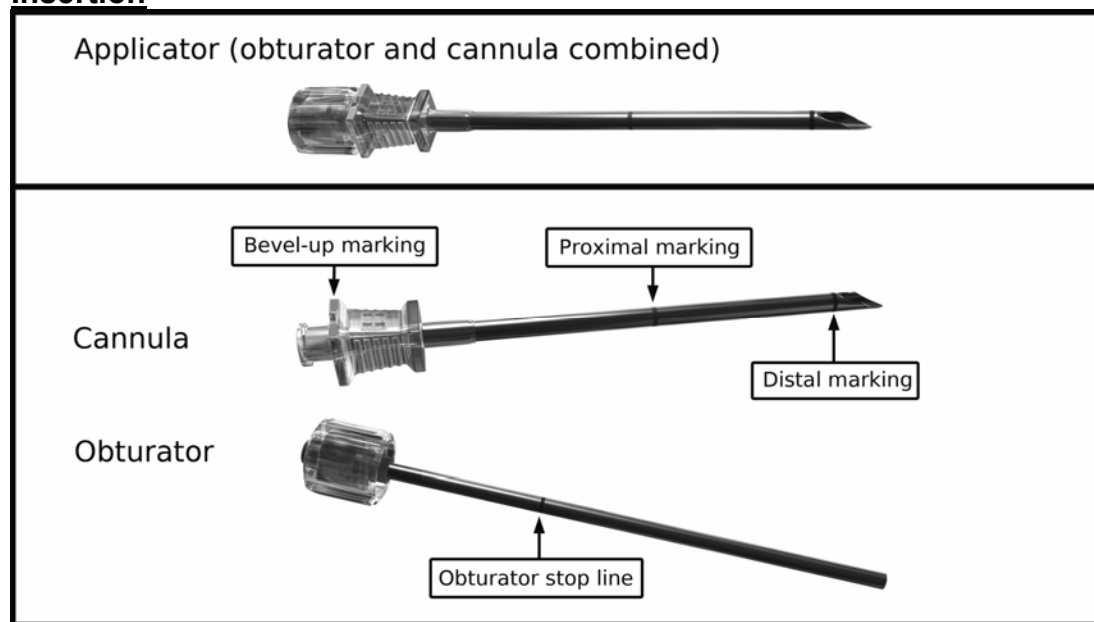
7.3.5 Submission Specific Primary Safety Concerns

Because Probuphine is a novel implantable formulation of buprenorphine, the review of safety data specific to the implants and insertion and removal procedures was emphasized.

Probuphine requires an in-office surgical procedure for insertion of the implants at the beginning of a treatment cycle, and a second procedure to remove the implants six months later at the end of the treatment cycle. Initially, four implants are inserted, and an additional procedure is needed if a dose increase of one additional implant is required.

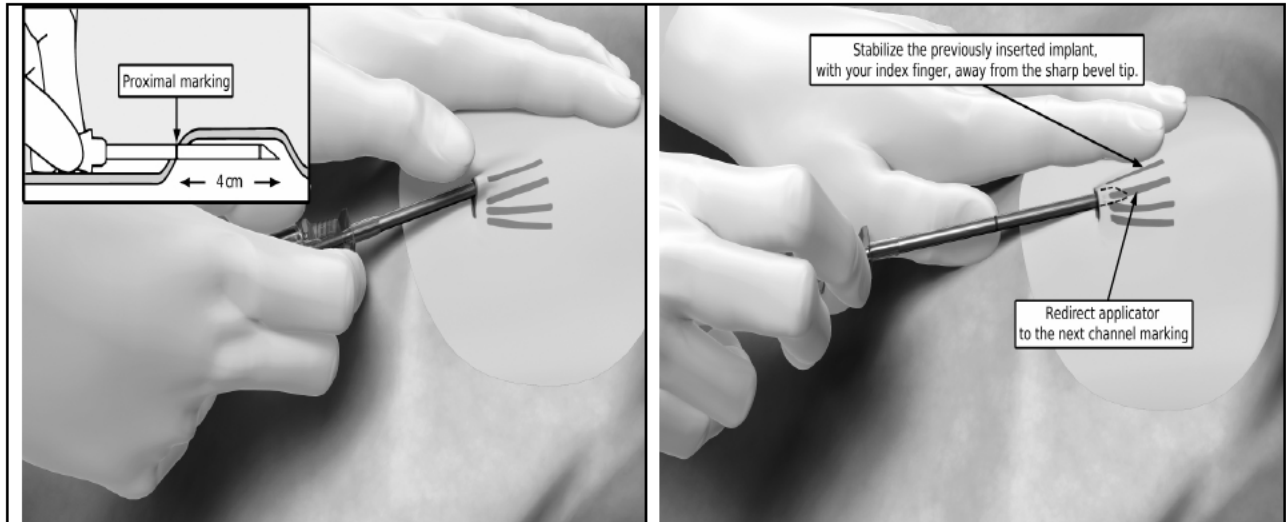
Insertion and Removal Procedures

Insertion



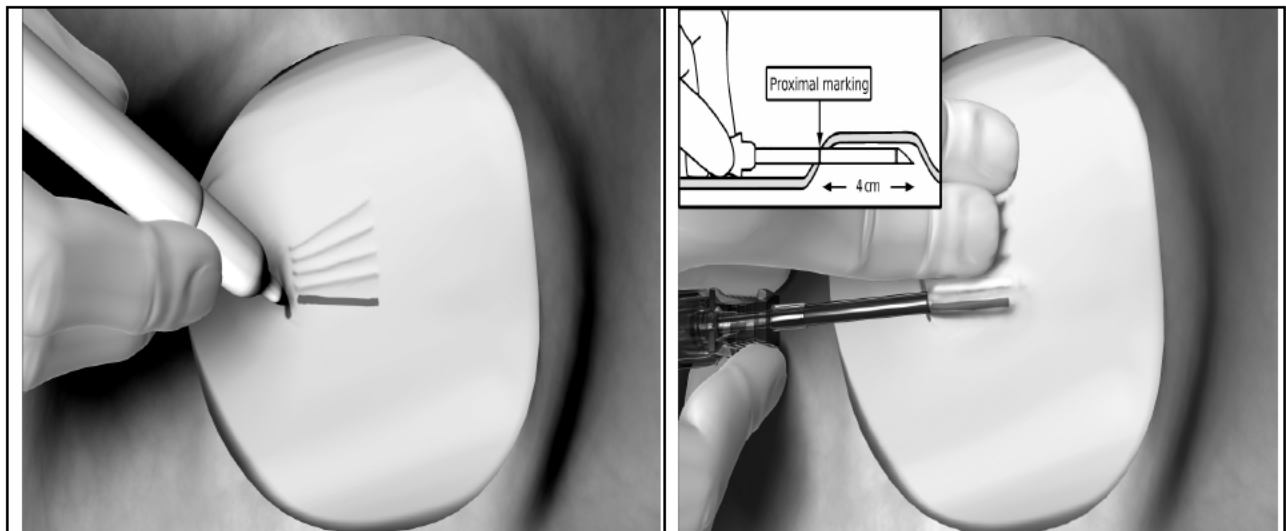
Source: Proposed (draft) label

Initial four implants



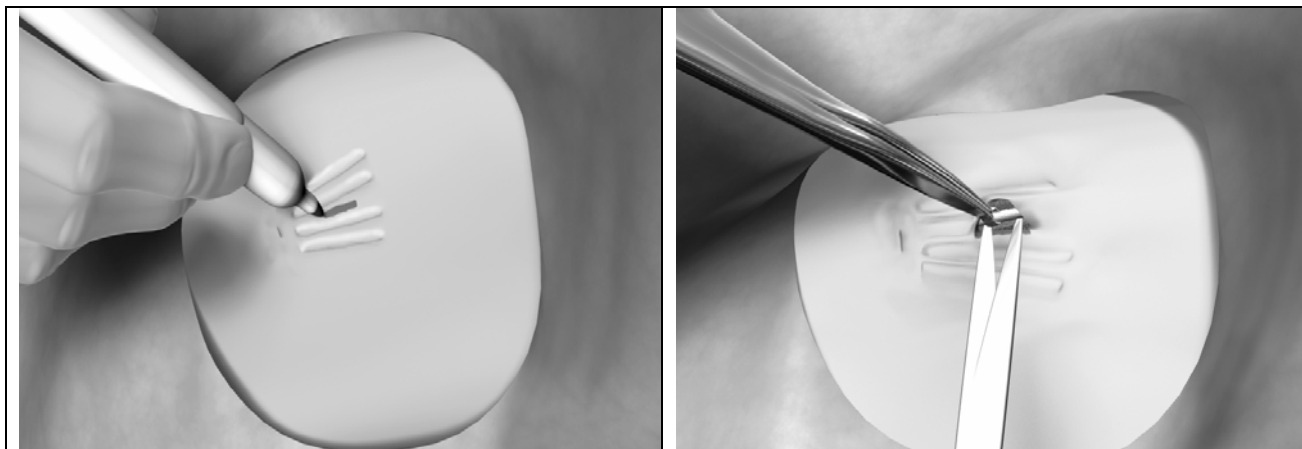
Source: Proposed (draft) label

Dose Increase (Fifth Implant)



Source: Proposed (draft) label

Removal



Source: Proposed (draft) label

In the course of the Probuphine Phase 3 clinical development program, there were surgical equipment and procedure modifications. The above images reflect the new equipment and procedures that were instituted approximately midway through the Phase 3 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 straight removal clamp were employed in the removal procedures. 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.

Extent of Experience with Implant Insertion and/or Removal Procedures – Probuphine Safety Database from Phase 3 Studies

The primary source of safety data available on the Probuphine insertion and removal procedures, and the indwelling implants originate from the Phase 3 safety and efficacy trials and the follow-on extension trials. Because patients in the placebo arm were subjected to the same insertion and removal procedures, these data are examined along with that of the Probuphine data to provide a more complete picture of the safety experience with insertion and removal of these implants.

Throughout the Phase 3 safety and efficacy trials and the extension studies, 478 patients underwent the minor 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. Lost-to-follow up in this case, thus, is identified here as a safety consideration, since those lost to follow-up may still have the implants in place and the consequences, if any, of Probuphine implants remaining in place indefinitely, is unknown..

Of the 478 patients who underwent the implant insertion procedure, 369 had Probuphine implants inserted. Of the Probuphine insertions, 222 took place in the controlled studies and 147 took place during the open-label studies. Of the 147 patients who underwent insertion procedures during the open-label extensions, 107 were repeat Probuphine exposures and 40 were new Probuphine exposures who had been in placebo or open-label sublingual buprenorphine arms during the controlled studies. There were 109 patients who underwent insertion procedures to have placebo implants inserted during the controlled studies. This represents a relatively small database and there may not have been ample procedures performed to fully characterize the safety profile associated with the insertion and removal procedures.

Extent of Experience with Implant Insertion and/or Removal – Implanting Physicians

In studies 805 and 806, the implanting physicians were members of a variety of specialty practices. The table below provides a summary of the number of physicians performing insertion and removal procedures in each of the studies by specialty. The numbers of physicians in a particular specialty who performed the procedures are represented in the yellow columns. The table also provides the numbers and proportions of patients who underwent removal and insertion procedures by the physicians in a particular specialty practice. These patients are represented in the columns with no shading or color-coding.

	PRO-805						PRO-806					
	Insertions			Removals			Insertions			Removals		
	# MDs	N=163 patients n (%) of patients		# MDs	N=148 patients n (%) of patients		# MDs	N=168 patients n (%) of patients		# MDs	N=147 patients n (%) of patients	
Specialty		n	%		n	%		n	%		n	%
Anesthesiology	2	12	7	2	12	8	3	8	5	3	7	5
Family Medicine	7	36	22	6	36	24	7	62	37	7	54	37
Internal Medicine	1	2	1	1	1	1	1	5	3	1	4	3
Neurosurgery	1	2	1	1	1	1	-	-	-	-	-	-
OB/GYN	6	43	26	6	35	24	5	45	27	5	35	24
Occupational Medicine	1	4	2	1	2	1	-	-	-	-	-	-
Orthopedic Surgery	-	-	-	1	3	2	-	-	-	-	-	-
Psychiatry	4	40	25	3	29	20	1	7	4	1	7	5
Surgery	3	24	15	2	29	20	3	24	14	3	23	16
Urology	-	-	-	-	-	-	2	17	10	2	17	12
Surgical Subspecialties		69	42		68	46		86	51		75	51

Most of the implanting physicians were family medicine physicians or obstetrics and gynecology physicians, followed by psychiatrists, and surgeons. Physicians in these specialties and subspecialties also performed the majority of the procedures.

The specialty types and the number of procedures performed by the various specialties generally remained stable across the studies. However, in 806 compared to 805, a much smaller number of psychiatrists were performing the procedures, and the amount of procedures performed by psychiatrists was substantially fewer. Titan also commented at the Advisory Committee meeting that the psychiatrists who volunteered to be trained as implanting physicians had prior experience in another specialty (such as OB/Gyn) before entering the field of psychiatry. At the same time, while the number of family medicine physicians stayed the same across the studies, more procedures were performed by family medicine physicians, members of a procedurally-oriented

specialty. Again, in 806, modified surgical equipment, techniques, and training were implemented. Blue font was used in the table to highlight surgery and surgical subspecialties. A number of procedures were performed by surgically-trained physicians, and the proportion increased in Study PRO-805 compared to Study PRO-806 with the new modifications to the equipment, techniques, and training.

Implant Site Adverse Events

Summaries of implant site adverse events are presented by study. Modifications to the surgical equipment and procedures were made during the clinical development program, and occurred approximately after Studies PRO-805 and PRO-807 completed and before studies PRO-806 and PRO-811 commenced. The training program also evolved. In Studies PRO-805 and PRO-807, the training comprised an instructional DVD, self-guided written instructions, and on-site training by the implant medical monitor, if needed. For Studies 806 and 811, the competency-based training components included a training manual, a training video, a half-day training class, and a hands-on training using a “meat model.”

Examining the implant site adverse events by study may provide some insight as to whether implementation of the device and procedure modifications, and revised training program was met with differences in the numbers and types of implant adverse events before and after implementation of the device and procedure modifications. It should be noted that these are all the implant site adverse events that occurred, and this encompasses a spectrum of events from non-serious adverse events, like erythema and pain that are not unexpected, to the more important procedural complications. Nonetheless, exploiting this “natural experiment” resulting from the introduction of the equipment and procedure modifications during Phase 3 development, still provides some indication of potential improvements in, or worsening of, the safety experience following introduction of the modifications.

Table 23 Implant Site Treatment-Emergent Adverse Events by Classification in Study PRO-805

Implant Site TEAE from CRF or Pre-Specified List	Probuphine N = 108 n (%)	Placebo N=55 n (%)
Any Implant Site TEAE per CRF	62 (57.4)	25 (45.5)
Implant site erythema	27 (25.0)	12 (21.8)
Implant site itching	27 (25.0)	8 (14.5)
Implant site pain	24 (22.2)	6 (10.9)
Implant site edema	14 (13.0)	5 (9.1)
Implant site bleeding	13 (12.0)	7 (12.7)
Implant site infection	4 (3.7)	1 (1.8)
Other Implant Site TEAE	27 (25.0)	15 (27.3)
Implant site scar	10 (9.3)	7 (12.7)
Implant site bruising	6 (5.6)	8 (14.5)
Implant site reaction	6 (5.6)	0 (0.0)
Implant site hemorrhage	4 (3.7)	1 (1.8)
Implant site pain	4 (3.7)	2 (3.6)
Impaired healing	3 (2.8)	0 (0.0)
Implant site erythema	3 (2.8)	0 (0.0)
Implant site hematoma	2 (1.9)	1 (1.8)
Implant site irritation	2 (1.9)	0 (0.0)
Complication of device removal	1 (0.9)	0 (0.0)
Implant expulsion	1 (0.9)	0 (0.0)
Implant site edema	1 (0.9)	0 (0.0)
Implant site pruritus	1 (0.9)	1 (1.8)
Implant site rash	1 (0.9)	1 (1.8)
Incision site complication	1 (0.9)	0 (0.0)
Incision site hemorrhage	1 (0.9)	0 (0.0)
Cellulitis	0 (0.0)	1 (1.8)

Source: Summary of Clinical Safety, p. 112

Table 24 Implant Site Treatment-Emergent Adverse Events in ≥ 5% of Subjects in Study PRO-807

	Probuphine N=62 n (%)
Any Implant Site TEAE	28 (45.2)
Implant site erythema	16 (25.8)
Implant site itching	12 (19.4)
Implant site pain	12 (19.4)
Implant site bleeding	10 (16.1)
Implant site edema	8 (12.9)
Other implant site TEAEs^a	
General Disorders and Administrative Site Conditions	13 (21.0)
Implant site bruising	6 (9.7)
Implant site hemorrhage	4 (6.5)

Source: Summary of Clinical Safety, p. 121

As noted earlier, in Study PRO-805 and Study PRO-807, the case report form (CRF) presented a check list of 6 possible implant site TEAEs, as well as “Other implant site TEAE” and “non-implant site TEAEs.” Only “Other implant site TEAEs” and “non-implant site TEAEs” had free-text recorded. The determination of whether or not an event was an implant site TEAE was based solely on the designation from the individual study CRF check box.

In Study PRO-805, more than half of the subjects experienced an implant site adverse event (n=87 subjects, 53%) experienced an implant site adverse event. In Study PRO-807, a little less than half (45%) of the subjects experienced an implant site adverse event. These numbers may, in fact, underestimate the total number of subjects who experienced an implant site adverse event, because the subjects represented in the “Other implant site TEAEs” categories may include subjects who were not already captured by the check list of 6 possible implant site TEAEs.

Studies PRO-806 and PRO-811 occurred after the equipment and procedure modifications were implemented. In Study PRO-806 and Study PRO-811, there was a CRF check box to designate TEAEs as implant site related. All TEAEs had free text descriptions that were coded; again, the determination of implant/non-implant status was based on the CRF check box.

Table 25 Implant Site Treatment-Emergent Adverse Events in >1 Subject by Preferred Term in Study PRO-806

System Organ Class Preferred Term	Probuphine N=114 n (%)	Placebo N=54 n (%)
Any Implant Site TEAEs	31 (27.2)	14 (25.9)
General Disorders and Administration Site Conditions	21 (18.4)	11 (20.4)
Implant site erythema	4 (3.5)	0.0
Implant site hematoma	8 (7.0)	6 (11.1)
Implant site hemorrhage	2 (1.8)	2 (3.7)
Implant site edema	2 (1.8)	0.0
Implant site pain	6 (5.3)	5 (9.3)
Implant site pruritus	5 (4.4)	2 (3.7)
Implant site swelling	2 (1.8)	0.0
Injury, Poisoning and Procedural Complications	8 (7.0)	3 (5.6)
Procedural pain	4 (3.5)	0.0
Procedural site reaction	3 (2.6)	2 (3.7)
Skin and Subcutaneous Tissue Disorders	3 (2.6)	1 (1.9)
Ecchymosis	2 (1.8)	0.0

Source: Summary of Clinical Safety, p. 117

Table 26 Implant Site Treatment-Emergent Adverse Events in >1 Subject by Preferred Term in Study PRO-811

	Probuphine N = 85 n (%)
Any Implant Site TEAE	12 (14)
Implant site erythema	1 (1)
Implant site haematoma	2 (2)
Implant site haemorrhage	3 (4)
Implant site pruritus	1 (1)
Implant site rash	2 (2)
Implant site reaction	1 (1)
Cellulitis	1 (1)
Implant site abscess	1 (1)
Implant site infection	1 (1)
Subcutaneous abscess	1 (1)

Source: Table generated from PRO-811 Study Report

In Study PRO-806, approximately one quarter (n=45, 27%) of all the patients in the study experienced an implant site adverse event. In PRO-811, the final Phase 3 study, the proportion continued to decline, and by this time there were 14% of patients experiencing implant site adverse events. This is a dramatic decrease in events compared to that observed for studies PRO-805 and PRO-807 where about half the patients experienced an implant site adverse event (53% and 45% respectively.) The decline in adverse events may be attributable to the modifications to the device and the procedures, and the revised training and certification program.

The training program, however, has never been validated and the improved adverse event profile could merely be a result of the implanting physicians becoming more adept at the procedures over time, and with more opportunities for repeated procedures.

Procedural Complications

An assessment of the procedural complications associated with insertion and removal is important for the review of safety associated with an implantable formulation that requires a minor surgical procedure for administration.

Procedural Complications – Insertions

All insertion procedures were successful on the first attempt. There was a single case in which one of the implants was dropped, and not inserted because it was contaminated and not suitable for insertion. This case is noted solely for completeness, but does not represent an insertion difficulty for this product.

There were six cases that required manipulation of the rods after they were inserted.

Study	Pt Info	Physician Specialty	Case Summary
805	(b) (6) 32 F Probuphine	Occupational Medicine	- In course of inserting a 5th implant, initial implant #3 found to be exposed. - Implant removed and new implant inserted.
805 & 807	(b) (6) 51 F Probuphine	Psychiatrist	Implant protrusion or expulsions replaced on 4 occasions (1 in PRO-805 and 3 in PRO-807)
805	(b) (6) 27 M Probuphine	Family Medicine	2 implants “extruding from incision site” 3 weeks after insertion; 2 new implants placed.
805	(b) (6) 46 F Probuphine	Family Medicine	“Skin infection” 2 wks after initial 4 implants inserted. - Implants removed, 4 replacement implants inserted into contralateral arm.
805	(b) (6) 37 M Probuphine	Family Medicine (same for Pt 030-010)	“Implant site erythema” 3 wks after insertion of initial 4 implants. 1 wk later returned for 5th implant. 4 initial implants removed, 4 replacement implants + 5th in contralateral arm.
806	(b) (6) 35 M	Obstetrics and	Mild protrusion of 1 of initial implants noted when pt returned for 5th implant. Protruding implant removed and replaced.

Study	Pt Info	Physician Specialty	Case Summary
	Placebo	Gynecology	

These occurred most often in patients in Study 805, which again predates the surgical equipment, procedure, and training modifications, usually occurred with Probuphine implants, and occurred among an equal number of men and women. Except for occupational medicine, these cases occurred among the specialties that performed most of the procedures, which appears consistent with procedure volume rather than a procedure operator matter.

There were no cases in which there were difficulties obtaining adequate anesthesia.

Procedural Complications – Removals

There were more difficulties with the removals than with the insertions. In 20 cases (4.7%), a second attempt was required to remove the implants. The nearly 5% of cases in which this occurred represents a relatively high rate given the small numbers of procedures performed.

As illustrated in the table below showing the number of cases by study, Study PRO-805 had the greatest number of cases, followed by study PRO-807. There were no cases in 806 but still a notable proportion in 811, the last study performed.

Study Identifier	Cases Requiring a Second Attempt at Removal
PRO-805	15 (10)
PRO-807 (PRO-805 Extension)	3 (5)
PRO-806	0
PRO-811 (PRO-806 Extension)	2 (3)

Ultrasound was used in 13 cases where a second attempt at removal was required, amounting to 65% of the cases requiring multiple attempts, and 3% of the total cases. Of these 13 cases in which ultrasound was used, eleven cases were in Studies PRO-805 and PRO-806. General anesthesia was required in one case where a second attempt at removal was required. This was for “uncooperative nature” of the patient. At the Advisory Committee meeting it was noted that this patient also had experienced a deep insertion into the brachial muscle.

The following tables display the cases requiring multiple attempts by treatment arm and implanting physician in each of the studies.

PRO-805

	Probuphine		Placebo		Total	
	All Removals	Unsuccessful 1st Attempt n (%)	All Removals	Unsuccessful 1st Attempt n (%)	All Removals	Unsuccessful 1st Attempt n (%)
All Specialties	96	11 (12)	51	4 (8)	147	15 (10)
Anesthesiology	8	1 (13)	4	0 (0)	12	1 (8)
Family Medicine	25	6 (24)	11	0 (0)	36	6 (17)
Internal Medicine	1	0 (0)	n/a	n/a	1	0 (0)
Neurosurgery	n/a	n/a	1	1 (100)	1	1 (100)
OB/GYN	22	1 (5)	13	0 (0)	34	1 (3)
Occupational Medicine	1	1 (100)	1	1 (100)	2	2 (100)
Orthopedic surgery	1	0 (0)	1	0 (0)	2	0 (0)
Psychiatry	19	2 (11)	10	2 (20)	29	4 (14)
Surgery	19	0 (0)	10	0 (0)	29	0 (0)

Surgical Subspecialties

PRO-806

	Probuphine		Placebo		Total	
	All Removals	Unsuccessful 1st Attempt n (%)	All Removals	Unsuccessful 1st Attempt n (%)	All Removals	Unsuccessful 1st Attempt n (%)
All Specialties	99	0 (0)	48	0 (0)	147	0 (0)
Anesthesiology	4	0 (0)	3	0 (0)	7	0 (0)
Family Medicine	38	0 (0)	16	0 (0)	54	0 (0)
Internal Medicine	1	0 (0)	3	0 (0)	4	0 (0)
Neurosurgery	n/a	n/a	n/a	n/a	n/a	n/a
OB/GYN	20	0 (0)	15	0 (0)	35	0 (0)
Occupational Medicine	n/a	n/a	n/a	n/a	n/a	0 (0)
Orthopedic surgery	n/a	n/a	n/a	n/a	2	0 (0)
Psychiatry	5	0 (0)	2	0 (0)	7	0 (0)
Surgery	18	0 (0)	5	0 (0)	23	0 (0)
Urology	13	0 (0)	4	0 (0)	17	0 (0)

Surgical Subspecialties

PRO-807 and PRO-811

	PRO-807		PRO-811	
	All Removals	Unsuccessful 1st Attempt n (%)	All Removals	Unsuccessful 1st Attempt n (%)
All Specialties	57	3 (5)	78	2 (3)
Anesthesiology	4	1 (20)	5	0 (0)
Family Medicine	12	0 (0)	35	1 (3)
Internal Medicine	n/a	n/a	1	0 (0)
Neurosurgery	n/a	n/a	n/a	n/a
OB/GYN	14	0 (0)	16	0 (0)
Occupational Medicine	n/a	n/a	n/a	n/a
Orthopedic surgery	n/a	n/a	n/a	n/a
Plastic Surgery, Critical Care Surgery	3	1 (25)	n/a	n/a
Psychiatry	16	1 (6)	4	0 (0)
Psychiatry, Surgery	5	0 (0)	n/a	n/a
Surgery	n/a	n/a	14	1 (7)
Urology	n/a	n/a	n/a	n/a

Surgical Subspecialties

The cases in which a second attempt was required for removal occurred more frequently among patients in the Probuphine arm. Physicians belonging to surgical specialties and subspecialties demonstrated the best outcomes overall.

In addition to cases that required a second attempt at removal, there were also cases in which the implants were not recovered. This was the result of loss to follow up and failure to return for removal, rather than a procedural complication.

Probuphine		Placebo	
Lost/Total Inserted Implants (% Unaccounted For)	Affected Subjects	Lost/Total Inserted Implants (% Unaccounted For)	Affected Subjects
146 / 1610 (9.1%)	36	37 / 489 (7.6%)	9

Finally, at the time of removal, fragmentation of the implant into two to three fragments was common. This, however, is not considered a major safety concern, as the health care practitioner performing the procedure can be able to tell with fair certainty that all pieces were removed.

The procedural complications associated with insertion and removal of the implants in the clinical trial database are not worrisome overall, although the rate of complications associated with removal in this small database is considered relatively high. Because the database is small, however, it may not allow for full characterization of these safety issues.

As described in further detail in Section 9.3 below, an Advisory Committee meeting was held to seek the panel's input on the efficacy and safety findings in this new drug application. Because of the extensive experience with implantable drug products in Obstetrics and Gynecology practice, specifically implantable contraceptives, Obstetrician/Gynecologists were invited to participate on the panel. Although the Division's perspective on the insertion and removal procedures prior to the AC meeting proceedings was that the procedures appeared to place undue burden on the patient and health care provider and exposed the patient to substantial risks, the Obstetrician/Gynecologists on the panel did not consider the procedures to be very involved and viewed them as relatively easy to perform and learn, even for health care providers who are not procedurally-oriented. The key driver in successful insertion and removal is to prevent deep insertions, and this in turn, can be achieved by ensuring that health care providers performing the procedures perform enough procedures to gain dexterity in inserting and removing the implants.

Allergic Potential of Implants

Another submission-specific primary concern is the potential for allergic reactions to occur as a result of the implants, an indwelling foreign body.

The Applicant performed an evaluation of possible allergic reaction treatment-adverse events (TEAEs) in the database. The following table summarizes those TEAEs that occurred in $\geq 1\%$ of total subjects in the pooled double-blind studies.

Table 27 Treatment-Emergent Adverse Events of Special Interest – Allergic Reactions Reported by $\geq 1\%$ of Total Subjects in Pooled Double-Blind Studies

MedDRA Preferred Term	Probuphine N=222		Placebo N=109		SL BPN N=119		Total N=450	
	n (%)	ER	n (%)	ER	n (%)	ER	n (%)	ER
Person-Years	112.9		40.3		58.2		211.3	
Possible Allergic Reactions	58 (26.1)	5.1	25 (22.9)	6.0	11 (9.2)	1.9	94 (20.9)	4.4
Implant site pruritus	34 (15.3)	3.0	14 (12.8)	3.5	0 (0.0)	0.0	48 (10.7)	2.3
Cough	9 (4.1)	0.8	1 (0.9)	0.2	3 (2.5)	0.5	13 (2.9)	0.6
Rhinorrhea	4 (1.8)	0.4	3 (2.8)	0.7	1 (0.8)	0.2	8 (1.8)	0.4
Rash	5 (2.3)	0.4	1 (0.9)	0.2	1 (0.8)	0.2	7 (1.6)	0.3

Source: Summary of Clinical Safety, p. 147

Possible allergic reaction TEAEs occurred with similar frequency in the Probuphine and placebo arm, and a little more commonly in Probuphine vs. placebo when comparing percentages. This was largely driven by implant site pruritis which is not unexpected with the indwelling implants that are local irritants. These data do not suggest a new safety concern related to allergic phenomenon. Labeling for sublingual buprenorphine tablet formulations already describes allergic reactions with buprenorphine, and additional labeling beyond the current labeling does not appear warranted at this time based on these data.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events are displayed in the following table. The common adverse events pertaining to the systemic effects of buprenorphine are consistent with the common adverse events seen in current labeling for the sublingual formulations.

Common Non-Implant Site Treatment-Emergent Adverse Events (≥ 5% in the Probuphine group and more commonly than in the Placebo/SL BPN group) in the Pooled Double-Blind Studies

System Organ Class MedDRA Preferred Term	PROBUPHINE N=222 n (%)	Placebo/SL BPN N=228 n (%)
Any Non-Implant Site TEAE	158 (71)	158 (70)
Infections and Infestations	89 (40)	89 (39)
Upper respiratory tract infection	24 (11)	20 (9)
Nasopharyngitis	20 (9)	18 (8)
Gastrointestinal Disorders	67 (30)	54 (24)
Nausea	19 (9)	13 (6)
Constipation	16 (7)	9 (4)
Vomiting	15 (7)	10 (4)
Toothache	14 (6)	7 (3)
Psychiatric Disorders	51 (23)	56 (25)
Depression	14 (6)	8 (4)
Nervous System Disorders	52 (23)	47 (21)
Headache	33 (15)	29 (13)
Dizziness	11 (5)	6 (3)
Musculoskeletal and Connective Tissue Disorders	37 (17)	35 (15)
Back pain	17 (8)	12 (5)
Respiratory, Thoracic and Mediastinal Disorders	35 (16)	20 (9)
Oropharyngeal pain	13 (6)	8 (4)

Source: Modified Version of Post-text Table 8.2.4.1.1

7.4.2 Laboratory Findings

Summaries of laboratory data were reviewed. Overall, there were few changes from baseline in laboratory results. There were elevations in liver function tests seen in the Probuphine and comparator arms. (See Section 7.3.4. above for additional details).

Because this is an implantable drug product, basophil and eosinophil laboratory data were examined to assess for potential allergic phenomenon associated with the indwelling implant. There were few differences observed with respect to basophils. However, there were a greater number of categorical shifts from normal to above the upper limit of normal in subjects on Probuphine compared to subjects on the combined placebo and sublingual buprenorphine arms. Similarly there were mean increases from baseline in the eosinophil count for the Probuphine arm relative to the placebo/sublingual buprenorphine arm. Relevant information about laboratory results is discussed in sections above on allergic reactions and hepatic effects.

7.4.3 Vital Signs

No consistent effects on vital signs were observed across treatment groups in the pooled double-blind studies.

7.4.4 Electrocardiograms (ECGs)

See Section 7.3.4 Significant Adverse Events for further details.

7.4.5 Special Safety Studies/Clinical Trials

There were no special studies/clinical trials designed to evaluate a specific safety concern or concerns associated with Probuphine.

7.4.6 Immunogenicity

There are no specific data on the effect of immunogenicity on safety, efficacy, and/or clinical pharmacology and pharmacokinetics for Probuphine.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

All patients who were assigned to treatment arms that received implants in the Phase 3 studies received four or five implants. Subjects assigned to implant arms in the double-blind studies received 4 implants of either Probuphine or placebo. These subjects could receive a 1-implant dose increase (arriving at 5 implants total) if protocol dose increase

criteria were met as described in the protocol summaries in Section 5 of this review. The same dosing procedures were used for the open-label Probuphine treatment administered in the extension studies.

The Applicant displayed treatment-emergent adverse events for the All Probuphine group by the number of implants at the time the TEAE started. The Applicant also calculated person-years based on the actual time that subjects had 4 or 5 implants. Denominators for the 5 implant TEAEs are the total number of subjects who received a 5th implant. The denominator for the 4 implant group is the total number of patients in the All Probuphine group, because all patients initially received four implants, and were a member of the four implant group at some point during the study.

To account for the differences among treatment groups in terms of duration in the study, treatment-emergent adverse event (TEAE) summaries included both frequency and event rate (ER), defined as event/10 years of person-time.

To evaluate dose-dependency of adverse events, the summaries of adverse events in the four-implant and five-implant group were reviewed to identify adverse events occurring with greater frequency in the five-implant group, the group that is presumably exposed to higher plasma buprenorphine levels.

Of the patients in the All Probuphine Group, 56 received a fifth implant. Most of the adverse events in these summaries occurred more commonly in the group having four implants. Compared with the patients who had adverse events when four implants were indwelling, patients with five implants indwelling at the time of the event were more likely to report minor infections or gastrointestinal complaints which are not unexpected in association with systemic buprenorphine exposure. Additionally, subjects who had a fifth implant placed were more likely to report device expulsion and procedural pain, the latter potentially attesting to the higher likelihood of experiencing pain with each procedure. The former suggests either that placing a fifth implant increases the likelihood of device expulsion, or that requirement for a fifth implant led to greater surveillance and detection of device expulsion.

Table 28 Treatment-Emergent Adverse Events by Number of Implants

	All Probuphine Group			
	4 Implants Total N=262		5 Implants Total N=56	
Person-Years	161.5		23.1	
	n (%)	ER	n (%)	ER
Any TEAE	201 (76.7)	12.4	38 (67.9)	16.4
Upper respiratory tract infection	25 (9.5)	1.5	6 (10.7)	2.6
Nasopharyngitis	18 (6.9)	1.1	6 (10.7)	2.6
Nausea	18 (6.9)	1.1	5 (8.9)	2.2

	All Probuphine Group			
	4 Implants Total N=262		5 Implants Total N=56	
Abdominal discomfort	10 (3.8)	0.6	3 (5.4)	1.3
Urinary tract infection	7 (2.7)	0.4	2 (3.6)	0.9
Rash	7 (2.7)	0.4	1 (1.8)	0.4
Tooth infection	4 (1.5)	0.2	2 (3.6)	0.9
Device expulsion	3 (1.1)	0.2	2 (3.6)	0.9
Nasal congestion	3 (1.1)	0.2	2 (3.6)	0.9
Procedural pain	2 (1.1)	0.2	4 (7.1)	1.7
Lymphadenopathy	1 (0.4)	0.1	2 (3.6)	0.9

Source: Integrated Summary of Safety

7.5.2 Time Dependency for Adverse Events

The Applicant performed time-to-onset analyses for the special adverse events of interest. On average, subjects in the Probuphine arm in the double-blind studies had earlier onset for possible respiratory depression events, possible hepatic injury, possible gastrointestinal disorders, and possible psychiatric disorders. Except for possible gastrointestinal disorders, these events were observed more commonly in the placebo arm or occurring at similar rates across the arms.

Possible CNS depression events and possible orthostatic events had earlier time-to-onset in the placebo group compared with the Probuphine treatment arm.

Possible allergic reactions, possible drug abuse, dependence, and/or withdrawal events had similar time to onset between the two arms.

These findings are not inconsistent with the current safety profile for buprenorphine and current labeling for these events appears adequate.

7.5.3 Drug-Demographic Interactions

Drug-demographic interactions were assessed based on demographic parameters of gender (male and female), age (18 to 34 years and 35 to 65 years), and race (White, Black, and other).

As assessed by the Applicant, although there were some small differences in the frequencies or rates of some types of TEAEs in specific subgroups, the differences between the groups being examined were generally small. The rates of implant site and non-implant site TEAEs were generally similar in subgroups based on gender, age, and race. Assessment of these findings made during this review is overall consistent with the Applicant's assessment.

7.5.4 Drug-Disease Interactions

All patients in the study were opioid-dependent. There were no specific drug-disease interactions observed.

7.5.5 Drug-Drug Interactions

No formal clinical studies with Probuphine have been performed to evaluate drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity data have not been provided in this new drug application.

7.6.2 Human Reproduction and Pregnancy Data

No formal clinical studies on the use in pregnancy and lactation have been conducted with Probuphine.

7.6.3 Pediatrics and Assessment of Effects on Growth

Probuphine has not been evaluated in pediatric populations.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

Because Probuphine is implanted by a health care provider and the dose cannot be increased by the patient, overdose on Probuphine is unlikely.

Drug Abuse Potential

The drug abuse potential is reduced with implanted formulations compared to tablets, though still present, as buprenorphine can be extracted from the implants, and in the clinical trials, there has been implant expulsion, protrusion, and extrusion. On the basis of subjects who returned for implant removal and implant-site inspections, no evidence of diversion of Probuphine implants was detected by the Applicant; however there were 3 cases in which the implants were expelled sufficiently to be finally removed by the subjects themselves. There is no additional evidence that any subject attempted to remove their implants or have their implants removed prior to returning at the end of the study for implant removal. Of the 1610 Probuphine implants that were inserted in the clinical studies, 146 implants (9.1%) were not accounted for as a result of subjects who failed to return for implant removal, including 12 implants in subjects lost to follow-up due to incarceration or inpatient drug treatment program. Theoretically, failure to return

for implant removal could be interpreted as possible diversion. Used implants, once removed, also contain substantial quantities of residual buprenorphine which could be extracted for purposes of abuse if the product is not properly disposed.

Withdrawal

The occurrence of possible drug abuse, dependence, and/or withdrawal syndrome treatment-emergent adverse events was about the same in the Probuphine (81 subjects, 36.5%) and placebo (39 subjects, 35.8%) groups, but lower in the SL buprenorphine group (34 subjects, 28.6%). Preferred terms captured in the search for possible drug abuse, dependence, and/or withdrawal syndrome events included insomnia, nausea, anxiety, depression, dizziness, hyperhidrosis, abdominal discomfort, fatigue, rhinorrhea, somnolence, asthenia, hypoesthesia, and tremor.

7.7 Additional Submissions / Safety Issues

No additional safety submissions beyond the revised REMS were made by the Applicant. No additional safety issues beyond those associated with the REMS and the safety issues described throughout this review of safety are under evaluation.

8 Postmarket Experience

At the time of this application, Probuphine is not marketed in any country.

9 Appendices

9.1 Literature Review/References

No new clinical data from the literature were included in support of this submission. References for cited literature in this review were provided as footnotes throughout the document.

9.2 Labeling Recommendations

The submitted proposed labeling is in Physician's Labeling Rule (PLR) format. The approved labeling for Suboxone/Subutex tablets forms the foundation for Probuphine labeling, with new information related to the novel delivery system and the clinical trials, included throughout in relevant sections.

The following are key issues in labeling:

- The proposed wording of the indication is problematic because it implies use of Probuphine for a broader population than studied, and does not fully convey the conditions under which Probuphine was to be administered. Probuphine was studied in opioid-dependent patients who initially went through induction with buprenorphine over the course of 10 – 16 days, during which they were stabilized on 12–16 mg/day of sublingual buprenorphine for at least three consecutive days prior to insertion of Probuphine implants. Patients stabilized on less than 12 mg per day or more than 16 mg per day were not eligible to receive Probuphine (or placebo) implants. In light of the lower buprenorphine exposure of Probuphine relative to 16 mg of buprenorphine/naloxone, use of Probuphine should be discouraged in patients stabilized on more than 16 mg/day of sublingual buprenorphine.
- Use of rescue medication was required by some patients throughout the entire course of the study (and would likely have been required by many more had persistent illicit drug use been a criterion for rescue). The label, however, provides inadequate information on the use of rescue sublingual buprenorphine beyond the initial induction phase that takes place prior to insertion of the implants.
- A dose increase is possible with Probuphine; however, the label does not provide any indication of the need for or guidance on assessing patients with respect to making a determination of the need for a fifth implant.
- Section 6.1 Adverse Events in Clinical Trials provides separate summaries (b) (4) in order to distinguish those adverse events that are related to the implants and insertion and removal procedures from those that relate to the systemic effects of buprenorphine, the active pharmaceutical ingredient.

- Implant Site (b) (4): A summary of implant site-related AEs was provided comparing Probuphine-treated patients to Placebo-treated patients with respect to common implant site reactions, and includes event rates. (b) (4)

[Redacted]

Additionally, in order to present a complete picture of implant and procedural safety, the table should provide totals since patients who received either the Probuphine or placebo implants underwent the same procedures. A summary of insertion and removal procedure complications was not provided and should be included.

- Non-implant Site (b) (4): The common non-implant site adverse events table includes (b) (4)

[Redacted] This should be revised to display those common non-implant site adverse events occurring in $\geq 5\%$ of patients at the MedDRA Higher Level Group Term in the Probuphine group and more commonly than in the combined placebo/open-label sublingual buprenorphine arm.

- Section 14.1 Clinical Studies does not include important aspects of the study design that are key to interpreting the results of the study, in particular, as it relates to the use of rescue medication in the study. With respect to rescue medication, the following should be made clear:
 - (1) subjects had to meet certain protocol-specified criteria based on withdrawal symptoms and “cravings” or subject request. In the first controlled study, subjects could receive sublingual buprenorphine when one or more criteria were met. In the second controlled study, all three had to be met.
 - (2) Secondly, use of rescue medication was used to determine the need for a dose increase, meaning an additional implant in the implant arms or a higher dose of sublingual buprenorphine if the patient was not already at 16 mg.
 - (3) Finally, rescue medication use was used to make treatment failure determinations. If, after a dose increase, a patient again met the same threshold criteria based on buprenorphine use for which the dose increase was required, that patient was deemed a treatment failure and withdrawn from the study. Neither urine toxicology data, nor self-reported illicit opioid use was factored into the determination of treatment failure.

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

(b) (4)

(b) (4)

- The initial proposed REMS submitted at the time of the NDA submission was revised substantially, and recently submitted. As such, the submission did not allow for review during this review cycle and labeling comments related to the REMS are not presently available.

9.3 Advisory Committee Meeting

On March 21, 2013, a Psychopharmacologic Drugs Advisory Committee (PDAC) meeting was held to discuss NDA 204442, Probuphine (buprenorphine hydrochloride) subdermal implant, and its safety and efficacy for the proposed indication of maintenance treatment of opioid dependence. The following specific discussion topics and voting questions were posed to the committee for deliberation, and encompassed the unresolved issues on which advisory committee consultation was sought:

1. **DISCUSSION:** Please comment on whether the Applicant conducted adequate dose exploration in the development program to determine the most effective dose.
 - a. **VOTE:** Do the data from the clinical trials provide substantial evidence of effectiveness of Probuphine for the maintenance treatment of opioid dependence?
2. **DISCUSSION:** Please comment on the Applicant's assessment of the safety aspect of Probuphine in general, as well as on safety concerns specific to the placement and removal of the implants.
 - a. **VOTE:** Has the Applicant adequately characterized the safety profile of Probuphine in this patient population?
3. **VOTE:** Is the Risk Evaluation and Mitigation Strategy (REMS) proposed by the Applicant, which consists of restricted distribution and a training/certification program for healthcare professionals who will implant the product, adequate to address the risks of potential complications associated with the implantation procedure and abuse, misuse, and accidental overdose. Include in your deliberations any concerns related to the proposed model of care and training/certification program.

4. **DISCUSSION:** Please discuss whether the absence of any information on each of the following matters should be considered a critical deficiency in the application:
 - a. the potential for removal of the implants by non-medical personnel for the purpose of diversion.
 - b. the potential for long-term exposure to the components of the rods if an individual never has the implants removed.
 - c. the potential for patients to require implantation into an arm which has received an implant previously in order to remain on treatment, which would necessitate identification of multiple implantation sites per arm, or use of previously implanted sites.
5. **VOTE:** Based on the data presented and discussed today, do the efficacy, safety, and risk-benefit profile of Probuphine support the approval of this application?

A brief summary of the committee proceedings for each of the individual discussion topics and questions follows:

1. **DISCUSSION:** Please comment on whether the Applicant conducted adequate dose exploration in the development program to determine the most effective dose.
 - a. **VOTE:** Do the data from the clinical trials provide substantial evidence of effectiveness of Probuphine for the maintenance treatment of opioid dependence?

The committee overall felt that there had not been adequate dose exploration in the development program to determine the most effective dose. The committee expressed concerns about the clinical pharmacology findings which demonstrated that the plasma buprenorphine levels attained with Probuphine are less than levels attained with the target 16 mg sublingual buprenorphine dose. The committee members also had concerns regarding the uncertainties surrounding treatment of patients who require more or less than the target induction dose range of 12 – 16 mg sublingual buprenorphine used in the clinical trials. Moreover, the use of rescue sublingual buprenorphine was viewed as further support of the inadequate dose exploration.

On the voting question, the majority of committee members voted affirmatively (10 voted 'Yes', and 5 voted 'No'). Committee members contended that the data demonstrated that Probuphine was more effective than placebo, as efficacious as other products currently on the market, and that the primary endpoint criteria were met. At the same time, however, the committee members continued to express concerns that optimal dosing had not been determined.

2. **DISCUSSION:** Please comment on the Applicant's assessment of the safety aspect of Probuphine in general, as well as on safety concerns specific to the placement and removal of the implants.

- b. **VOTE:** Has the Applicant adequately characterized the safety profile of Probuphine in this patient population?

On the whole, the committee did not consider the safety of Probuphine, both as it related to the systemic effects of Probuphine, and the potential safety issues that may be associated with the insertion and removal procedures. Obstetrician/Gynecologists were invited to participate on the panel because of Agency concerns that the potential procedural complications that may arise as a consequence of Probuphine administration could conceivably outweigh any benefits that would be offered to the patient. The Obstetrician/Gynecologists were being asked to provide insight into the issues of safety based on the implantable contraceptives, in particular Norplant, the implantable contraceptive most analogous to Probuphine both from the number of implants used per treatment cycle and the insertion and removal procedures. The Obstetrician/Gynecologists, from their vast experience with these implantable contraceptives expressed that the insertion and removal procedures are not complicated procedures and with appropriate training, most clinicians can be taught to successfully perform the procedures. The key factor driving competency, the Obstetrician/Gynecologists contended, is that the implanting health care professional performs enough procedures to become comfortable with the procedures.

The perspective of the Obstetrician/Gynecologists allayed concerns about the procedural safety for this product. However, the committee members still noted that there were differences between the population of patients that would use implantable contraceptives and the population of patients that would use Probuphine. Members felt that training for placement and removal of the implants was important to minimize safety concerns. The majority of the committee agreed that the Applicant had adequately characterized the safety profile of buprenorphine; there were 12 Yes votes (2 voting no, and one abstention). This was because of the prior clinical experience with sublingual buprenorphine which attests to the systemic effects, and the implantable contraceptives, which address the procedural safety associated with the implants and insertion and removal procedures.

3. **VOTE:** Is the Risk Evaluation and Mitigation Strategy (REMS) proposed by the Applicant, which consists of restricted distribution and a training/certification program for healthcare professionals who will implant the product, adequate to address the risks of potential complications associated with the implantation procedure and abuse, misuse, and accidental overdose. Include in your deliberations any concerns related to the proposed model of care and training/certification program.

There was no consensus among the committee members with respect to the adequacy of the REMS proposed by the Applicant to address the risks of potential complications associated with the implantation procedure and abuse, misuse, and accidental overdose. The votes were varied with 5 Yes votes, 4 No votes, and 6 abstentions. The Applicant had revised their REMS shortly before the meeting because they had recently

learned that their REMS was not in compliance with DEA and SAHMSA regulations. The REMS described by the Applicant had not yet been submitted to the Agency for review, and as such the Agency was unable to provide perspective on the revised REMS, and at the meeting could only discuss the formal REMS submissions to date. The new submissions are to be reviewed by DRISK, but as they were submitted at the end of the review cycle, there was not enough time for DRISK to review and comment.

4. **DISCUSSION:** Please discuss whether the absence of any information on each of the following matters should be considered a critical deficiency in the application:
 - a. the potential for removal of the implants by non-medical personnel for the purpose of diversion.
 - b. the potential for long-term exposure to the components of the rods if an individual never has the implants removed.
 - c. the potential for patients to require implantation into an arm which has received an implant previously in order to remain on treatment, which would necessitate identification of multiple implantation sites per arm, or use of previously implanted sites.

The committee expressed no concerns about the removal of implants by non-medical personnel for the purposes of diversion or about long-term exposure of the components of the implants. They did, however, express concerns about the treatment duration limitations stemming from the limited implantation sites, but did not view this as a critical deficiency. It was noted that sites other than the arms should be explored, as long-term treatment could be necessary for some patients. During the meeting, it came to light that it may not be necessary to limit implant sites to the inner upper arm.

5. **VOTE:** Based on the data presented and discussed today, do the efficacy, safety, and risk-benefit profile of Probuphine support the approval of this application?

The committee voted 10-4 in favor of approval of this application. There was one abstention.

The majority of the committee agreed that, based on the data presented and discussed, the efficacy, safety, and risk-benefit profile of Probuphine support the approval of this application. The committee members who voted “Yes” noted that, although they voted “Yes,” additional data were needed to fully assess both the safety and efficacy of Probuphine and that the REMS was still an area of foremost concern. Overall, these members indicated that the benefits outweighed the risks. Because of the many unresolved issues pertaining to dose-finding and the REMS, the committee’s support of this product appeared to be based, in some part, on the potential of the product, rather than what the currently available safety and efficacy data for the product demonstrate. Additionally, the committee’s favorable opinion appeared to be given in the context of the limited pharmacologic treatment options available for this potentially fatal disease, and the advantage that Probuphine offers in the way of “passive compliance.” Said

another way, with Probuphine the difficult choice that patients must make on a daily basis to take their treatment medication rather than taking the substance to which they are addicted is eliminated. The committee members who voted “No” noted that the dose exploration was inadequate, which would also complicate labeling in that the dosing would be limited to only patients who could reach an induction dose of 12 – 16 mg, and expressed concerns with the REMS). The one member who abstained noted similar concerns with the REMS and felt that additional data, particularly regarding patient selection, was needed for a decisive vote.

9.4 Additional Appendices

Review of Individual Study Protocols: Phase 3 Extension Studies – PRO-807 and PRO-811

PRO-807

Title:	An Open-Label, Multi-Center Study of Probuphine in Patients with Opioid Dependence	
Protocol & Amendment Dates	• Original Protocol: July 2, 2007 • Amendment No. 1: May 21, 2008	
Study Initiation & Completion Dates	• Initiation: March 20, 2008 • Completion: February 19, 2009	

PRO-807 Objective/Rationale:

The *primary objective* was to evaluate the safety of Probuphine in patients who have completed 24 weeks of treatment and who will be re-treated with Probuphine over an additional 24 weeks.

The *key secondary objective* was to evaluate the efficacy of Probuphine through pharmacokinetic analyses in patients who have completed 24 weeks of treatment and who will be re-treated with Probuphine over an additional 24 weeks.

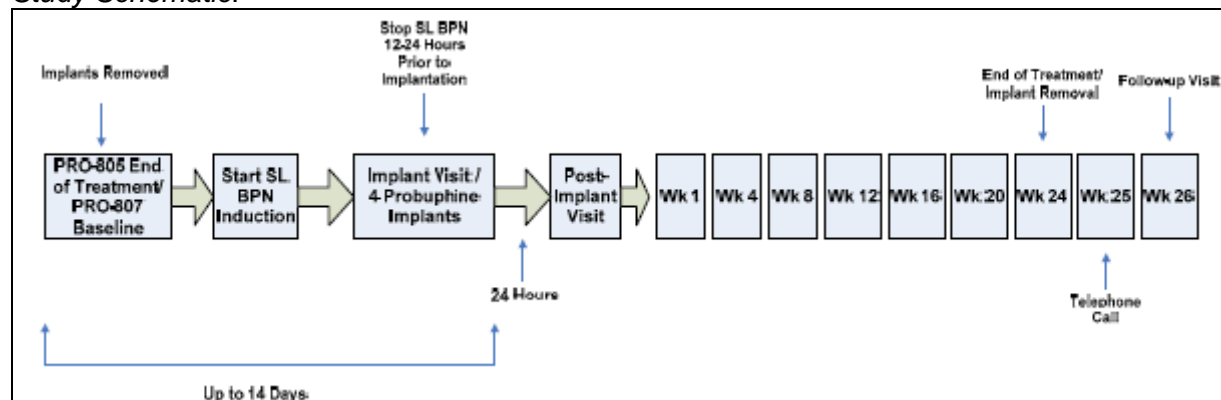
PRO-807 Overall Study Design

This was a 6-month, open-label, multi-center extension study. Following removal of the PRO-805 implants, patients had to enroll in Study PRO-807 within 7 days. Patients were to undergo repeat induction in this extension study, PRO-807, with SL buprenorphine (as Suboxone®) to a dose of 12–16 mg/day as clinically appropriate and were to complete induction within 13 days after removal of the PRO-805 implants. Patients had to be maintained at a fixed dose of 12–16 mg/day for at least 3 consecutive days just prior to PRO-807 implantation. The Implant Visit was to occur within 14 days after removal of the PRO-805 implants.

Patients initially received 4 Probuphine implants and were also allowed to receive supplemental SL buprenorphine (Suboxone®) throughout the study, if clinically indicated (under protocol-defined guidelines). Insertion of an additional Probuphine implant was permitted 2 weeks after the initial Implant Visit, under protocol-defined criteria.

Safety, pharmacokinetics, and efficacy measures were to be collected during the 24-week treatment period. At the end of the study, patients were to have their implants removed, and return for a Follow-Up Visit 2 weeks later.

Study Schematic:



Source: PRO-807-A1 protocol, p. 74

PRO-807 Study Population

Planned enrollment was 60–75 patients, who had completed PRO-805, at approximately 25 sites in the United States. The protocol specified that subjects had to meet a set of initial entry criteria and then meet an additional set of implantation criteria in order to be eligible for insertion of the implants.

Initial Screening Criteria

Inclusion Criteria

- Completed 24 weeks of treatment in PRO-805
- Deemed appropriate for entry into this extension study by the Investigator
- Reliable means of contraception

Exclusion Criteria

- Laboratory criteria: AST or ALT $\geq 3 \times \text{ULN}$; Total bilirubin $\geq 1.5 \times \text{ULN}$; and/or creatinine $\geq 1.5 \times \text{ULN}$
- Current diagnosis of chronic pain requiring opioids for treatment
- Pregnancy or lactation
- Use of agents metabolized through CYP 3A4
- Current anti-coagulant therapy (such as warfarin) or INR > 1.2
- Benzodiazepine use other than physician-prescribed use
- Significant medical or psychiatric symptoms, cognitive impairment, or other factors which in the opinion of the Investigator would preclude compliance with the protocol, patient safety, adequate cooperation in the study, or obtaining informed consent
- Concurrent medical conditions (such as severe respiratory insufficiency) that may prevent the patient from safely participating in study; and/or any pending legal action that could prohibit participation and/or compliance in study

Implantation Criteria

- Continue to satisfy all inclusion criteria and do not meet any exclusion criteria
- Undergone induction with SL buprenorphine to a dose of 12–16 mg/day as clinically appropriate within 13 days (vs. 10 in PRO-805 & 16 in PRO-806) after removal of the PRO-805 implants and received a fixed dose of 12–16 mg/day SL buprenorphine for at least 3 consecutive days just immediately prior to implantation.
 - Patients who undergo induction with SL buprenorphine to a dose < 12 mg/day or > 16 mg/day are ineligible

- No significant withdrawal symptoms (defined as a score of ≤ 12 on the Clinical Opiate Withdrawal Scale [COWS])
- No significant cravings for opioids (defined as a score of ≤ 20 -mm on the 100-mm Opioid Craving VAS)

PRO-807 Study Procedures

PRO-807 Study Procedures: Study Treatments

Sublingual Buprenorphine Induction

Following removal of the PRO-805 implants, patients were to undergo induction with sublingual (SL) buprenorphine (BPN) as Suboxone® to a dose of 12–16 mg/day as clinically appropriate and to complete induction within 13 days after removal of the PRO-805 implants. Patients had to receive a fixed dose of 12–16 mg/day SL BPN for at least 3 consecutive days just prior to implantation.

Implantation (Probuphine Implants)

SL buprenorphine was to be discontinued 12–24 hours prior to implantation. Ideally, implants were to be inserted in the arm opposite the arm where the PRO-805 implants were located. An alternative implantation site could be considered if medically indicated (e.g., it was not feasible to insert implants into the inner upper arm). The selection of an alternate implant insertion site had to be discussed with the Implant Medical Monitor in advance.

Implant insertion under the skin, usually into the inner side of the patient's upper arm, was to be performed under local anesthesia using a specialized investigational applicator provided by Titan. According to the protocol, the Probuphine Applicator that was to be used in PRO-806 is similar in design to the commercially-approved applicators currently used for the insertion of other implantable drugs, such as Implanon®. Patients were to be monitored closely for adverse events and vital signs for at least 30 minutes following implantation by medically qualified study staff. The protocol permitted insertion of an additional implant (dose increase) any time 2 weeks after the initial Implant Visit, under protocol-defined criteria based on supplemental sublingual buprenorphine dosing (described below in a subsequent portion of this review)

Implant Packaging and Storage

The protocol described the packaging and storage of the implants as follows:

Each implant is individually packaged in a foil-lined pouch and (b) (4). Pouched implants are labeled and packaged into an individual Patient Kit (Box). All Initial Implant Kits contain 4 Probuphine implants. All Implant Dose Increase Kits contain only 1 implant.

All implant kits should be stored at room temperature (15–25°C [59–77°F]), in a secured, double locked area and in accordance with applicable laws, regulations and institutional requirements. Detailed dispensing records must be maintained, including date received, quantity received, date dispensed, and remaining inventory.

After implant removal, all implants should be returned as outlined in the Manual of Procedures.

Supplemental Sublingual Buprenorphine Dosing

The protocol permitted supplemental SL buprenorphine (Suboxone®) during the study. The rules guiding administration of sublingual buprenorphine dosing, per protocol, were as follows:

Patients were to meet *1 or more* of the following criteria (*1 or more for PRO-805; all 3 for PRO-806*):

1. Withdrawal symptoms scoring > 12 on COWS
2. Request for dose increase by patient deemed appropriate by physician
3. Cravings > 20 mm on the Opioid Craving VAS

The primary reason for the patient's need for Supplemental SL buprenorphine was to be noted in the Case Report Form (CRF).

Supplemental SL buprenorphine was to be administered in increments of 2 mg or more as clinically indicated. Investigators were advised that, as is the case when using other opioid agonist medications, a period of time should elapse between supplemental SL buprenorphine doses in order to determine clinical response. Investigators were advised that peak buprenorphine blood levels with Probuphine are seen within the first day post-implantation and were advised any SL buprenorphine, if needed soon after implantation, must be prescribed bearing that in mind.

Subjects were required to obtain supplemental SL buprenorphine at their study clinic or pharmacy for each dose. Supplemental SL BPN doses were to be administered under observation at the clinic/pharmacy and witnessed by a staff member that the SL tablet had completely dissolved under the subject's tongue. The protocol permitted take-home dosing of Suboxone® for weekends/holidays or other circumstances at the discretion of the Investigator.

Dose Increases and treatment failures

- Implant dose increase (or 1 additional Probuphine implant): SL buprenorphine requirement ≥ 3 days/week for 2 consecutive weeks or ≥ 8 days over 4 consecutive weeks
 - The one additional implant could be inserted any time after 2 weeks from the initial Implant Visit into the same arm as the initial PRO-807 Probuphine implants or the opposite arm if medically indicated
[To allow for stabilization of blood levels, the additional implant (Implant Dose Increase) was not to be inserted within the first 2 weeks after insertion of the initial 4 implants]
- Treatment Failure: After implant dose increase, patient continues with same supplemental SL buprenorphine needs that led to implant dose increase

When an Implant Dose Increase was required, the patient was to attend the Implant Visit, the Post-Implant Visit, and a Week 1 Telephone Call would follow. The patient would then resume with the original visit schedule in order to complete 24 weeks from the date of the initial Implant Visit (Visit 3). If a patient met these protocol-defined criteria for a dose increase, but elected not to receive a fifth implant, he/she was withdrawn from the study.

Implant Removal

As stipulated in the protocol, patients had implants removed under local anesthesia through a small incision during the End of Treatment Visit.

Psychosocial Counseling

Psychosocial counseling was permitted as clinically indicated, and recorded on the appropriate CRF. If counseling was clinically indicated, it was recommended that the sites follow the US National Institutes of Health/National Institute on Drug Abuse Manual titled “Individual Drug Counseling.”¹²

PRO-807 Study Procedures: Evaluations and Procedures

The following evaluations and procedures took place over the course of the study as outlined in the Time and Event Schedule that follows immediately:

Evaluation/Study-Specific Procedure	Comments
Informed Consent Form (ICF)	Patients had up to 7 days from the PRO-805 End of Treatment Visit, to decide if they wanted to participate in PRO-807
Eligibility Criteria Review / Enrollment	Patient had to meet the I/E Criteria prior to starting induction; patients could, however, begin induction prior to receipt of laboratory results if necessary to prevent onset of withdrawal following implant removal in the context of the parent study
Medical/Medication History and Substance Abuse History and Treatment	Changes since collection in PRO-805 Screening visit
Psychiatric History (MINI)	
Physical Examination	
Vital Signs	
Implant Insertion	Initial implant insertion and implant dose increase if protocol-specified criteria were met
Implant Site Examination/Treatment Compliance	
Quality of Life (QOL)	Assessed via the follow-up version of the Addiction Severity Index (ASI) at the End of Treatment Visit
Withdrawal Symptoms and Cravings	Subjective Opioid Withdrawal Scale (SOWS), Clinical Opioid Withdrawal Scale (COWS), Opioid Craving Visual Analog Scale (VAS). ○ In addition, if a patient reports opioid cravings or withdrawal symptoms at a visit where the measures are not typically scheduled, the SOWS, COWS, and Opioid Craving VAS may be administered as part of the overall clinical evaluation of the patient’s status and potential need for rescue medication.

¹² Reference cited: Mercer D, Woody G. Individual Drug Counseling Manual. An Individual Drug Counseling Approach to Treat Cocaine Addiction: The Collaborative Cocaine Treatment Study Model. National Institute on Drug Abuse Therapy Manuals for Drug Abuse, Manual 3. 1999.

Evaluation/Study-Specific Procedure	Comments												
Illicit Drug Use Self-Report	Patients were to be questioned about illicit drug use. The drug name, number of days used, daily use, average cost per day, and whether the patient 'got high' was to be documented.												
Clinical Global Impression – Self	Patients were to rate their current severity of opioid related problems and their improvement in symptoms of opioid dependence from baseline, using a 7-point Likert-type scale.												
Clinical Global Impression – Observer	The treating physician and study personnel will rate the patient's severity of opioid dependence covering 8 specific problem areas, using a 7-point Likert-type scale, as well as global severity of opioid dependence over the last week and the patient's degree of global improvement since baseline using a 7-point Likert-type scale.												
Psychosocial Counseling	As clinically indicated												
Electrocardiogram (ECG)													
Clinical Laboratory Evaluations	<table border="1"> <tr> <td data-bbox="521 833 708 884">Hematology</td> <td data-bbox="712 833 1440 884">Hematocrit, Hemoglobin, RBC, MCV, MCH, MCHC, RBC Morphology, WBC with differential, and platelets</td> </tr> <tr> <td data-bbox="521 890 708 999">Chemistry (including liver profile)</td> <td data-bbox="712 890 1440 999">Urea nitrogen, calcium, bicarbonate, chloride, creatinine, glucose, magnesium, potassium, sodium, albumin, alkaline phosphatase, amylase, AST (SGOT), ALT (SGPT), total bilirubin, total cholesterol, GGT, LDH, lipase, total protein</td> </tr> <tr> <td data-bbox="521 1005 708 1062">Coagulation Profile</td> <td data-bbox="712 1005 1440 1062">Prothrombin time (PT), INR</td> </tr> <tr> <td data-bbox="521 1068 708 1098">Pregnancy Test</td> <td data-bbox="712 1068 1440 1098">Serum or urine; females of childbearing potential only</td> </tr> <tr> <td data-bbox="521 1104 708 1213">Urine Toxicology</td> <td data-bbox="712 1104 1440 1213">Illicit Opioids (including prescription analgesics; excluding BPN and its metabolites [for sample collected prior to Induction]), amphetamines, antidepressants, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, methaqualone, phencyclidine, phenothiazine, propoxyphene</td> </tr> <tr> <td data-bbox="521 1220 708 1249">Other</td> <td data-bbox="712 1220 1440 1249">Plasma BPN and norBPN levels</td> </tr> </table>	Hematology	Hematocrit, Hemoglobin, RBC, MCV, MCH, MCHC, RBC Morphology, WBC with differential, and platelets	Chemistry (including liver profile)	Urea nitrogen, calcium, bicarbonate, chloride, creatinine, glucose, magnesium, potassium, sodium, albumin, alkaline phosphatase, amylase, AST (SGOT), ALT (SGPT), total bilirubin, total cholesterol, GGT, LDH, lipase, total protein	Coagulation Profile	Prothrombin time (PT), INR	Pregnancy Test	Serum or urine; females of childbearing potential only	Urine Toxicology	Illicit Opioids (including prescription analgesics; excluding BPN and its metabolites [for sample collected prior to Induction]), amphetamines, antidepressants, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, methaqualone, phencyclidine, phenothiazine, propoxyphene	Other	Plasma BPN and norBPN levels
	Hematology	Hematocrit, Hemoglobin, RBC, MCV, MCH, MCHC, RBC Morphology, WBC with differential, and platelets											
	Chemistry (including liver profile)	Urea nitrogen, calcium, bicarbonate, chloride, creatinine, glucose, magnesium, potassium, sodium, albumin, alkaline phosphatase, amylase, AST (SGOT), ALT (SGPT), total bilirubin, total cholesterol, GGT, LDH, lipase, total protein											
	Coagulation Profile	Prothrombin time (PT), INR											
	Pregnancy Test	Serum or urine; females of childbearing potential only											
	Urine Toxicology	Illicit Opioids (including prescription analgesics; excluding BPN and its metabolites [for sample collected prior to Induction]), amphetamines, antidepressants, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, methaqualone, phencyclidine, phenothiazine, propoxyphene											
Other	Plasma BPN and norBPN levels												
Urine toxicology samples: Urine toxicology samples will be collected using a urine collection cup containing a temperature sensor and specimen authenticity will be verified at the site by measurement of urine temperature. The temperature of a urine sample within 4 minutes of voiding should fall within the range of range of 32.2 degrees Celsius to 37.7 degrees Celsius (90 degrees Fahrenheit to 100 degrees Fahrenheit). If test results are outside these ranges, the patient will be asked to immediately provide another urine sample. If this second sample is outside of the temperature range, the sample will be counted as 'missing', and documented on the appropriate CRF. Pharmacokinetic samples: Samples for plasma for BPN and norBPN levels should be collected 12–24 hours after the most recent SL BPN dose and prior to implantation.													
Supplemental SL BPN	Suboxone®												
Implant Removal													
Adverse Events	- AEs were followed once patients signed the ICF until 14 days after study drug treatment discontinuation (i.e., removal of implants) and were required to be documented. - AEs designated as study drug related, and all serious AEs, were to be followed until resolution or stabilization. - AEs reported by the patient at times other than specified in												

Evaluation/Study-Specific Procedure	Comments
	Schedule of Events should also have been recorded.
Concomitant Medications / Procedures	
Telephone Contact	Patients were to be contacted by telephone 1 week ($\pm$ 2 days) after the removal of implants to capture any AEs that occurred since removal. If a significant AE was described by the patient which had the possibility of being related to study treatment, the patient was to visit study site for an unscheduled follow-up assessment (separate from the Week 26 Follow-Up Visit).

Event	Baseline ^{1,2}	Induction ²⁰	Implant	Post-Implant ³	Treatment ⁴		End of Treatment ⁵	Follow-Up	
			0		1,4	8,12,16,20	24	25	26
Visit Number	1	2 (2i, 2ii, etc.)	3	4	5-6	7-10	11		12
Informed Consent	• ⁶								
Eligibility Criteria Review ²¹	•		•						
Enrollment	•								
Medical / Medication History / Substance Abuse History and Treatments	• ⁷								
Physical Examination ⁸	•*					Wk 12	•		
Vital Signs ⁹	•*	•	• ¹⁰	•	•	•	•		•
Implant Site Examination/Treatment Compliance				•	•	•	•		•
Dispense Treatment Identification Card			•						
Quality of Life (ASI)	•*						•		
Withdrawal Symptoms and Craving (SOWS, COWS, Opioid Craving VAS) ¹⁷	•**	•	•		•	•	•		•
Illicit Drug Use Self-Report	•**	• ²³			•	•	•		•

Clinical Review
 Rachel Skeete, MD, MHS
 NDA 204442
 Probuphine[®] (buprenorphine implant)

Event	Baseline ^{1,2}	Induction ²⁰	Implant	Post-Implant ³	Treatment ⁴		End of Treatment ⁵	Follow-Up	
Week			0		1,4	8,12,16,20	24	25	26
Visit Number	1	2 (2i, 2ii, etc.)	3	4	5-6	7-10	11		12
CGI - Self	•*					•	•		
CGI - Observer	•*					•	•		
ECG	•*						•		
Pregnancy Test ¹¹	•**		•		Wk 4	•	•		
Hematology and Chemistry	•*				Wk 4	Wk 12	•		
Coagulation Profile	•*				Wk 4	Wk 12	•		
Urine Toxicology		• ²²			Wk 4	•	•		
Plasma BPN/norBPN levels	•*		• ¹⁸		Wk 4	•	•		
Induction (SL BPN)		•							
Implant ^{12,13}			Insertion				Removal		
Supplemental SL BPN				If needed					

Event	Baseline ^{1,2}	Induction ²⁰	Implant	Post-Implant ³	Treatment ⁴		End of Treatment ⁵	Follow-Up	
Week			0		1,4	8,12,16,20	24	25	26
Visit Number	1	2 (2i, 2ii, etc.)	3	4	5-6	7-10	11		12
ONE Implant Dose Increase ¹⁴					Anytime >2 Weeks, if needed				
Adverse Events		•	• ¹⁵	•	•	•	•	•	•
Concomitant Medications / Procedures		•	•	•	•	•	•		•
Wound Care Information Sheet ¹⁹			•				•		
Telephone Contact ¹⁶								•	

1. Assessments/procedures marked with 1 asterisk (*) are performed at End of Treatment Visit in PRO-805, and will serve as the PRO-807 Baseline Visit data. Induction can begin prior to receiving hematology, chemistry and coag results; however, these must be available prior to the Implant Visit.
2. Assessments/procedures marked with 2 asterisks (**) are also performed at End of Treatment Visit in PRO-805, however if the PRO-807 Baseline Visit occurs > 24 hours after the PRO-805 End of Treatment Visit, the assessments must be re-administered during the PRO-807 Baseline Visit. If the PRO-807 Baseline Visit occurs within 24 hours after the PRO-805 End of Treatment Visit, these assessments will not be re-administered.
3. Post-Implant Visit must be 1 day after Implant Visit.
4. Week 1 Visit should occur 7 ± 2 days after Implant Visit; Week 4 Visit should occur 3 weeks ± 2 days after Week 1 Visit. All subsequent treatment visits should be conducted every 4 weeks ± 3 days.
5. End of Treatment Visit should be conducted 4 weeks ± 3 days of Visit 10.
6. Patients must voluntarily provide written informed consent before any study-related procedure is performed.
7. Record current Medical History Conditions and Substance Abuse Treatments patients currently have or are undergoing.
8. A complete physical exam of all major body systems should have been performed.
9. Vital signs (temperature, blood pressure, pulse rate and respiration rate) along with pupil diameter and weight will be measured.
10. Vital signs (temperature, blood pressure, pulse rate and respiration rate) will be measured just prior to implantation then every 15 minutes after implantation for 30 minutes.
11. A serum pregnancy test will be required at Baseline and End of Treatment. A urine pregnancy test will be required monthly starting at Week 4 (females of childbearing potential only). A urine pregnancy test will be required prior to implantation at Visit 3.

12. The Interactive Voice Response System (IVRS) will be used by the sites, preferably on the day of implantation, to obtain lot numbers of kits to be dispensed.
13. The Implant Visit must occur within 14 days after the PRO-805 End of Treatment Visit. Probuphine implantation must occur 12–24 hours after the last SL BPN dose.
14. Patients may receive 1 additional implant 2 weeks after the initial Implant Visit (see Section 5.4.2, Implant Dose Increase). Plasma samples for BPN and norBPN should be taken prior to Implant Dose Increase. Patients will attend the Implant Visit, the Post-Implant Visit, and a Week 1 Telephone Call will follow. Patients will then resume with the original visit schedule in order to complete 24 weeks from the date of the initial Implantation (Visit 3) (see Section 8.3.3).
15. Patient will be monitored for at least 30 minutes for AEs.
16. Patients will be contacted by telephone 1 week ($\pm$ 2 days) after removal of implants to capture any AEs that occurred since removal.
17. If a patient reports of cravings or withdrawal symptoms at a visit where the measures are not scheduled, the SOWS, COWS and Opioid Craving VAS may be administered.
18. BPN/norBPN should be collected 12–24 hours after the most recent SL BPN (if applicable) and prior to implantation (including Implant Dose Increase).
19. Wound Care Information Sheet will be given to the patient after each insertion/removal procedure.
20. Induction should be completed within 13 days after removal of the PRO-805 implants. Patients must have undergone induction with SL BPN to a dose of 12–16 mg/day as clinically appropriate and have received a fixed dose of 12–16 mg/day of SL BPN for at least 3 consecutive days just prior to implantation.
21. Inclusion and Exclusion Criteria must be met at the Baseline Visit in order for patients to be eligible for Induction. The Implantation Criteria must be met prior to implantation.
22. Urine Toxicology (in-office urine toxicology kit results to be reviewed prior to starting induction).
23. Illicit Drug Use Self-Report (to be collected on the 3rd day of the fixed dose of induction)

Source: PRO-807-A1, Protocol PRO-807 Amendment #1, p. 34 – 37

PRO-807 Study Procedures: Patient Early Withdrawal Criteria

Protocol-specified criteria for early withdrawal from the study were 1 or more of the following:

- subject request
- subject non-compliance defined as refusal or inability to adhere to the study protocol:
- treatment failure, defined as having either of the following supplemental buprenorphine requirements any time after an implant dose increase:
 - ≥ 3 days/wk of supplemental SL buprenorphine for 2 consecutive wks
 - ≥ 8 days of supplemental SL buprenorphine over 4 consecutive wks
- 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 other investigational treatment
- patient refusal to receive an Implant Dose Increase after meeting protocol-defined criteria
- intercurrent illness or circumstances (e.g., “incarceration ≥ 7 days”) that would, in the judgment of the investigator, affect assessments of clinical status to a significant extent, require discontinuation of drug, or both
- requirement for continual use of opioid analgesics >7 days or general anesthesia for surgery
- at the request of Titan, regulatory agencies, or the Institutional Review Board (IRB)
- loss to follow-up

Patients who met the above criteria were to be seen for an End of Treatment Visit, for implant removal and clinical evaluations as outlined for that visit, unless any of the evaluations were performed within one week of discontinuation, in which case they did not have to be repeated.

PRO-807 Study Procedures: Safety Considerations

Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) was to be established to safeguard the interests and safety of the study participants.

Concomitant Medications

- Opioid Analgesics – If continual use required for > 7 days, implants were removed and the subject withdrawn from study. Same in cases where general anesthesia was required for surgery.

- Cytochrome P450 3A4 inhibitors and inducers
 - Subjects excluded if on CYP3A4 inhibitors. Medical monitor was to be consulted if these inhibitors were required during study. Examples of CYP3A4 inhibitors included azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), and HIV protease inhibitors (e.g., ritonavir, indinavir, and saquinavir)
 - Use of CYP 3A4 inducers, such as phenobarbital, carbamazepine, phenytoin and rifampicin, were to be avoided. Medical monitor was to be consulted prior to starting any patients on any of these agents.
- Sedatives – use of other narcotic anesthetics, benzodiazepines, phenothiazines, other tranquilizers, or other CNS depressants (including alcohol and sedative/hypnotics) was to be minimized during Probuphine treatment. Medical monitor consultation required if these sedatives were required during study.

The protocol specified that patients should be explicitly advised of the danger of IV self-administration of benzodiazepines while under treatment with Probuphine.

Treatment Identification Card

Patients were to receive a wallet card indicating that they are receiving buprenorphine via a SC implant. The card was to be presented to health care providers by the patient in the event of an emergency or requirement for medications such as opioid analgesics.

Wound Care Information Sheet

Per protocol, patients received written instructions that explain how to care for the surgical site after implant insertion and/or removal.

Implant Site Examination

The implant site was to be visually inspected for evidence of erythema, edema, itching, pain, infection, bleeding, abnormal healing, and any other abnormalities. If there was any evidence of removal and the patient confirmed the removal of some or all of the implants, and the patient was to be withdrawn from study. If there was evidence of attempted removal, the patient was to be withdrawn from the study and all implants were to be removed. If, upon removal, the Implanting Physician had difficulty locating the implants, they were advised that ultrasound could be used to facilitate their localization. Due to the non-biodegradable nature of the Probuphine and placebo implants, it was vital that no patient be lost to follow-up to ensure that proper implant removal and Follow-Up Visits are completed as outlined in this protocol.

Possible Impairment

Patients were to be instructed to avoid operating heavy machinery after implantation and exercise caution in activities requiring alertness, such as driving, during the first few days after implant insertion or until such time that they are reasonably certain that their ability to engage in such activities is not adversely affected.

PRO-807 Statistical Considerations

Titan outlines the following statistical methods for the protocol.

Safety Analyses

All safety analyses will include all patients who received an implant in PRO-807.

Adverse event, physical exam abnormality, vital sign, patient disposition and reason for study termination, concomitant medications, and laboratory evaluation summaries were to provided based on analyses of safety data.

Efficacy Analyses

The following endpoints were to be presented descriptively and summarized.

- Pharmacokinetics
- Cumulative percentage of urine samples negative for illicit opioids
- Retention in treatment
- Self-report of illicit drug use (illicit BPN, amphetamines, barbiturates, benzodiazepines, cocaine, methadone, etc.)
- Supplemental SL BPN use
- Subjective withdrawal symptom scores
- Objective withdrawal symptom scores
- Opioid craving scores
- Quality of life
- CGI - Self
- CGI - Observer

PRO-807 Key Protocol Amendments:

Amendment #1

- Implantation: If deemed appropriate by the Implanting Physician, an alternate location for insertion of implants will be used.
- Implantation: Provided information on the specialized investigational applicator being used for this trial.
- Additional Dosing: Implant Dose Increase: If a patient meets the protocol-defined criteria for a dose increase, but elects not to receive a fifth implant, he/she must be withdrawn from the study.
- Patient Early Withdrawal Criteria: Added a criterion to Patient Early Withdrawal section, namely *patient refusal to receive an Implant Dose Increase after meeting protocol-defined criteria*
- Eligibility Criteria Review / Enrollment: Patients may begin induction prior to receipt of laboratory results if necessary to prevent onset of withdrawal following implant removal in the content of the parent study.
- Induction (Visit 2, 2i, 2ii, etc): Clarification that induction can begin prior to receiving hematology, chemistry, coag results; however, these must be available prior to the Implant Visit. Also, clarification was provided on Urine Tox (in-office urine tox kit). Illicit Drug Use Self-Report (to be collected on the 3rd day of the fixed dose of induction).
- Implant Visit (Visit 3 or Implant Dose Increase Visit): The assessments under this section, with the exception of implantation and completion of the Implant Insertion Procedure Data Collection Form, can be performed by either the Implanting Physician or any other qualified study staff member.
- End of Treatment Visit (Visit 11) / Week 24: Added an Implant Removal Procedure Data Collection Form to be completed by the Implant Physician.

PRO-807 Major Protocol Violations

(b) (6)	Exclusionary opioid-craving VAS scores prior to implantation (i.e., ≥20 mm)
	• opioid craving VAS of 21 at the implantation visit (Visit 3)
	• opioid craving VAS of 22 at the implantation visit (Visit 3)
	Induction SL BPN criteria (longer than 16 days or not stable before implantation)
	• did not receive a fixed dose of SL BPN for 3 consecutive days prior to implant, as required for implant insertion. This subject started induction on (b) (6). The subject reached a dose of 24 mg on (b) (6) and received doses of 16 mg on (b) (6) and (b) (6). The subject received the implants on (b) (6).
	Took prohibited opioids during the study
	• took oxycodone on 2 occasions, once for headache and back pain and once for jaw pain
	• took oxycodone on 2 occasions, once for headache and back pain and once for jaw pain, and hydrocodone on 2 occasions, once for jaw pain and once for insomnia
	Exclusionary opioid-craving VAS scores prior to implantation (i.e., ≥20 mm)
	• opioid craving VAS of 0 at the implantation visit (Visit 3) but had a score of 47 at the induction visit (Visit 2)
• opioid craving VAS of 12 at the implantation visit (Visit 3) but had a score of 22 the day before the visit	
Induction SL BPN criteria (longer than 16 days or not stable before implantation)	
• did not receive a fixed dose of SL BPN for 3 consecutive days prior to implant. This subject started induction on (b) (6). The subject reached a dose of 16 mg on (b) (6) and received doses of 12 mg on (b) (6) and (b) (6); the subject received the implants on (b) (6).	

PRO-811

Title:	A Phase 3, Six-Month, Open-Label Re-Treatment Study of Probuphine in Opioid Addiction
Protocol & Amendment Dates	• Protocol No. PRO-811: September 28, 2010 • Amendment No. 1: November 1, 2010 • Amendment No. 2: July 27, 2011
Study Initiation & Completion Dates	• Initiation: November 29, 2010 • Completion: November 30, 2011

PRO-811 Objective/Rationale:

The *primary objective* was to evaluate the safety of Probuphine in subjects who have completed 24 weeks of treatment and who will be re-treated with Probuphine over an additional 24 weeks.

The *key secondary objective* was to evaluate the efficacy of Probuphine through pharmacokinetic analyses in subjects who have completed 24 weeks of treatment and who will be re-treated with Probuphine over an additional 24 weeks.

Another secondary objective was to evaluate additional measures of efficacy and safety in subjects who have completed 24 weeks of treatment with Probuphine, placebo implants, or sublingual buprenorphine (SL BPN), and who will be re-treated with Probuphine over an additional 24 weeks.

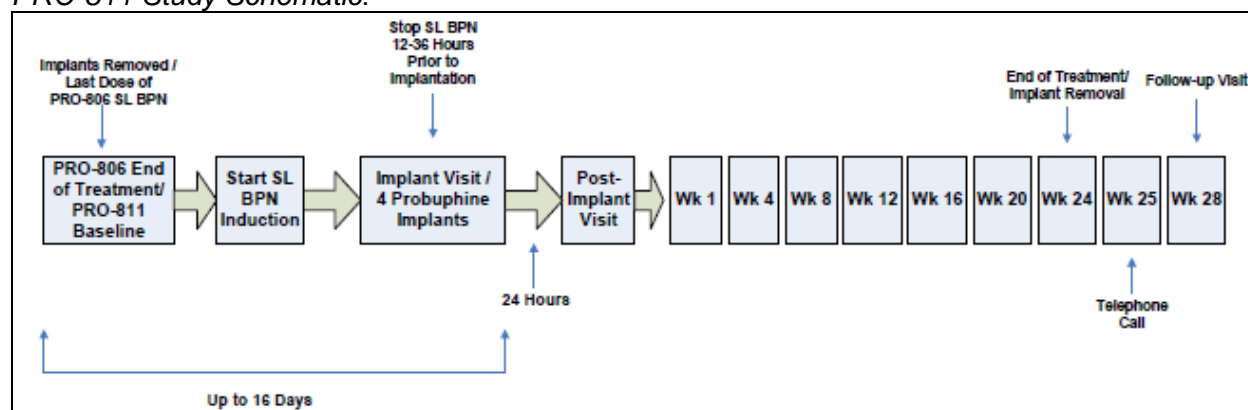
PRO-811 Overall Study Design

This was a 6-month, open-label, multi-center extension study. After completing the PRO-806 End-of-Treatment Visit, subjects assigned to daily SL BPN in PRO-806 continued their ending SL BPN dose through the PRO-811 induction period, which could last up to 16 days. Approximately the first 15 subjects assigned to SL BPN in PRO-806 who qualified for PRO-811 were allowed to enroll in the study. Subjects assigned to one of the two implant groups in PRO-806 were to undergo induction with SL BPN to a dose of 12–16 mg/day as clinically appropriate, following removal of the PRO-806 implants. Subjects from the implant groups were to be maintained at a fixed dose of 12–16 mg/day for at least 3 consecutive days just prior to PRO-811 implantation. The Implant Visit must occur within 16 days of the start of induction. (NOTE: Subjects who completed PRO-806 prior to when PRO-811 was open for enrollment at the clinical site, would still be eligible for screening in PRO-811.)

Subjects initially received 4 Probuphine implants and were also allowed to receive supplemental SL BPN (Suboxone®) throughout the study, if clinically indicated and under protocol-defined guidelines. Insertion of an additional Probuphine implant was permitted 2 weeks or later after the initial Implant Visit, under protocol-defined criteria.

Safety, pharmacokinetics, and efficacy measures were to be collected during the 24-week treatment period. At the end of the study, subjects were to have their implants removed, and were to return for a Follow-Up Visit 4 weeks later.

PRO-811 Study Schematic:



PRO-811 Study Population

Planned enrollment was up to 120 subjects, with a history of opioid dependence who had completed 24 weeks of treatment in PRO-806, at approximately 20 sites in the United States (US). The protocol specified that subjects had to meet a set of initial entry criteria and then meet an additional set of implantation criteria in order to have the rods inserted.

Initial Screening Criteria (Prior to Induction)

Inclusion Criteria

- Completed 24 weeks of treatment in PRO-806
- Deemed appropriate for entry into this extension study by the Investigator
- Reliable means of contraception

Exclusion Criteria

- Laboratory criteria: AST or ALT $\geq$ 3xULN; Total bilirubin $\geq$ 1.5xULN; and/or creatinine $\geq$ 1.5xULN
- Current diagnosis of chronic pain requiring opioids for treatment
- Pregnancy or lactation
- Use of agents metabolized through CYP 3A4
- Coagulopathy within past 90 days, and/or current anti-coagulant therapy such as warfarin
- Significant medical or psychiatric symptoms, cognitive impairment, or other factors which in the opinion of the Investigator would preclude compliance with the protocol, subject safety, adequate cooperation in the study, or obtaining informed consent
- Current medical conditions such as severe respiratory insufficiency that may prevent the patient from safely participating in study, or any pending legal action that could prohibit participation and/or compliance in study

Implantation Criteria

- Continue to satisfy all inclusion criteria and do not meet any exclusion criteria
- Undergone induction with SL buprenorphine, reaching a dose of 12–16 mg/day within 16 days of the start of induction, and received a fixed dose of 12–16 mg/day SL buprenorphine for at least 3 consecutive days immediately prior to implantation.
- Free from significant withdrawal symptoms, scoring $\leq$ 12 on the Clinical Opiate Withdrawal Scale [COWS] as measured at the Implant Visit
- Free from significant cravings for opioids, scoring $\leq$ 20-mm on the 100-mm Opioid Craving VAS, as measured at the Implant visit

PRO-811 Study Procedures

PRO-811 Study Procedures: Study Treatments

Sublingual Buprenorphine Induction

Subjects who were assigned to receive either Probuphine or placebo implants in PRO-806 had to be re-induced with Suboxone prior to entering PRO-811 (NOTE: Subjects who were assigned to daily SL buprenorphine in PRO-806 did not need to be re-induced, and could be maintained on their ending dose of SL BPN until all screening results were available, and they were ready to be enrolled and implanted). Subjects who were assigned to receive either Probuphine or placebo implants in PRO-806 underwent induction with sublingual (SL) buprenorphine (BPN) as Suboxone[®]. Induction was to have been completed within 16 days of Screening (as in PRO-806; within 10 and 13 days of Screening for PRO-805 and PRO-807, respectively). Patients had to receive a fixed dose of 12–16 mg/day SL buprenorphine for at least 3 consecutive days just prior to randomization.

Implantation (Probuphine Implants)

SL buprenorphine received during induction was to be discontinued 12–36 hours prior to implantation. Ideally, implants were to be inserted in the arm opposite the arm where the PRO-806 implants were located. Small (2–4 mg) doses of SL BPN were permissible during the 12 hours prior to implantation, at the Investigator's discretion, for the clinical management of

subjects' withdrawal symptoms in advance of their insertion procedures. In the case of extenuating circumstances where implantation must be significantly delayed and the Investigator wished to extend induction beyond the 16 days, the Investigator had to consult the Titan Medical Monitor to discuss the case and receive Titan approval, in order for the subject to remain in the study. Some baseline assessments may have had to be repeated, depending on the circumstances and the length of the delay.

Implant insertion under the skin, usually into the inner side of the patient's upper arm, was to be performed using a specialized investigational applicator provided by Titan. According to the protocol, the Probuphine Applicator that was to be used in PRO-811 is similar in design to the commercially-approved applicators currently used for the insertion of other implantable drugs, such as Implanon[®]. At the discretion of the implant physician, an alternative site other than the upper arm could be used, following consultation with the Titan Implant Medical Monitor. Subjects were to be monitored closely for adverse events and vital signs for at least 30 minutes following implantation by medically qualified study staff. The protocol permitted insertion of an additional implant (dose increase) any time 2 weeks after the initial Implant Visit, under protocol-defined criteria based on supplemental sublingual buprenorphine dosing (described below in the section on *Supplemental Sublingual Buprenorphine Dosing*).

Supplemental Sublingual Buprenorphine Dosing

The protocol permitted supplemental SL buprenorphine (Suboxone[®]) during the study. However, SL buprenorphine was not supposed to be used for 24 hours prior to the collection of a plasma sample. The rules guiding administration of sublingual buprenorphine dosing, per protocol, were as follows:

Patients were to meet all of the following criteria (*1 or more for PRO-805 and -807; all three for the parent study, PRO-806*):

1. Withdrawal symptoms with a score of > 12 on COWS
2. Cravings with a score of > 20 mm on the Opioid Craving VAS
3. Request for supplemental dosing by subject deemed appropriate by physician

The primary reason for the administration of Supplemental SL buprenorphine was to be noted in the Case Report Form (CRF).

Supplemental SL buprenorphine was to be administered in increments of 2 mg or more as clinically indicated. Investigators were advised that, as is the case when using other opioid agonist medications, a period of time should elapse between supplemental SL buprenorphine doses in order to determine clinical response. Investigators were advised that peak buprenorphine blood levels with Probuphine are seen within the first day following insertion of the implants and were advised to be very cautious when prescribing supplemental SL buprenorphine during that time.

Subjects were required to obtain supplemental SL buprenorphine at their study clinic or pharmacy. Supplemental SL buprenorphine doses were to be administered under observation at the clinic in order to verify that the SL tablet had completely dissolved under the subject's tongue. The protocol permitted a maximum of 3 days of take-home SL BPN for weekends, holidays, or other circumstances at the discretion of the investigator; a daily SL buprenorphine take-home dosing log was to be completed by subjects receiving take-home doses.

Dose Increases and treatment failures

- **Implant dose increase** (1 additional Probuphine implant): SL buprenorphine requirement ≥ 3 days/week for 2 consecutive weeks or ≥ 8 days over 4 consecutive weeks
 - The one additional implant could be inserted any time after 2 weeks from the initial Implant Visit into the same arm as the initial implants, unless an alternative site is deemed clinically necessary by the implanting clinician [To allow for stabilization of blood levels, the additional implant (Implant Dose Increase) was not to be inserted within the first 2 weeks after insertion of the initial 4 implants]
- **Treatment Failure:** After receiving protocol-defined implant dose increase, patient continues with same supplemental SL buprenorphine needs that led to implant dose increase

When an Implant Dose Increase was required, the patient was to attend the Implant Visit, the Post-Implant Visit, and a Week 1 Visit. The patient would then resume with the original visit schedule in order to complete 24 weeks from the insertion of the initial four implants. If a patient met these protocol-defined criteria for a dose increase, but elected not to receive a fifth implant, he/she was withdrawn from the study.

Implant Removal

As stipulated in the protocol, patients had implants removed under local anesthesia through a small incision during the End of Treatment Visit.

Psychosocial Counseling

Psychosocial counseling was permitted as clinically indicated, and recorded on the appropriate CRF. If counseling was clinically indicated, it was recommended that the sites follow the Manual entitled "Individual Drug Counseling: Adapted from the Naltrexone and Fluoxetine for Heroin Addiction Study."¹³

PRO-811 Study Procedures: Evaluations and Procedures

The following evaluations and procedures took place over the course of the study as outlined in the Time and Event Schedule that follows immediately:

Evaluation/Study-Specific Procedure	Comments
Informed Consent Form (ICF)	
Eligibility Criteria Review / Enrollment	Patient had to meet the I/E Criteria prior to starting induction; patients could, however, begin induction prior to receipt of laboratory results if necessary to prevent onset of withdrawal following implant removal in the context of the parent study
Current Medical	Changes since collection in PRO-805 Screening visit

¹³ Mercer D, Woody G. Individual Drug Counseling: adapted from the Naltrexone and Fluoxetine for Heroin Addiction Study; Philadelphia Veterans' Affairs Medical Center.

Evaluation/Study-Specific Procedure	Comments
Conditions or Surgical Procedures, Current Medications and Current Substance Abuse Treatment	
Physical Examination and Abbreviated Review of Systems	
Vital Signs	
Implant Insertion	Initial insertion of implants and implant dose increase if protocol-specified criteria were met
Implant Site Examination/Treatment Compliance	
Withdrawal Symptoms and Cravings	Subjective Opioid Withdrawal Scale (SOWS), Clinical Opioid Withdrawal Scale (COWS), Opioid Craving Visual Analog Scale (VAS). o In addition, if a subject reports opioid cravings or withdrawal symptoms at a visit where the measures are not scheduled, the SOWS, COWS, and Opioid Craving VAS may be administered as part of the overall clinical evaluation of the subject's status and potential need for supplemental SL buprenorphine.
Illicit Drug Use Self-Report	Subjects were to be questioned about illicit drug use. The drug name, number of days used, daily use, average cost per day, and whether the patient 'got high' was to be documented.
Clinical Global Impression – Self	Subjects were to rate their current severity of opioid-related problems and their improvement in symptoms of opioid dependence from baseline, using a 7-point Likert-type scale.
Clinical Global Impression – Observer	The treating physician and study personnel were to rate the subject's global severity of opioid dependence over the last week and the subject's degree of global improvement since baseline using a 7-point, Likert-type scale.
Beck Depression Inventory (BDI-II)	Self-report, multiple choice questionnaire used to assess the severity of depressive symptoms comprising 21 questions. A final score is totaled to indicate the overall level of depressive symptoms.
Patient Satisfaction Survey	Each subject was to rate their satisfaction with treatment across multiple domains including the induction process, implant insertion/removal procedures, control of opioid-related symptoms. The survey administered at Baseline Visit was to capture experiences related to the PRO-806 study treatment, while the survey administered at Follow-Up Visit (Week 28) will capture experiences related to the PRO-811 study treatment. In instances where the survey was not completed at Follow-Up Visit, a post visit phone contact may be conducted to obtain responses.
Psychosocial Counseling	As clinically indicated
Electrocardiogram (ECG)	

Evaluation/Study-Specific Procedure	Comments	
Clinical Laboratory Evaluations	Hematology	Hematocrit, Hemoglobin, red blood cells (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RBC Morphology, white blood cells (WBC) with differential, and platelets
	Chemistry (including liver profile)	Urea nitrogen, calcium, bicarbonate, chloride, creatinine, glucose, magnesium, potassium, sodium, albumin, alkaline phosphatase, amylase, AST (SGOT), ALT (SGPT), total bilirubin, total cholesterol, gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), lipase, total protein
	Coagulation Profile	Prothrombin time (PT), INR
	Pregnancy Test	Serum or urine; females of childbearing potential only
	Urine Toxicology	Illicit opioids (including prescription analgesics, excluding BPN and its metabolites), amphetamines, antidepressants, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, methaqualone, phencyclidine, phenothiazine, propoxyphene
	Other	Plasma BPN and NorBPN levels
Supplemental SL Buprenorphine	Suboxone®	
Implant Removal		
Adverse Events	- AEs that occur between the time the subject signed the ICF and 30 days after implant removal were required to be documented. - AEs designated as study drug related, and all serious AEs, were to be followed until resolution or stabilization. - AEs reported by the subject at times other than specified in Schedule of Events should also have been recorded.	
Pregnancy	Pregnancies among trial participants were to be reported immediately to the Sponsor. Subjects who became pregnant were to have study treatment discontinued and be removed from the study as soon as possible. Pregnancies were to be followed until the birth of the child or the termination of the pregnancy.	
Concomitant Medications / Procedures		
Telephone Contact	Subjects were to be contacted by telephone 1 week ($\pm$ 2 days) after the removal of implants to capture any AEs that occurred since removal. If a significant AE was described by the subject and was judged by the Investigator as being possibly related to study treatment, the subject was to visit the study site for an unscheduled follow-up assessment (separate from the Week 28 Follow-Up Visit).	

PRO-811 Schedule of Events

Event	Baseline ^{1,2}	Induction ³	Implant	Post-Implant ⁴	Treatment ⁵		End of Treatment ⁸	Follow-Up	
		(Up to 16 days)	Day 1		1, 4	8, 12, 16 and 20	24	25	28
Informed Consent	• ⁷								
Eligibility Criteria Review ⁸	•		•						
Enrollment	•								
Current Medical/Surgical, Medications, Substance Abuse Treatments	• ⁹								
Physical Examination ¹⁰	•								
Abbreviated Review of Systems						Wk 12	•		
Vital Signs ¹¹	•*	•	• ¹²	•	•	•	•		•
Implant Site Examination/Treatment Compliance ¹³				•	•	•	•		•
Dispense Treatment Identification Card			•						
Withdrawal Symptoms and Craving (SOWS, COWS, Opioid Craving VAS) ¹⁴	•**	•	•		•	•	•		•
Illicit Drug Use Self-Report	•**	• ¹⁵			•	•	•		•
CGI – Self / Observer	•*					•	•		
BDI-II	•*						•		
ECG	•*						•		
Patient Satisfaction Survey	•								•

Clinical Review
 Rachel Skeete, MD, MHS
 NDA 204442
 Probuphine® (buprenorphine implant)

Event	Baseline ^{1,2}	Induction ³ (Up to 16 days)	Implant Day 1	Post-Implant ⁴	Treatment ⁵		End of Treatment ⁶ 24	Follow-Up	
					1, 4	8, 12, 16 and 20		25	28
Pregnancy Test ¹⁶	•**	•	•		Wk 4	•	•		
Chemistry, Hematology and Coagulation Profile	•*				Wk 4	Wk 12	•		
Urine Toxicology		• ¹⁷							
Plasma BPN/norBPN levels	•*	• ¹⁸	• ¹⁸		Wk 4	•	•		
Induction (SL BPN) ¹⁹		•							
Implant ^{20,21}			Insertion				Removal		
Implant Insertion Procedure Assessment			•						
Implant Removal Procedure Assessment							•		
Supplemental SL BPN ²²			If needed, protocol-defined						
ONE Implant Dose Increase ²³					Anytime >2 Weeks, if needed				
Adverse Events		•	• ²⁴	•	•	•	•	•	•
Concomitant Medications / Procedures		•	•	•	•	•	•		•
Wound Care Information Sheet ²⁵			•				•		
Telephone Contact ²⁶								•	

1. Assessments/procedures marked with 1 asterisk (*) are performed at the End of Treatment Visit in PRO-806, and will serve as the PRO-811 Baseline Visit data.
2. Assessments/procedures marked with 2 asterisks (**) are also performed at End of Treatment Visit in PRO-806. If the PRO-811 Baseline Visit occurs > 24 hours after the PRO-806 End of Treatment Visit, these assessments must be re-administered during the PRO-811 Baseline Visit. If the PRO-811 Baseline Visit occurs within 24 hours after the PRO-806 End of Treatment Visit, these assessments will not be re-administered.
3. At least one visit will occur during the induction period. Induction should be completed within 16 days. Subjects must have undergone induction with SL BPN to a dose of 12–16 mg/day as clinically appropriate and have received a fixed dose of 12–16 mg/day of SL BPN for at least 3 consecutive days just prior to implantation.
4. The Post-Implant Visit must be 1 day after the Implant Visit.
5. The Week 1 Visit should occur 7 ($\pm$ 2) days after the Implant Visit. All subsequent Treatment Visits should be conducted within a window of $\pm$ 2 days.
6. The End of Treatment Visit should be conducted 4 weeks $\pm$ 3 days following the Week 20 Visit.
7. Subjects must voluntarily provide written informed consent prior to any study-related procedures being performed.
8. Prior to initiating induction, all Inclusion and Exclusion Criteria must be met. Subjects may begin induction prior to receipt of laboratory results if necessary to prevent onset of withdrawal following implant removal in the context of the parent study. Baseline Visit assessments that will be greater than 4 weeks old at the time of Implant Visit may need to be repeated prior to the Implant Visit, as directed by the Medical Monitor. The Implantation Criteria must be met prior to implantation.
9. Record current Medical Conditions or Surgical Procedures, current Medications and current Substance Abuse Treatments (See Section 8.3.1)
10. A complete physical exam of all major body systems will be performed at Baseline Visit.
11. Vital signs (temperature, blood pressure, pulse rate and respiration rate) along with pupil diameter and weight will be measured.
12. Vital signs (temperature, blood pressure, pulse rate and respiration rate) will be measured just prior to implantation, and 15 and 30 minutes after implantation.
13. The implant site will be visually inspected. If there is evidence of removal or attempted removal of the implants, the subject will be withdrawn from the study.
14. If a subject reports of cravings or withdrawal symptoms at a visit where the measures are not scheduled, the SOWS, COWS and Opioid Craving VAS may be administered and entered as "unscheduled" assessments.
15. Illicit Drug Use Self-Report (to be collected on the 3rd day of the fixed dose of induction).
16. A serum pregnancy test will be required at Baseline and End of Treatment. A urine pregnancy test will be required prior to implantation and then every 4 weeks thereafter (for females of childbearing potential only). A urine pregnancy test should be conducted at the Baseline Visit, prior to the start of induction, in addition to the sample sent for analysis by the central laboratory, if induction is to begin prior to receipt of lab results.
17. Urine Toxicology (in-office urine toxicology kit results to be reviewed prior to starting induction).
18. ONE trough PK sample should be collected 24 hours following the previous dose of SL BPN; this may be accomplished on the last day of Induction or the Implant Visit prior to implantation. For dose increases, the trough may be obtained the morning prior to the insertion of the 5th implant. The PK sample should occur as close to 24 hours (or more) following the previous dose of supplemental SL BPN (if applicable) as possible.
19. Induction SL BPN should be discontinued 12–36 hours prior to implantation. Small (2–4 mg) doses may be administered during the 12 hours prior to the procedure, at the Investigator's discretion, to manage subjects in acute withdrawal.
20. Implant kits shall be dispensed in accordance with the Study Drug and Supplies Procedures located in the Manual of Procedures.
21. The Implant Visit should occur within 16 days of starting induction. Probuphine implantation must occur 12–36 hours after the last SL BPN dose.
22. Subjects may receive supplemental SL BPN (Suboxone®) at any time after implantation under protocol-defined criteria. Supplemental SL BPN will be administered under observation at the clinic except for "take-home" doses. Peak BPN levels with Probuphine are achieved within the first day following insertion of the implants. Investigators are therefore advised to be very cautious when prescribing supplemental SL BPN during that time. Supplemental SL BPN should not be taken less than 24 hours prior to scheduled BPN/norBPN plasma collection.
23. Subjects may receive 1 additional implant > 2 weeks after the initial Implant Visit under protocol-defined criteria. Subjects will repeat the following visits: Implant Visit, Post-Implant Visit, and Week 1 Visit; thereafter, they will resume the original visit schedule in order to complete 24 weeks on-treatment (see Section 8.3.3).
24. Subjects will be monitored for at least 30 minutes after implantation for AEs.
25. A Wound Care Information Sheet will be given to the subject after each insertion/removal procedure.
26. Subjects will be contacted by telephone 1 week ($\pm$ 2 days) after the removal of implants to capture any AEs that occurred.

Source: PRO-811-A2, Protocol PRO-811 Amendment #2, p. 36–38

PRO-811 Study Procedures: Subject Early Withdrawal Criteria

The protocol stipulated that subjects must be discontinued under the following circumstances:

- subject request
- subject non-compliance, defined as refusal or inability to adhere to the study protocol:
- treatment failure, defined as having either of the following supplemental buprenorphine requirements any time after an implant dose increase:
 - $\geq$ 3 days/wk of supplemental SL buprenorphine for 2 consecutive wks
 - $\geq$ 8 days of supplemental SL buprenorphine over 4 consecutive wks
- 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 other investigational treatment
- subject refusal to receive an implant dose increase after meeting protocol-defined criteria
- intercurrent illness or circumstances (e.g., incarceration $\geq$ 7 days) that would, in the judgment of the investigator, affect assessments of clinical status to a significant extent, require discontinuation of drug, or both
- requirement for continual use of opioid analgesics >7 days or general anesthesia for surgery
- at the request of Titan, regulatory agencies, or the Institutional Review Board (IRB)
- loss to follow-up

Subjects who met the above criteria were to be seen for an End of Treatment Visit where possible, during which implants would be removed, study-related SL buprenorphine returned, and clinical evaluations performed. If any of the evaluations required for the End of Treatment visit had already been performed during the week prior to the actual visit, they did not need to be repeated during the visit.

PRO-811 Study Procedures: Safety Considerations

Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) was to be established to safeguard the interests and safety of the study participants.

Concomitant Medications

- Opioid Analgesics – If a subject required any opioids for >7 days continually, implants were removed and the subject withdrawn from study. Same in cases where general anesthesia was required for surgery.
- Cytochrome P450 3A4 inhibitors and inducers
 - Subjects excluded if on CYP3A4 inhibitors. Medical monitor was to be consulted if these inhibitors were required during study. Examples of CYP3A4 inhibitors included azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), and HIV protease inhibitors (e.g., ritonavir, indinavir, and saquinavir)
 - Use of CYP 3A4 inducers, such as phenobarbital, carbamazepine, phenytoin and rifampicin, was to be avoided. Medical monitor was to be consulted prior to starting any patients on any of these agents.
- Sedatives – use of other narcotic anesthetics, benzodiazepines, phenothiazines, other tranquilizers, or other CNS depressants (including alcohol and sedative/hypnotics) was to be minimized during treatment with Probuphine or SL buprenorphine. Medical monitor consultation required if these sedatives were required during study.

The protocol specified that subjects should be advised of the danger of concomitant use of sedatives while on-study and should be explicitly advised of the danger of IV self-administration of benzodiazepines while under treatment with Probuphine or SL buprenorphine.

Treatment Identification Card

Subjects were to receive a wallet card indicating that they are receiving buprenorphine as part of the study. The card was to be presented to health care providers by the patient in the event of an emergency or requirement for medications such as opioid analgesics.

Wound Care Information Sheet

Per protocol, subjects received written instructions that explain how to care for the surgical site after implant insertion and/or removal.

Implant Site Examination – Diversion and Implant Site Reactions

The implant site was to be visually inspected at each visit. The implant site was to be visually inspected for evidence of erythema, edema, itching, pain, infection, bleeding, abnormal healing, and any other abnormalities. If there was any evidence of removal of the implants by the subject (or if the subject confirmed the removal of some or all of the implants), the subject was to be withdrawn from study. If there was evidence of attempted removal, the patient was to be withdrawn from the study and all implants were to be removed. If, upon removal, the Implanting Physician had difficulty locating the implants, they were advised that ultrasound could be used to facilitate their localization. Due to the non-biodegradable nature of the Probuphine implants, it was vital that no patient be lost to follow-up to ensure that proper implant removal and Follow-Up Visits were completed as outlined in this protocol.

Titan noted that initiatives have been implemented to reduce the incidence of broken implants (at the removal procedure), including enhanced training, improved surgical equipment, and revisions to the procedure instructions. Titan has also instituted the Probuphine Clinical Training and Certification program to ensure that clinicians who perform the implant insertion and removal procedures meet competency standards.

PRO-811 Statistical Considerations

Titan outlines the following statistical methods for the protocol.

Safety Analyses

All safety analyses will include all subjects who received an implant in PRO-811.

Adverse event, pregnancy, physical examination and abbreviated review of systems, vital sign, subject disposition and reason for study termination, concomitant medications, and laboratory evaluation summaries were to be provided based on analyses of safety data.

Efficacy Analyses

The following endpoints were to be presented descriptively and summarized.

- Pharmacokinetics
- Retention in treatment
- Self-report of illicit drug use (illicit BPN, amphetamines, barbiturates, benzodiazepines, cocaine, methadone, etc.)
- Supplemental SL BPN use
- Subjective withdrawal symptom scores
- Objective withdrawal symptom scores
- Opioid craving scores
- BDI-II
- CGI - Self
- CGI - Observer

PRO-811 Key Protocol Amendments:

Amendment #1

- Statement added regarding possible post-study treatment referral.

Amendment #2

- Subject early withdrawal criteria revised. The term “analgesics” has been removed so that subjects requiring **any** opioids for > 7 days would be discontinued.
- Addition of a second Patient Satisfaction Survey administered at Follow-Up Visit (Week 28), or afterward by phone if missed.

PRO-811 Major Protocol Violations

Of the protocol violations that occurred, 7 subjects were enrolled and implanted in violation of the protocol criteria as follows:

	Exclusionary laboratory values:
(b) (6) Probuphine	• Ultimately, discontinued due to ALT elevation. Elevated ALT levels began prior to induction, so the subject was not eligible for an implant; however, the subject received implants. • The subject experienced moderate, nonserious AEs of elevated AST and GGT levels, and was then discontinued from the study. The investigator reported subsequently that the outcome of the events of ALT, AST, and GGT was recovered/resolved.
	Exclusionary opioid-craving VAS and COWS scores:
(b) (6) Placebo	• performed VAS and COWS after implantation • scores were ultimately within protocol criteria.
(b) (6) Probuphine	• VAS score of 95 mm at the implant visit • COWS score of 0
	Induction SL BPN criteria (longer than 16 days or not stable before implantation):
(b) (6) SL BPN arm	• started induction on (b) (6) and was implanted on (b) (6) (19 days from start date)
(b) (6) Probuphine	• started induction on (b) (6) and was implanted on (b) (6) (28 days from start date)
(b) (6) Probuphine	• only on a stable dose for 2 days (vs. 3 days) before implantation
(b) (6) Probuphine	• started induction on (b) (6) and was implanted on (b) (6) (18 days from start date)

Additionally, one subject (Subject (b) (6), on Probuphine) received an implant dose increase but did not meet the protocol-specified requirements.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RACHEL SKEETE
04/07/2013

CELIA J WINCHELL
04/07/2013
See my CDTL review