

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204442Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

### ADDENDUM TO COMPLETE RESPONSE REVIEW

NDA: 204442	Submission Date: 8/27/15; 1/19/16
Submission Type	Resubmission to Complete Response
Brand/Code Name:	Probuphine®
Generic Name:	Buprenorphine HCl
Clinical Pharmacology Primary Reviewer:	David Lee, Ph.D.
Clinical Pharmacology Team Leader:	Yun Xu, Ph.D.
OCP Division:	Division of Clinical Pharmacology 2
OND Division:	Division of Anesthesia, Analgesia, and Addiction Products
Sponsor:	Titan Pharmaceuticals, Inc./ US Agent: Braeburn Pharmaceuticals
Relevant NDA(s)	-
Relevant IND(s):	70852
Formulation; Strength(s):	80 mg buprenorphine HCl implant polymer rod
Proposed Indication:	For the maintenance treatment of opioid dependence and should be used as part of a complete treatment program to include counseling and psychosocial support.
Proposed Dosage Regimen:	Four implants once every 6 months as needed. [PROBUPHINE implants should be used only in patients who are opioid tolerant and are currently on a maintenance dose of 8 mg or less of sublingual Subutex or Suboxone equivalent; PROBUPHINE should be removed by the end of the sixth month and may be replaced by new implants (in the opposite arm, if possible) at the time of removal of implants, if continued treatment is desired.]

#### Summary on the Post-Marketing Requirement (PMR)

Probuphine is intended for the maintenance treatment of opioid dependence and is intended for 6 months of treatment. The Sponsor has provided efficacy, safety and pharmacokinetics data when Probuphine is implanted only in area of the inner side of the upper arm. With two implantation sites per arm, total of four sites are available for each patient. It is possible that the treatments may continue further after all four proposed implantation sites in upper arms have been used or are unavailable, or become unavailable. This includes re-implantation at the previously administered sites, that is, at the scarred or inflamed previously used sites. Therefore, additional information needs to be obtained, as Post-Marketing Requirement (PMR), to optimally support the usage of Probuphine. The Applicant needs to obtain pharmacokinetics and safety information when a) Probuphine is re-implanted at scarred or inflamed previously implanted sites; and, b) implantation sites other than the arm, if the previously used sites cannot be re-used.

## Recommendations

Probuphine is intended for the maintenance treatment of opioid dependence and is intended for 6 months of treatment. The Sponsor has provided efficacy, safety and pharmacokinetics data when Probuphine is implanted only in area of the inner side of the upper arm. For each arm, two implantation sites can be used so there are totally four sites available for one patient. According to the proposed Dosage and Administration section, implants must be removed by the end of the 6 months. If continued treatment is desired at the end of the first six-month treatment cycle, implants may be replaced by new implants in an area of the inner side of the upper arm that has not been previously used (in the opposite arm, if possible, unless this site is unavailable) at the time of removal. If continued treatment is desired at the completion of two six-month treatment periods, new PROBUPHINE implants may be inserted into a previously unused area of the opposite arm for a subsequent six-month treatment cycle, unless unavailable. The treatments can be continued up to 4 treatment periods (two proposed sites per arm for a total of four implantation sites per subject). After all sites have been used, or are unavailable, or become unavailable, patients should be transitioned back to a transmucosal buprenorphine-containing product for continued treatment. However, it is possible that the treatments may continue further after all four proposed implantation sites in upper arms have been used or are unavailable, or become unavailable. This includes re-implantation at the previously administered sites, that is, at the scarred or inflamed previously used sites.

To date, there is no clinical efficacy, safety or pharmacokinetic (whether scarring or inflammation at previously implanted sites have any effects on buprenorphine exposure) data to support using the previously implanted sites for re-implantation. Additionally there is no clinical efficacy, safety or buprenorphine exposure information from other implantation sites, such as abdomen or thigh, other than the arm if the previously used sites cannot be re-used.

The comments reflecting the need of obtaining the necessary information were communicated to the Applicant in the CR letter dated April 30, 2013. After discussion within the review team, it is agreed that the Applicant needs to conduct studies to address these concerns as Post-Marketing Requirement (PMR). Therefore, the following information needs to be obtained as PMR to optimally support the usage of Probuphine, especially if the product will be used for more than two years:

- (1) The Applicant needs to assess the impact of implanting Probuphine in previously implanted sites, and evaluate its pharmacokinetics and safety to address the effect of scarring or inflammation at previously implanted sites on re-implantation and bioavailability of Probuphine.
- (2) The Applicant needs to evaluate the impact, pharmacokinetics and safety of Probuphine in implantation sites other than the inner side of upper arm (e.g., abdomen, thigh, etc.).

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/s/  
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DAVID J LEE  
02/10/2016

YUN XU  
02/11/2016

CHANDRAHAS G SAHAJWALLA  
02/11/2016

**CLINICAL PHARMACOLOGY REVIEW  
MEMORANDUM**

NDA: 204442	Submission Date: 8/27/15; 1/19/16
Submission Type	Resubmission to Complete Response
Brand/Code Name:	Probuphine®
Generic Name:	Buprenorphine HCl
Clinical Pharmacology Primary Reviewer:	David Lee, Ph.D.
Clinical Pharmacology Team Leader:	Yun Xu, Ph.D.
OCP Division:	Division of Clinical Pharmacology 2
OND Division:	Division of Anesthesia, Analgesia, and Addiction Products
Sponsor:	Titan Pharmaceuticals, Inc./ US Agent: Braeburn Pharmaceuticals
Relevant NDA(s)	-
Relevant IND(s):	70852
Formulation; Strength(s):	80 mg buprenorphine HCl implant polymer rod
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Proposed Dosage Regimen:	Four implants once every 6 months as needed. [PROBUPHINE implants should be used only in patients who are opioid tolerant and are currently on a maintenance dose of 8 mg or less of sublingual Subutex or Suboxone equivalent; PROBUPHINE should be removed by the end of the sixth month and may be replaced by new implants (in the opposite arm, if possible) at the time of removal of implants, if continued treatment is desired.]

Executive Summary

With respect to Clinical Pharmacology, no new study result was submitted in the resubmission. Looking at the overall information, it is reasonable to speculate that at steady state, Probuphine (4 implants; provides 320 mg buprenorphine HCl) provides 1) less buprenorphine C<sub>ss</sub> than SL buprenorphine 8 mg tablets, and, 2) may provide comparable buprenorphine exposure between SL buprenorphine 4 up to 8 mg.

Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted on 8/27/15 and 1/19/16. From a clinical pharmacology perspective, the information submitted in the NDA is acceptable, pending agreement on the labeling language.

Additionally, to date, there is no clinical efficacy, safety or pharmacokinetic (whether scarring or inflammation at previously implanted sites have any effects on buprenorphine exposure) data to support using the previously implanted sites for re-implantation. Additionally there is no clinical efficacy, safety or buprenorphine exposure information from other implantation sites, such as abdomen or thigh, other than the arm if the previously used sites cannot be re-used.

The comments reflecting the need of obtaining the necessary information were communicated to the Applicant in the CR letter dated April 30, 2013. After discussion within the review team, it is agreed that the Applicant needs to conduct studies to address them as Post-Marketing Requirement (PMR).

Currently the detail PMR language to be conveyed to the Applicant is still under discussion. An addendum to the Clinical Pharmacology Resubmission review will be put into DARRTS when the language is finalized. Briefly the following information needs to be obtained as PMR to optimally support the usage of Probuphine, especially if the product will be used for more than two years:

- (1) Evaluate the effect of scarring or inflammation at previously implanted sites on the re-implantation and bioavailability of Probuphine,
- (2) Evaluate other implantation sites other than the arm, if the previously used sites cannot be re-used.

## Background

On October 29, 2012 (cover-letter date) Titan Pharmaceuticals, Inc. submitted a New Drug Application (NDA) for Probuphine® [buprenorphine hydrochloride in ethylene vinyl acetate polymer (EVA), 80-mg buprenorphine hydrochloride in (b) (4) mg of EVA polymer per rod or implant] under Section 505(b)(2) of the Food, Drug, and Cosmetic Act. The Applicant developed an implant for the maintenance treatment of opioid dependence. The original application assessed patients who were opioid tolerant and have begun treatment with sublingual buprenorphine at a daily dose range of 12-16 mg over a period of at least 3 days. Prior to insertion of Probuphine, sublingual buprenorphine were discontinued in order to avoid overdose. The initial dosing proposal for Probuphine was 4 or 5 implants per administration once every 6 months. At 6 months, the implants must be removed or may be replaced by new implants in the opposite arm, if necessary. The original application was reviewed under a priority review status (based on the fact that Probuphine offers potential to reduce misuse, abuse, and diversion). Additionally, the Applicant stated that Probuphine may prevent and reduce pediatric exposure from ingestion and accidental poisoning, and improve treatment compliance compared with currently marketed buprenorphine products. The Applicant proposed Suboxone® sublingual (SL) tablet (NDA 20733) and Subutex® (NDA 20732) as the listed drugs. It is noted that, according to the product labels, Suboxone® SL tablet and Subutex® have comparable systemic buprenorphine systemic exposure at 16 mg dose levels. Buprenorphine is a commercially available for the treatment of opioid dependence in SL formulations [Suboxone® (SL formulation discontinued), Subutex® (discontinued), Zubsolv® (SL tablet), Bunavail (buccal film), and generic equivalents], and, for the treatment of moderate to severe pain in injectable (Buprenex®), transdermal (Butrans®) and SL (Belbuca™) formulations. With

respect to clinical pharmacology information submitted in the original submission, the Applicant conducted a relative bioavailability study between 4 implants of Probuphine (totally 320 mg of buprenorphine dose) with 16 mg sublingual buprenorphine using Suboxone as reference product (Study PRO-810). The Applicant also provided buprenorphine exposure information comparing 2 and 4 implants (Study TTP-400-02-01). Additionally, the Applicant submitted buprenorphine concentration information from two Phase 3 studies (Study PRO-805 and 806) and two extension studies (2nd administration of four implants in the ‘opposite arm’; Study PRO-807 and 811, respectively). The to-be-marketed formulation was used in all clinical studies. For findings from the original submission, see Clinical Pharmacology Review dated April 1, 2013.

#### Brief summary of clinical pharmacology findings from the original submission

No new clinical pharmacology study result was submitted in this resubmission. The study results mentioned below were captured in the clinical pharmacology review of the original NDA submission and are briefly summarized for this review.

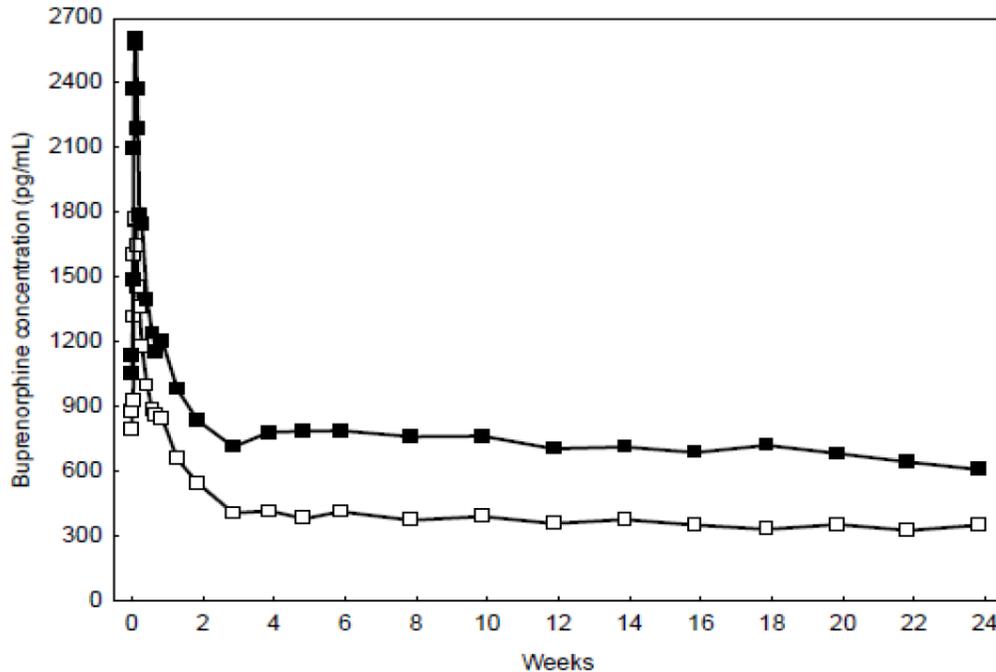
#### Study TTP-400-02-01

Study TTP-400-02-01 compared buprenorphine exposure of two 90-mg (Group A) and four 90-mg buprenorphine HCl implants (Group B) (Note: the Applicant stated that “the implants contained an average of 83 mg buprenorphine.”). Subjects in both dose groups were on “maintenance therapy” with sublingual (SL) buprenorphine via Subutex® at enrollment (8 mg and 16 mg daily for Groups A and B, respectively; also, subjects were allowed supplemental SL buprenorphine), however, SL buprenorphine doses were discontinued at least 24 hours prior to implant insertion.

Mean plasma buprenorphine concentrations in both groups after insertion of implants over the 24-week treatment period are shown in Figure 1. Stable plasma buprenorphine concentrations were maintained from approximately Week 2 through Week 24 for both 2 and 4 implants. Comparing the average buprenorphine steady state concentration,  $C_{ss}$ , for two and 4 implants ( $0.37 \pm 0.07$  and  $0.72 \pm 0.11$  ng/mL, respectively), the data suggested dose linear increase in buprenorphine exposure.

Based on the PK profile, it is reasonable to conclude that the steady state buprenorphine exposure is maintained up to 24 weeks, the last PK sampling point, after Probuphine implantation.

Figure 1 Study TTP-400-02-01 – Mean Plasma Buprenorphine Concentrations for Dose Groups A and B after Probuphine insertion

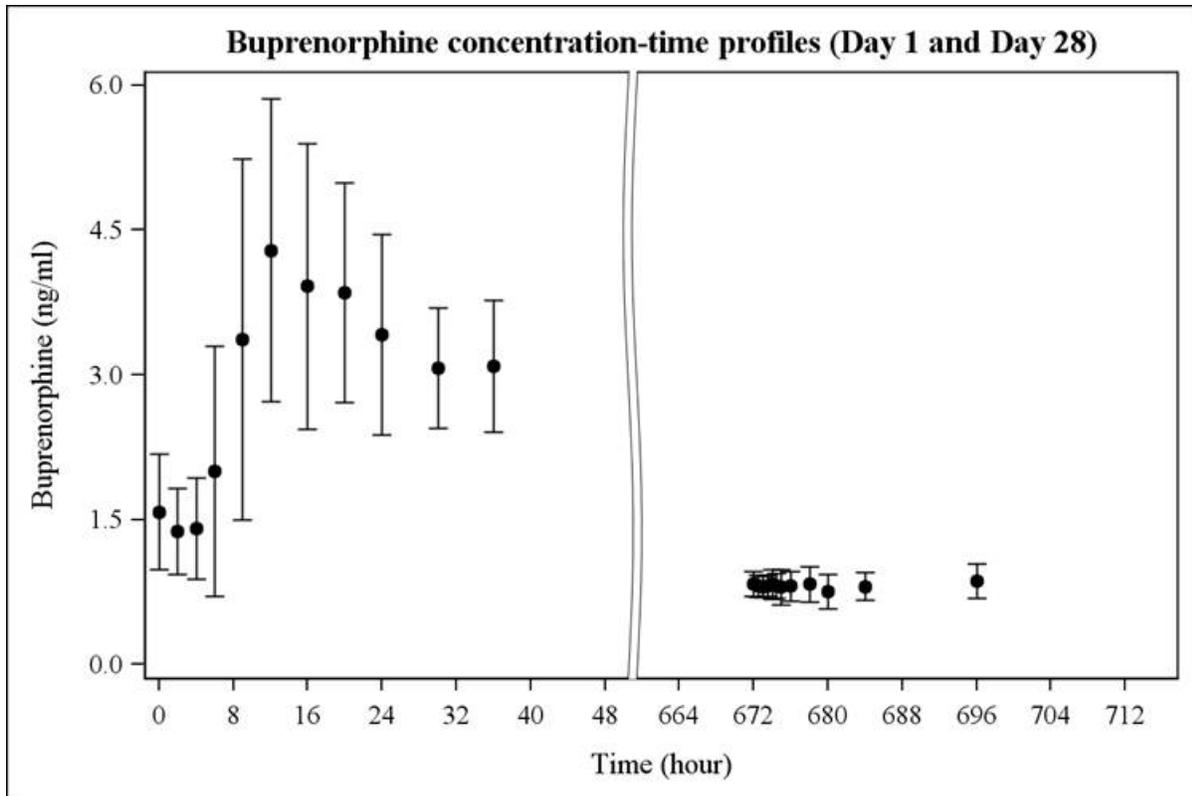


Open boxes = Dose Group A (2 Probuphine implants); Closed boxes = Dose Group B (4 Probuphine implants)

### Study PRO-810

Study PRO-810 was an open-label, planned 26-week, single-center, relative bioavailability PK study comparing the buprenorphine steady state AUC<sub>0-24</sub> of four implants (320 mg buprenorphine HCl) to the reference drug Suboxone SL tablets (16 mg/day; contains buprenorphine and naloxone, available as 2 mg/0.5 mg and 8 mg/2 mg strengths). Subjects underwent induction period with SL buprenorphine for at least 8 days, with stabilization at 16 mg/day by Day -5. Buprenorphine concentration profiles after the Probuphine insertion (Day 1 and on Day 28) are shown in Figure 2. See Table 1 for relevant pharmacokinetic parameters obtained from the study. Based on the PK profile on Day 28 after Probuphine implantation, the buprenorphine concentrations are stable at steady state with little fluctuation. The relative bioavailability of 4 implants based on the mean AUC<sub>0-24</sub> values at steady state (Day 28) compared with SL buprenorphine (16 mg once daily) on Day-1 was 31.3%.

Figure 2 Buprenorphine Concentration versus time (Days) profiles after Probuphine implantation on Day 1 and Day 28



On March 21, 2013, the concerns identified in the original submission was discussed (e.g., efficacy, Risk Evaluation and Mitigation Strategy, and safety concerns with implantation procedures, etc.) at the Psychopharmacologic Drugs Advisory Committee (PDAC) meeting. Subsequently, the Agency sent the Complete Response letter (CRL) to the Applicant dated April 30, 2013, with the identified major deficiencies (opioid blockade study, study of higher doses of Probuphine, Human Factors Usability Evaluation) and additional recommendations (e.g., to evaluate the effect of scarring or inflammation at previously implanted sites on the re-implantation and bioavailability of Probuphine, to evaluate other implantation sites other than the arm, to evaluate efficacy in patients with lower sublingual BPN requirements, and modification of the implant to include a radio-opaque marker to facilitate removal, etc.).

On November 19, 2013, a Type C (Post-Action) meeting was held to discuss the Applicant’s new proposal for moving forward with Probuphine development program, namely, 1) limiting Probuphine’s indication to the treatment of patients stabilized on sublingual buprenorphine at doses of 8 mg or less; and 2) Committing to a one-year (post launch) patient registry that will generate “real world” data on drug use patterns, psychosocial functioning, and medical consequences in Probuphine-treated outpatients.

Current Resubmission

With respect to Clinical Pharmacology, no new information was submitted in the resubmission. The newly proposed dosing for Probuphine is 4 implants per administration once every 6 months and implants should be used only in patients who are opioid tolerant and are currently on a maintenance dose of 8 mg or less of sublingual Subutex or Suboxone equivalent.

As per the cover letter dated August 27, 2015, the Applicant states that the current resubmission is submitted to address:

- “• To provide substantial evidence of effectiveness and resolve the deficiency regarding demonstration of clinical benefit, the Sponsor conducted a new Phase 3 study, PRO-814, under the protocol titled, "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" (NDA 204442, SN0028). This study provides evidence that four Probuphine implants are effective in maintenance treatment of opioid dependence in patients previously stabilized on 8 mg/day or less of SL BPN.
- To address the need for validation of Sponsor's training program for the Probuphine insertion and removal procedures, the Sponsor conducted an evaluation and validation under the protocol titled "Human Factors Evaluation of the Probuphine Subdermal Implant Training Program" (NDA 204442, SN0023 and SN0025). This human factors study validated the effectiveness of the training program for physicians and physician extenders who meet the criteria established for being "proceduralists."
- The Sponsor developed a toxicokinetic bridging program (NDA 204442, SN0022) to support reliance on the reference label in deriving safety margins for Section 8.1 (Pregnancy) and Section 13 .1 (Carcinogenesis, Mutagenesis, and Impairment of Fertility).”

On January 12, 2016 the findings from the Study PRO-814 was discussed at the PDAC Meeting. At the Advisory Committee meeting, one of the statements made by the Applicant was that “*that buprenorphine plasma exposure with Probuphine is approximately equivalent to that of the buprenorphine plasma exposure achieved with 6 mg of sublingual buprenorphine.*” Subsequently on January 15, 2016, an information request was sent to the Applicant to “Provide the supporting data” to the statement made. On January 19, 2016 the Applicant submitted supporting information which included exposure information from Study PRO-810 (original NDA application) and estimated steady-state concentrations (C<sub>ss</sub>) for sublingual buprenorphine 8 mg from Subutex and Suboxone drug product labels.

### Discussion

The Suboxone (N20733) and Subutex (N20732) SL tablet package inserts indicate both C<sub>max</sub> and AUC of buprenorphine increased in a linear fashion with the increase in dose (in the range of 4 to 16

mg). It should be noted that both Suboxone and Subutex Labels do not provide buprenorphine C<sub>ss</sub> values. However, Since buprenorphine exposure increased in a linear fashion with the increase in dose for SL buprenorphine, there is no evidence that buprenorphine can inhibit or induce its own metabolism, and the dosing interval is every 24 hours, it is reasonable to assume that AUC<sub>ss(0-24)</sub> is similar to AUC<sub>inf</sub> after a single dose. Therefore, the estimated steady-state buprenorphine (C<sub>ss</sub>) value can be obtained by utilizing the pharmacokinetic equation [AUC<sub>ss(0-24)</sub>/24h or AUC<sub>inf</sub> after a single dose/24h; SL tablet is administered as a single daily dose]. The ‘Projected Suboxone 8 mg SL buprenorphine concentrations’ was also obtained by taking ½ buprenorphine exposure information from the Suboxone 16 mg SL treatment arm in Study PRO-810. Estimated C<sub>ss</sub> values were obtained for Suboxone and Subutex and compared to that of the results obtained from Study PRO-810. It is noted that for Probuphine, the buprenorphine concentrations are stable at steady state with little fluctuation based on the PK profile on Day 28 after Probuphine implantation in study PRO-810. Therefore, only C<sub>ss</sub> is reported for Probuphine at steady state on Day 28. The C<sub>max</sub> and C<sub>trough</sub> values are very close to the C<sub>ss</sub> value.

Table 1 was constructed, based on the submitted information by the Applicant (Study PRO-810 (original NDA submission) (b) (4)

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Table 1 Inter-study comparison of buprenorphine concentration from Study PRO-810, (b) (4) : C<sub>max</sub>, AUC and estimated steady-state buprenorphine (C<sub>ss</sub>) concentration [Mean (±SD) as indicated]

Source	C <sub>max</sub> (ng/mL)	AUC <sub>inf</sub> after a single dose (ng.h/mL)	AUC <sub>ss(0-24)</sub> (ng.h/mL)	C <sub>ss</sub> <sup>1</sup> (ng/mL) Estimated: AUC <sub>ss(0-24)</sub> /24h or AUC <sub>inf</sub> /24h	C <sub>trough</sub> (ng/mL)
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				after a single dose	
Study PRO-810 Probuphine (total 320 mg buprenorphine) (Day 28)	-	-	19.6 (±3.37)	0.82 <sup>2</sup>	-
Study PRO-810 Suboxone 16 mg SL (average of Day-2 and Day- 1)	9.51 <sup>3</sup>	-	64.46 <sup>4</sup>	2.69 <sup>5</sup>	1.48 <sup>6</sup>
Projected Suboxone 8 mg SL based on Study PRO- 810 <sup>7</sup>	4.76 <sup>7</sup>	-	32.23 <sup>7</sup>	1.35 <sup>7</sup>	0.74 <sup>7</sup>
8 mg SL Suboxone <sup>(b)</sup> <sub>(4)</sub>	3.37 (±1.80)	30.45 (±13.03)		1.27 <sup>8</sup>	
8 mg SL Subutex <sup>(b)</sup> <sub>(4)</sub>	2.88 (±1.14)	28.39 (±10.22)		1.18 <sup>9</sup>	

1 C<sub>ss</sub> calculated based on the following formula: AUC<sub>ss</sub>(0-24)/24h or AUC<sub>inf</sub>/24h after a single dose

2 C<sub>ss</sub> estimate (19.6/2=0.82)

3 C<sub>max</sub> [(8.61+10.4)/2=9.51] average of Day -2 and -1

4 AUC<sub>ss</sub>(0-24) [(66.25+62.67)/2=64.46] avg. of Day -2 and -1; AUC(0-24) as SL dosing was QD

5 C<sub>ss</sub> estimate (64.46/24=2.69); AUC<sub>ss</sub>(0-24)/24h

6 C<sub>trough</sub> average on Day-2, Day-1 and Day 1, 0h (implantation day); [(1.39+1.46+1.58)/3=1.48]

7 Values calculated by taking ½ of Suboxone 16 mg information based on dose proportionality

8 C<sub>ss</sub> estimate (30.45/24=1.27); AUC<sub>inf</sub>/24h

9 C<sub>ss</sub> estimate (28.39/24=1.18); AUC<sub>inf</sub>/24h

Estimated C<sub>ss</sub> value for Probuphine treatment arm from Study PRO-810 is 0.82 ng/mL [AUC<sub>ss</sub>(0-24)/24]. The estimated buprenorphine C<sub>ss</sub> values for Suboxone and Subutex at 8 mg are 1.27 and 1.18 ng/mL, respectively. The results suggested that the estimated buprenorphine C<sub>ss</sub> values from 8 mg SL tablets are slightly higher than that of observed from Probuphine 320 mg buprenorphine HCl.

The Applicant stated that “While pharmacokinetic equivalency between the 6-month Probuphine product with the 24-hr SL buprenorphine products cannot be perfectly established, pharmacokinetic data support the suggestion that Probuphine produces plasma concentrations comparable to those produced by SL buprenorphine between 4 and 8 mg” (*Conclusion* section submitted on January 19, 2016). The Applicant’s statement is reasonable based on the information submitted.

Unfortunately, no buprenorphine concentration information is available from SL buprenorphine 6 mg, to further contemplate on the “best” estimates. However, speculatively, if one presumes, again, that both C<sub>max</sub> and AUC of buprenorphine increased in a linear fashion with the increase in dose (in the range of 4 to 16 mg), the estimated AUC<sub>ss</sub>(0-24) and C<sub>ss</sub> values for Probuphine (4 implants;

provides 320 mg buprenorphine HCl) is approximately 2/3 of the corresponding values of SL buprenorphine 8 mg (Table 1). Therefore, it is reasonable to think that at steady state, buprenorphine plasma concentrations with Probuphine may provide approximately similar concentrations to that of the buprenorphine plasma concentrations achieved with SL buprenorphine 6 mg.

### Conclusion

Looking at the overall information, it is reasonable to speculate that Probuphine (4 implants) provides 1) less buprenorphine C<sub>ss</sub> than SL buprenorphine 8 mg tablets, and, 2) may provide (a conservative estimate) comparable buprenorphine concentrations between SL buprenorphine 4 up to 8 mg; unfortunately, no buprenorphine concentration information is available from SL buprenorphine 6 mg, to further contemplate on the “best” estimates. However, based on buprenorphine’s linear characteristic, buprenorphine plasma concentrations with Probuphine may provide similar concentrations to that of the buprenorphine plasma concentrations achieved with SL buprenorphine 6 mg. Ultimately, it is of this reviewer’s opinion that the information submitted in the resubmission is adequate to support the speculation that “Probuphine produces plasma concentrations comparable to those produced by SL buprenorphine between 4 and 8 mg.”

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DAVID J LEE  
02/01/2016

YUN XU  
02/01/2016



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## 1 Executive Summary

### 1.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in the current application for buprenorphine implant. From a clinical pharmacology perspective, the information submitted in the NDA is acceptable, pending agreement on the labeling language.

Comments to the Medical Team:

During the pre-NDA meeting (10/25/11) with the Applicant, the Agency conveyed to the Applicant that 1) only a minimum effective dose was identified while no higher doses were explored, that is, whether the effectiveness from 4 or 5 implants will be sufficient to outweigh the potential risks associated with Probuphine; 2) information on the effect of scarring or inflammation at previously used sites on the bioavailability of the implants should be developed to establish whether rotation of sites beyond four implantations is possible (the Applicant stated that there are two possible sites per arm). The Applicant

responded during the pre-NDA meeting that they plan to study the re-implantation of the implants at previously utilized sites as part of a post-marketing study and will collect the information on the effect of scarring or inflammation at previously-used sites on the bioavailability of Probuphine. During discussion in the internal team meeting, the review team agreed that the Sponsor should conduct these studies to address the concerns raised above.

From a clinical pharmacology perspective, the Applicant submitted adequate information on Probuphine to address the bioavailability requirement for the implant. However, from an overall drug development aspect, the concerns raised above may be important in terms of efficacy (whether higher doses of Probuphine are needed or bioavailability issues arising from using the previously used sites due to scarring and/or inflammation) and safety (local irritation from the previously used sites).

Therefore, we will recommend the medical team, to convey the following comments to the Sponsor as appropriate from a regulatory perspective.

- (1) Study evaluating the pharmacokinetics, safety and efficacy of Probuphine with higher dose(s).
- (2) Study evaluating the effect of scarring or inflammation at previously used sites on the bioavailability of Probuphine.

## **1.2 Phase IV Commitments**

Not applicable.

## **1.3 Summary of CP Findings**

Titan Pharmaceuticals, Inc. submitted a New Drug Application (NDA) for Probuphine® (buprenorphine hydrochloride in ethylene vinyl acetate polymer (EVA)) under Section 505(b)(2) of the Food, Drug, and Cosmetic Act. The Applicant has developed an implant for the maintenance treatment of opioid dependence. Patients must be opioid tolerant and have begun treatment with sublingual buprenorphine at a daily dose range of 12-16 mg over a period of at least 3 days in order to use this product. Prior to insertion of Probuphine, sublingual buprenorphine should be discontinued in order to avoid overdose. The proposed Probuphine dosage strength is 80-mg buprenorphine hydrochloride in (b) (4) mg of EVA polymer. Probuphine, four or five implants per administration, will be administered once every 6 months. At 6 months, the implants must be removed or may be replaced by new implants in the opposite arm, if necessary. Buprenorphine is a commercially available for the treatment of opioid dependence in sublingual (SL) formulations (Suboxone®, Subutex®, and generic equivalents), and, for the treatment of moderate to severe pain in injectable formulations (Buprenex®) and transdermal (Butrans®).

The Applicant requested a priority review status and has been granted for Probuphine based on the fact that Probuphine offers potential to reduce misuse, abuse, and diversion.

Additionally, the Applicant stated that Probuphine may prevent and reduce pediatric exposure from ingestion and accidental poisoning, and improve treatment compliance compared with currently marketed buprenorphine products.

The Applicant proposed Suboxone® sublingual tablet (NDA 20733) and Subutex® (NDA 20732) as the listed drugs. According to the product label approved on 10/08/2002, Suboxone® sublingual tablet and Subutex® have comparable systemic buprenorphine systemic exposure at 16 mg dose levels. The Applicant conducted a relative bioavailability study between 4 implants of Probuphine (totally 320 mg of buprenorphine dose) with 16 mg sublingual buprenorphine using Suboxone as reference product (Study PRO-810). The Applicant also provided buprenorphine exposure information comparing 2 and 4 implants (Study TTP-400-02-01). Additionally, the Applicant submitted buprenorphine concentration information from two Phase 3 studies (Study PRO-805 and 806) and two extension studies (2<sup>nd</sup> administration of four implants in the ‘opposite arm’; Study PRO-807 and 811, respectively). The to-be-marketed formulation was used in all clinical studies.

#### Relative Bioavailability

Study PRO-810 was open-label study to assess the relative bioavailability of Probuphine compared to sublingual (SL) buprenorphine. Following an induction period, subjects received 16 mg/day SL buprenorphine for a minimum of five consecutive days after which time subjects received 4 x Probuphine implants (80 mg buprenorphine/implant). The steady state C<sub>max</sub> and AUC<sub>0-24</sub> of buprenorphine following 16 mg sublingual buprenorphine were 10400±13400 pg/mL and 62666±36397 pg.h/mL, respectively. The steady state C<sub>max</sub> and AUC<sub>0-24</sub> on Day 28 after insertion of 4 x PROBUPHINE implants were 914±157 pg/mL and 19596±3372 pg.h/mL, respectively. The relative bioavailability of Probuphine implants (320 mg total buprenorphine) based on the mean AUC<sub>0-24</sub> values at steady state (Day 28) compared with SL buprenorphine (16 mg once daily) on Day-1 was 31.3%.

#### Dose linearity

The average buprenorphine steady state concentration, C<sub>avg</sub> (Weeks 4-24), for subjects receiving two implants (166 mg buprenorphine total) was 0.37±0.07 ng/mL, and that for subjects receiving four implants (332 mg buprenorphine total) was 0.72±0.11 ng/mL, suggesting dose linear increase in buprenorphine exposure in the dose range tested.

Although a clear conclusion can not be made comparing the systemic exposure between 4 and 5 implants in the Phase 3 studies, based on the fact that there is clear dose linearity between 2 and 4 implants, it is reasonable to think that a higher number of implants (e.g. 8 implants) will result in a higher systemic buprenorphine exposure compared to 4 implants.

### Pediatric population

The Applicant is requesting a partial waiver for the development of Probuphine in pediatric subjects with opioid dependence (b) (4) years of age. The Applicant is requesting a deferral for the development of Probuphine in pediatric patients who are (b) (4) years of age.

### Special population

No special population studies were submitted. This is a 505(b)(2) application and the Applicant will rely upon the Suboxone Label.

### Drug Interaction

No drug interaction studies were submitted. This is a 505(b)(2) application and the Applicant will rely upon the Suboxone Label.

## **2 QBR**

### **2.1 General Attributes of the Drug and Drug Product**

#### **2.1.1 What are known properties of buprenorphine?**

Buprenorphine is a partial agonist at the  $\mu$ -opioid receptor and an antagonist at the kappa-opioid receptor in the central nervous system. As a partial  $\mu$ -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. Buprenorphine dissociates slowly from opioid receptors. Opioid agonist ceiling-effects were 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. For all measures for which the drugs produced an effect, buprenorphine produced a dose-related response. However, there was a dose that produced no further effect. 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, O<sub>2</sub> 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 O<sub>2</sub> saturation to the same degree.

### 2.1.2 What is the to-be-marketed formulation?

The Probuphine formulation is a simple formulation (Table 1) as it contains the drug product, buprenorphine dispersed in ethylene vinyl acetate. The to-be-marketed formulation was used in all clinical studies.

Table 1. Drug product components and function

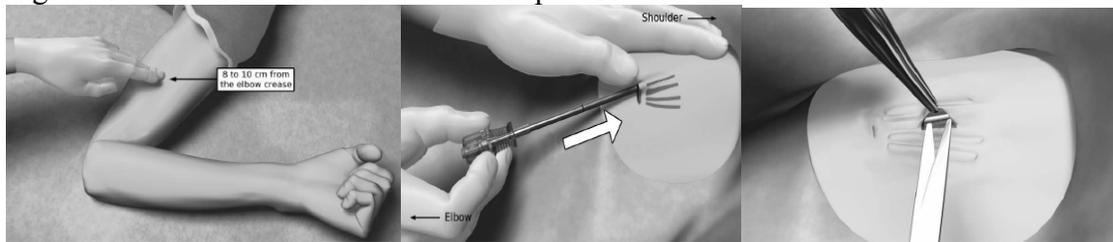
Table 1: Composition of Probuphine Finished Drug Product Implant			
Component	Quality Standard	Function	mg/implant
Buprenorphine hydrochloride	USP	Active pharmaceutical ingredient	80
Ethylene vinyl Acetate	In house specification	Excipient / Polymeric matrix	(b) (4)

### 2.1.3 What are the proposed dosage and route of administration?

Probuphine® is a sub-dermal implant with buprenorphine hydrochloride (buprenorphine) in a solid matrix of ethylene vinyl acetate polymer (EVA). Probuphine is intended to provide continuous delivery of buprenorphine (four or five implants at once) for 6 months for maintenance treatment of opioid dependence.

Patients must first undergo induction with a fixed dose of 12 to 16 mg/day sublingual buprenorphine for at least 3 consecutive days prior to receiving four Probuphine implants. Sublingual buprenorphine is discontinued 12 to 24 hours prior to implant insertion to minimize risk of buprenorphine overdose. Patients requiring greater than or equal to 3 days per week of supplemental sublingual buprenorphine for 2 consecutive weeks or 8 days total of sublingual buprenorphine over 4 consecutive weeks are eligible to receive one additional Probuphine implant at any time after 2 weeks from the initial implantation. All implants are removed after six months. Individuals may be treated for additional 6-month treatment periods, using a site on the opposite arm from that used for the prior Probuphine treatment. The following figure (Figure 1) illustrates the insertion and removal.

Figure 1. Insertion and removal of Probuphine



Buprenorphine is a commercially available opioid approved for the treatment of opioid dependence in sublingual (SL) formulations (Suboxone®, Subutex®, and generic equivalents), and, for the treatment of moderate to severe pain in injectable (Buprenex®) and transdermal (Butrans®) formulations.

## 2.2 General Clinical Pharmacology

### 2.2.1 What are the design features of the pivotal clinical trials and efficacy and safety measurements?

There were four, 24-week study duration, Phase 3 trials conducted for Probuphine (Study PRO-805 and its open label extension Study PRO-807; Study PRO-806 and its open label extension Study PRO-811). Study PRO-805 was a randomized, double-blind, placebo-controlled, safety and efficacy trial of four or five 80-mg Probuphine implants in subjects who completed induction with 12 to 16 mg/day of SL buprenorphine (Subutex or Suboxone). Study PRO-807 was an open-label, 24-week extension trial, assessing 2nd administration of four 80-mg Probuphine implants in subjects successfully completed Study 805. Study PRO-806 was a randomized, placebo-controlled, and active-controlled safety and efficacy trial of four 80-mg Probuphine implants or 12 to 16 mg daily SL buprenorphine in subjects completed induction with 12 to 16 mg/day of buprenorphine (Suboxone). Study PRO-811 was an open-label, 24 week extension trial, for subjects who successfully completed Study PRO-806; its trial design is similar to Study PRO-807.

Efficacy was evaluated using a number of primary and secondary endpoints. The primary endpoint was defined as the cumulative distribution function (CDF) of the percentage of urine samples negative for opioids comparing the placebo and Probuphine treatment groups, using a stratified Wilcoxon rank sum (van Elteren) test with (pooled) site; gender was used as stratification variables. Additionally, analysis was further modified to include imputation for subject self-reported illicit opioid use data: positive self-report data were used in lieu of urine toxicology results where such were contrary to the self-report data. Secondary and exploratory efficacy endpoints in all studies included self-reported illicit drug use (opioids and non-opioids), study completion rates, opioid withdrawal symptoms (Clinical Opiate Withdrawal Scale [COWS], Subjective Opiate Withdrawal Scale [SOWS]) and cravings (Visual Analog Scale [VAS]), Clinical Global Impressions scores for self and observer, and supplemental SL buprenorphine use. Additionally, Study PRO-806 included a formal non-inferiority assessment of Probuphine compared with sublingual Suboxone. According to the statistical reviewer, trials achieved statistical significance for the Applicant's pre-specified primary endpoints.

### **2.2.2 Is the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?**

There are no known dose-concentration-response relationships. It is however shown in two clinical pharmacology studies (see below discussion on Pro-TTP-400 and Pro-810 studies) that steady-state buprenorphine exposures obtained with four implants were approximately 0.72 to 0.83 ng/mL, which is lower than *trough* concentrations observed with 16 mg/day SL buprenorphine at steady state ( $1.6 \pm 0.6$  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-h before the implant insertion). From this information, one can speculate that buprenorphine steady state concentrations from four implants are approximately  $\frac{1}{2}$  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<sub>0-24</sub> values at steady state (Day 28) compared with SL buprenorphine (16 mg once daily for 5 Days) was 31.3%.

### **2.2.3 Protein binding, metabolism, enzyme induction/inhibition**

The following information was obtained from Suboxone sublingual 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).

#### 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 [See *Drug Interactions (7.1)*].

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.

### **2.2.4 What are the PK characteristics of the drug and its metabolite(s)?**

#### 2.2.4.1 What are the single dose PK parameters?

The average buprenorphine steady state concentration,  $C_{avg}$  (Weeks 4-24), for subjects receiving two implants (166 mg buprenorphine total) was  $0.37 \pm 0.07$  ng/mL, and that for subjects receiving four implants (332 mg buprenorphine total) was  $0.72 \pm 0.11$  ng/mL, suggesting dose linear increase in buprenorphine exposure.

#### **Dose linearity (Study TTP-400-02-01)**

Study TTP-400-02-01 compared buprenorphine exposure of two supposedly 90-mg Probuphine implants (Group A) and four 90-mg Probuphine implants (Group B). (Note: the Applicant stated that “the implants contained an average of 83 mg buprenorphine.”) Subjects in both dose groups were on maintenance therapy with sublingual (SL) buprenorphine via Subutex® at enrollment (8 mg and 16 mg daily for Groups A and B, respectively; also, subjects were allowed supplemental SL buprenorphine), however, SL buprenorphine doses were discontinued at least 24 hours prior to implant insertion. Plasma buprenorphine HCl and its metabolite, norbuprenorphine HCl, concentrations were measured by a validated liquid chromatography mass spectrometry method ( (b) (4) ). Ten mL of venous blood was collected at the following times: at the screening visit to assess trough and peak concentrations of buprenorphine HCl (before and 60 min after a sublingual dose); at the baseline clinic visit prior to Probuphine insertion; at 3, 6, 9, 12, 16, 20, 24, 30, 36, and 48 hours after Probuphine insertion; on Days 3, 4, 5, 6, 7, 10, 14 and 21 after Probuphine insertion; and at the clinic visits at Weeks 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24. Upon removal of the Probuphine implants at Week 24, blood was collected 10 and 30 minutes after removal, and at 1, 2, 4, 6, 9, 12, 24, 36, and 48 hours after removal. Urine samples for measuring unchanged buprenorphine and norbuprenorphine were also collected during the first 48 hours after insertion of implants and during the first 24 hours after implant

removal. Urine was collected for a 24-hour period during Days 1–2 and Days 2–3 after insertion of Probuphine implants and during Days 1–2 after Probuphine removal (assay conducted at <sup>(b) (4)</sup>). There were six subjects per group; all subjects received Probuphine treatment for 24 weeks, and no subjects withdrew from the study. Lastly, the removed implants were analyzed for their residual buprenorphine content.

The following table (Table 2) contains peak and trough buprenorphine and norbuprenorphine concentrations immediately before SL buprenorphine administration (trough, approx. 24 h after the previous SL buprenorphine dose) and at 60 minutes after SL buprenorphine administration (peak).

Table 2. Study TTP-400-02-01 – Sublingual Buprenorphine Pharmacokinetic Summary

Pharmacokinetic Parameter	Dose Group A <sup>a</sup> ng/mL, Mean (SD) n=5 <sup>b</sup>	Dose Group B <sup>c</sup> ng/mL, Mean (SD) n=6
Buprenorphine , predose (trough)	0.72 (0.30)	1.08 (0.54)
Buprenorphine , 60 minutes post dose (peak)	4.13 (1.39)	4.62 (2.43)
Norbuprenorphine , predose	1.50 (0.69)	2.50 (1.52)
Norbuprenorphine , 60 minutes post dose	2.47 (0.76)	4.72 (3.10)

SD=standard deviation

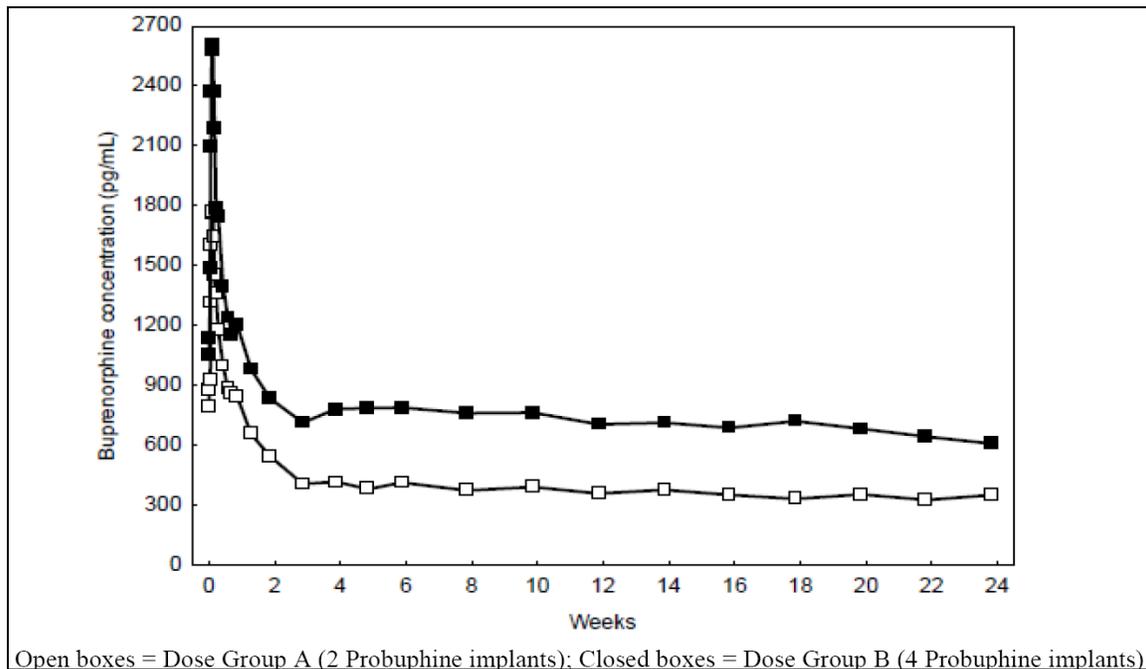
<sup>a</sup> Subjects in Dose Group A received 8 mg sublingual buprenorphine.

<sup>b</sup> One subject was excluded from the analysis due to a sampling or drug intake error.

<sup>c</sup> Subjects in Dose Group B received 16 mg sublingual buprenorphine.

Mean plasma buprenorphine concentrations in both groups after insertion of Probuphine implants over the 24-week treatment period are shown in Figure 2. Note that the initial buprenorphine concentrations (labeled as “C<sub>max</sub>” in subsequent table, Table 3) after the insertion are higher than at steady state (Weeks 4-24), due to SL buprenorphine administration. Stable plasma buprenorphine concentrations were maintained from Day 21 through the end of the 24-week treatment period.

Figure 2. Study TTP-400-02-01 – Mean Plasma Buprenorphine Concentrations for Dose Groups A and B after Probuphine insertion



For a comparison purpose, plasma buprenorphine concentrations for both implantations and that of the SL administrations are summarized in Table 3.

Table 3. Study TTP-400-02-01 – Comparison of Pharmacokinetic Properties of Sublingual Buprenorphine and Probuphine

<b>Buprenorphine Pharmacokinetic Parameter</b>	<b>Dose Group A<sup>a</sup> ng/mL, Mean (SD)</b>	<b>Dose Group B<sup>b</sup> ng/mL, Mean (SD)</b>
C <sub>max</sub> sublingual buprenorphine	4.13 (1.39)	4.62 (2.43)
C <sub>max</sub> Probuphine	2.00 (0.41)	3.23 (0.48)
Predose (trough) sublingual buprenorphine	0.72 (0.30)	1.08 (0.54)
C <sub>avg</sub> Probuphine (Day 21 through implant removal)	0.37 (0.07)	0.72 (0.11)

C<sub>avg</sub> = average plasma concentration; C<sub>max</sub> = maximum plasma concentration; SD = standard deviation

<sup>a</sup> Subjects in Dose Group A were on a maintenance dose of 8 mg sublingual buprenorphine prior to receiving 2 Probuphine implants.

<sup>b</sup> Subjects in Dose Group B were on a maintenance dose of 16 mg sublingual buprenorphine prior to receiving 4 Probuphine implants.

The average buprenorphine steady state concentration, C<sub>avg</sub> (Weeks 4-24), for subjects receiving two implants (166 mg buprenorphine total) was 0.37±0.07 ng/mL, and that for subjects receiving four implants (332 mg buprenorphine total) was 0.72±0.11 ng/mL, suggesting dose linear increase in buprenorphine exposure. The Applicant reported that the within-subject variability in observed buprenorphine concentrations during the

plateau phase was low, with coefficients of variations (CVs) ranging from 11-20% and 9-20% for subjects who received two and four implants, respectively. With respect to norbuprenorphine, mean ( $\pm$ standard deviation) steady state plasma concentrations of norbuprenorphine were  $0.12\pm 0.06$  ng/mL and  $0.32\pm 0.08$  ng/mL for two and four implants, respectively.

With respect to buprenorphine half-life determination after the implant removal, the Applicant reported that not all of the blood samplings were obtained as the subjects were placed on SL buprenorphine 24 h after removal. Based on the estimated half-life in 9 subjects, mean ( $\pm$ SD) terminal half-lives of buprenorphine after Probuphine removal were  $23.8\pm 8.6$  and  $13.7\pm 2.5$  hours for 2 and 4 implants, respectively. The reported half-life for the reference drug, Suboxone is 24 to 42 h.

Two successive 24-hour cumulative urine samples (0-24 and 24-48 h) were collected while subjects were hospitalized following insertion of Probuphine implants, and, during the first 24 hours after implant removal. The Applicant reported that urine samples collected after Probuphine removal were not analyzable due to the fact that seven subjects had urine buprenorphine concentrations below the limit of quantification and two subjects may have taken SL buprenorphine during the urine collection period. Renal clearance following implantation, unchanged buprenorphine was low in both dose groups ( $0.04\pm 0.03$  and  $0.03\pm 0.03$  mL/min for 2 and 4 implants, respectively). Renal clearance for norbuprenorphine was approximately 50-fold greater ( $2.17\pm 1.02$  and  $1.62\pm 1.24$  mL/min for 2 and 4 implants, respectively).

The results of the residual buprenorphine from the removed implants indicated that approximately 30% of the original buprenorphine was not released from the implants (Tables 4 and 5 for two and four implants, respectively)

Table 4: Residual buprenorphine content in Probuphine implants removed from subjects receiving two implants

Patient Number	Implant	Implant	Average	Standard
	1	2		
	mg	mg		
(b) (6)	39.7	42.3	41.0	
	38.6	41.4	40.0	
	32.6	37.7	35.2	
	34.6	33.2	33.9	
	28.9	39	34.0	
	30.5	36.8	33.7	
			36.3	4.30

Table 5: Residual buprenorphine content in Probuphine implants removed from subjects receiving four implants

Patient Number	Implant 1 mg	Implant 2 mg	Implant 3 mg	Implant 4 mg	Average mg	Standard Deviation
(b) (6)	32.7	32.8	24	32.2	30.4	
	36.3	42.6	42.9	33.3	38.8	
	42.2	32.8	31.6	45.0	37.9	
	40.3	40.2	38.8	37.6	39.2	
	44.4	43.8	30.2	41.2	39.9	
	37.5	31.2	34.8	35	34.6	
					36.8	5.43

With respect to supplemental SL buprenorphine usage, the Applicant reported that no subject received supplemental SL buprenorphine in the first month after Probuphine insertion. Additionally, the Applicant reported that, in total, five subjects received supplemental SL buprenorphine for a mean (SD) of 4.8 (5.1) days out of 168 (4.6) days in the treatment period, which three and two subjects received supplemental SL buprenorphine in two and four implant groups, respectively.

2.2.4.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The buprenorphine concentrations were measured at selected time points during the treatment in clinical studies PRO-805, 806, 807, 811. In summary, mean (SD) steady state plasma buprenorphine concentrations observed range from 0.746 (0.439) to 0.941 (0.832) ng/mL for subjects who received Probuphine implants in Phase 3 randomized trials. Results from individual studies are discussed below.

**Study PRO-805** was a Phase 3, randomized, double-blind, placebo-controlled study that established the efficacy of four to five 80-mg Probuphine implants over placebo for the treatment of opioid dependence over a 24-week implant period. Subjects completed induction period with 12 to 16 mg/day of SL buprenorphine (Subutex or Suboxone) and were randomized to treatment groups in a 2:1 ratio (Groups A four 80 mg Probuphine implants: B placebo). Sub-dermal insertion occurred within 12 to 24 hours after the last dose of SL buprenorphine. Subjects in either treatment group could receive an additional implant (i.e., a dose increase) under protocol-defined criteria. To ensure adequate psychosocial and pharmacologic treatment, all subjects received manual-guided psychosocial counseling and could receive supplemental SL buprenorphine if clinically indicated. Blood samples for the measurement of plasma buprenorphine and norbuprenorphine concentrations were collected at baseline prior to Probuphine implant insertion (12 to 24 hours after the last dose of SL buprenorphine), prior to implant dose increase, and at Weeks 1, 4, 8, 12, 16, 20, and 24.

The Applicant reported that mean (SD) steady state plasma buprenorphine concentration over Weeks 4 to 24 was 0.941 (0.832) ng/mL for subjects who received Probuphine implants. For placebo implant subjects, mean (SD) steady state plasma buprenorphine concentration over Weeks 4 to 24 was 0.495 (0.720) ng/mL, which can be attributed to the use of supplemental SL buprenorphine. The Applicant additionally reported gender information and stated that, in general, women had higher mean plasma buprenorphine concentrations than men (Table 6). Women in the placebo group had an almost 3-fold higher mean buprenorphine plasma concentration over Weeks 4 to 24 (0.946 [0.959] ng/mL) compared with men in the placebo group (0.337 [0.547] ng/mL). The mean buprenorphine plasma concentration for women in the placebo group was very similar to that for both men (0.916 [0.984] ng/mL) and women (0.992 [0.363] ng/mL) in the 4 or 5 Probuphine implant group. The buprenorphine concentration appears to be similar between women and men in the Probuphine implant group.

Table 6: Study PRO-805 – Mean (SD) Plasma Buprenorphine Concentrations (ng/mL) by Gender

	4 or 5 Probuphine Implants			Placebo Implants		
	Week 4	Week 24	Weeks 4-24	Week 4	Week 24	Weeks 4-24
Women	1.110 (0.628) n=33	0.694 (0.313) n=22	0.992 (0.363) n=34	0.634 (0.732) n=14	0.774 (1.240) n=3	0.946 (0.959) n=14
Men	0.966 (0.577) n=67	0.520 (0.184) n=50	0.916 (0.984) n=70	0.321 (0.573) n=37	0.389 (0.841) n=14	0.337 (0.547) n=40

**Study PRO-807** was a Phase 3, 24-week, open-label extension study that enrolled subjects who successfully completed Study PRO-805. Following removal of the initial implants from Study PRO-805, once again subjects underwent and completed induction with 12 to 16 mg/day of SL buprenorphine (Suboxone), maintaining this dose for at least 3 consecutive days just prior to Probuphine insertion. The second administration of Probuphine occurred within 14 days after removal of the implants for Study PRO-805. All subjects initially received 4 Probuphine implants, and were allowed to receive supplemental SL buprenorphine if clinically indicated. Upon meeting protocol-specified criteria, subjects could receive an additional (fifth) Probuphine implant. Blood samples were collected for measurement of plasma buprenorphine and norbuprenorphine concentrations at the following time points: baseline, 12 to 24 hours after the most recent SL buprenorphine dose prior to insertion, and Weeks 4, 8, 12, 16, 20, and 24 (or end of treatment). The overall mean (SD) steady state (Weeks 4 to 24) plasma buprenorphine concentration in subjects who received 4 Probuphine implants with or without supplemental SL buprenorphine was 0.886 (0.636) ng/mL, similar to that observed in the

preceding double-blind study (PRO-805; 0.936 [0.918] ng/mL). The mean plasma buprenorphine concentration in subjects receiving a fifth implant was 1.080 (0.456) ng/mL, slightly higher than that observed in PRO-805 (0.961 [0.381] ng/mL).

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**Study PRO-806** was a Phase 3, randomized, placebo- and active-controlled study. Subjects who successfully completed induction with SL buprenorphine (Suboxone), reaching a target dose of 12 to 16 mg/day, were randomly assigned in a 2:1:2 ratio to one of three treatment groups: Group A (4 Probuphine implants [80 mg each], blinded); Group B (4 placebo implants, blinded); Group C (12 to 16 mg once daily SL buprenorphine). Subjects randomly assigned to receive Probuphine or placebo implants (Groups A and B) could receive supplemental SL buprenorphine administered in increments of 2 mg or more as clinically indicated but were asked to refrain from taking supplemental SL buprenorphine during the 24 hours prior to collection of blood samples for PK. Subjects in Groups A and B could also receive one implant dose increase if they exceeded the protocol-specified level of supplemental SL buprenorphine.

Subjects randomly assigned to the SL buprenorphine arm (Group C) could receive a dose increase of 2 mg to 4 mg, not to exceed a maximum fixed dose of 16 mg/day, as determined by the investigator. One dose reduction was also permitted for subjects in Group C in response to an adverse event and if deemed clinically appropriate by the investigator; however, the new dose could not be lower than the minimum 12 mg/day.

Blood samples for measurement of plasma buprenorphine and norbuprenorphine concentrations were collected at Weeks 1, 4, 8, 12, 16, 20, and 24 (or end of treatment). In addition, one trough PK sample was obtained approximately 24 hours following the previous dose of SL buprenorphine prior to implant insertion (at the baseline or dosing visit). For dose increases, the blood sample for PK was obtained the morning prior to the insertion of the fifth implant or the initiation of the new SL buprenorphine dose.

Table 7 summarizes the overall mean plasma buprenorphine concentrations following treatment with Probuphine (excluding the subject with outlying plasma buprenorphine concentration values), placebo implants, or SL buprenorphine.

Table 7: Study PRO-806 – Overall Mean (SD) Plasma Buprenorphine Concentrations (ng/mL) Following Treatment with Probuphine Implants, Placebo Implants, or Sublingual Buprenorphine

Sampling Times	4 or 5 Probuphine Implants <sup>a</sup>	4 Probuphine Implants <sup>a</sup>	4 Probuphine Implants with Supplemental Sublingual Buprenorphine <sup>a</sup>	4 Probuphine Implants without Supplemental Sublingual Buprenorphine <sup>a</sup>	5 Probuphine Implants After the 5th Implant Without Regard to Receiving Supplemental Sublingual Buprenorphine <sup>b</sup>	4 or 5 Placebo Implants	Sublingual Buprenorphine 1, 2, 14, or 16 mg/day
Week 1	1.560 (0.748) n=101	1.560 (0.748) n=101	2.740 (1.290) n=2	1.540 (0.725) n=99	n=0	0.343 (0.458) n=38	1.590 (1.670) n=102
Week 4	0.990 (0.693) n=103	0.946 (0.681) n=92	3.800 n=1	0.914 (0.614) n=91	1.610 (0.816) n=9	0.740 (0.787) n=27	1.270 (1.580) n=93
Week 8	0.869 (0.539) n=95	0.823 (0.540) n=79	n=0	0.823 (0.540) n=79	1.120 (0.449) n=17	1.170 (1.270) n=18	1.370 (1.860) n=85
Week 12	0.897 (0.619) n=83	0.853 (0.617) n=67	2.220 n=1	0.833 (0.597) n=66	1.080 (0.614) n=16	1.800 (2.200)- n=7	1.280 (1.380) n=72
Week 16	0.739 (0.288) n=78	0.697 (0.277) n=61	n=0	0.697 (0.277) n=61	0.889 (0.284) n=17	1.820 (3.010) n=7	1.310 (1.250) n=65
Week 20	0.746 (0.439) n=70	0.731 (0.465) n=55	n=0	0.731 (0.465) n=55	0.801 (0.333) n=15	1.530 (0.817) n=4	1.240 (1.390) n=64
Week 24/End of Treatment	0.636 (0.301) n=77	0.611 (0.318) n=60	n=0	0.611 (0.318) n=60	0.724 (0.213) n=17	2.640 (2.380) n=5	0.988 (1.190) n=64

<sup>a</sup> Excludes one subject who received 4 Probuphine implants who had outlying plasma buprenorphine concentration values at Weeks 1, 4, and 12.

<sup>b</sup> An additional implant was not permitted within the first 2 weeks of the study.

At Week 20, the mean (SD) plasma buprenorphine concentrations were 0.746 [0.439], 1.240 [1.390] ng/mL and 1.530 (0.817) ng/mL (n=4) for Probuphine, SL buprenorphine and placebo groups, respectively. Placebo steady state buprenorphine concentration value was higher than the other two groups. Additionally, the Applicant stated that, in general, women had higher mean plasma buprenorphine concentrations than men (Table 8). This observation was more pronounced in the placebo implants group, while the difference is much smaller in the Probuphine group and the Sublingual Buprenorphine group.

Table 8: Study PRO-806 – Mean (SD) Plasma Buprenorphine Concentrations (ng/mL) by Gender

	4 or 5 Probuphine Implants <sup>a</sup>		Placebo Implants		Sublingual Buprenorphine	
	Week 4	Week 24	Week 4	Week 24	Week 4	Week 24
Female	1.210 (0.651) n=39	0.736 (0.250) n=29	1.060 (1.010) n=12	4.660 (2.040) n=2	1.550 (1.980) n=40	0.860 (0.654) n=24
Male	0.853 (0.686) n=64	0.576 (0.315) n=48	0.486 (0.432) n=15	1.290 (1.580) n=3	1.060 (1.170) n=53	1.060 (1.420) n=40

<sup>a</sup> Excludes one female subject who had outlying plasma buprenorphine concentration values at Weeks 1, 4, and 12.

**Study PRO-811** was an open-label, 24-week extension study for subjects who successfully completed Study PRO-806. Following the removal of the implants from Study PRO-806, subjects who were assigned to 1 of the 2 implant groups (Probuphine or placebo) in PRO-806 underwent once again induction period with SL buprenorphine (Suboxone) to a dose of 12 to 16 mg/day, and, were maintained at this fixed dose for at least 3 consecutive days just prior to Probuphine second administration for PRO-811. All subjects initially received 4 Probuphine implants and allowed to receive supplemental SL buprenorphine throughout the study, if clinically indicated. An additional Probuphine implant could be inserted 2 weeks or later after the initial implant, under protocol-defined criteria. Manual-guided individual drug counseling was provided as clinically indicated.

At Weeks 8, 16, and 24/End of Treatment, the mean (SD) plasma buprenorphine steady state concentrations were 0.832 (0.363), 0.730 (0.227), and 0.766 (0.895) ng/mL, respectively, for subjects receiving 4 or 5 implants (Table 9).

Table 9: Study PRO-811 – Overall Mean (SD) Plasma Buprenorphine Concentrations (ng/mL) Following Treatment with Probuphine Implants

Sampling Times	4 or 5 Probuphine Implants	4 or 5 Probuphine Implants Prior to the 5th Implant			5 Probuphine Implants After the 5th Implant <sup>a</sup>		
		Without Regard to Receiving Supplemental Sublingual Buprenorphine	Without Receiving Supplemental Sublingual Buprenorphine	Receiving Supplemental Sublingual Buprenorphine	Without Regard to Receiving Supplemental Sublingual Buprenorphine	Without Receiving Supplemental Sublingual Buprenorphine	Receiving Supplemental Sublingual Buprenorphine
Week 1	1.770 (0.735) n=2	1.770 (0.735) n=2	1.770 (0.735) n=2	n=0	n=0	n=0	n=0
Week 4	0.881 (0.367) n=74	0.871 (0.365) n=72	0.871 (0.365) n=72	n=0	1.260 (0.318) n=2	1.260 (0.318) n=2	n=0
Week 8	0.832 (0.363) n=75	0.825 (0.364) n=71	0.825 (0.364) n=71	n=0	0.971 (0.357) n=4	0.971 (0.357) n=4	n=0
Week 12	0.800 (0.353) n=66	0.764 (0.275) n=61	0.764 (0.275) n=61	n=0	1.240 (0.792) n=5	1.240 (0.792) n=5	n=0
Week 16	0.730 (0.227) n=65	0.718 (0.222) n=60	0.718 (0.222) n=60	n=0	0.873 (0.259) n=5	0.873 (0.259) n=5	n=0
Week 20	0.728 (0.308) n=63	0.701 (0.299) n=55	0.701 (0.299) n=55	n=0	0.916 (0.325) n=8	0.916 (0.325) n=8	n=0
Week 24/ End of Treatment	0.766 (0.895) n=62	0.720 (0.913) n=55	0.720 (0.913) n=55	n=0	1.130 (0.689) n=7	0.878 (0.209) n=6	2.630 n=1

<sup>a</sup> An additional implant was not permitted within the first 2 weeks of the study.

Again, women, as in previous Probuphine studies, consistently had slightly higher plasma buprenorphine concentration values than Men (Table 10).

Table 10: Study PRO-811 – Mean (SD) Plasma Buprenorphine Concentrations (ng/mL) by Gender

	4 or 5 Probuphine Implants					
	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24/ End of Treatment
Female	0.972 (0.359) n=28	0.955 (0.262) n=25	0.915 (0.318) n=23	0.829 (0.184) n=23	0.885 (0.335) n=22	1.050 (1.450) n=20
Male	0.825 (0.364) n=46	0.771 (0.393) n=50	0.738 (0.359) n=43	0.676 (0.232) n=42	0.644 (0.261) n=41	0.629 (0.391) n=42

### **Reviewer’s comments**

The results from Studies PRO-805, 806, 807, 811 demonstrated that in general women had slightly higher buprenorphine exposure, mostly in Probuphine treatments, compared to men. The subjects were allowed to receive supplemental SL buprenorphine during the trials. Even if the subjects were asked to refrain from taking supplemental SL buprenorphine during the 24 hours prior to collection of blood samples, considering buprenorphine has a relatively long half-life (from 24 to 42 hours), there is a possibility that the gender difference, particularly in the placebo groups, is due to the extra supplemental SL buprenorphine taken by women. Therefore, the findings of slight increase in buprenorphine concentrations in women may be confounded and may not be considered sufficient to make a conclusion.

Either 4 or 5 implants were used in the Phase 3 studies (Studies PRO-805 and PRO-806) and their extension studies (Studies PRO-807 and PRO-811). Sparse blood samples were taken to measure buprenorphine levels. However, these sampling time points were sporadic, and, the blood samples were not complete in some patients. In addition, the patients may take sublingual buprenorphine tablets during the study, which would confound the study results. Due to these reasons, a clear conclusion can not be made comparing the systemic exposure between 4 and 5 implants.

### **2.3 Intrinsic Factors**

No study was conducted to evaluate the Probuphine pharmacokinetics in special populations such as geriatric, hepatic impaired and renal impaired patients. Since this is a 505(b)(2) application, the Applicant referred to information regarding special population (geriatric, hepatic and renal) and drug interaction from Suboxone/Subutex Labeling.

#### **2.3.1 What is the buprenorphine exposure in pediatric subjects?**

The Applicant is requesting a partial waiver for the development of Probuphine in pediatric subjects with opioid dependence (b) (4) years of age. The Applicant stated

that existing therapies, specifically, sublingual (SL) buprenorphine formulations, provide a less invasive treatment approach as well as increased flexibility in the duration that maybe necessary to treat pediatric patients (b) (4). The Applicant further stated that Probuphine does not provide a meaningful therapeutic benefit over SL therapies for pediatric patients due to the surgical procedures required for Probuphine. Therefore, the Applicant stated that Probuphine will unlikely be used in a substantial number of the pediatric patients (b) (4). The Applicant is also requesting a deferral for the development of Probuphine in pediatric patients who are (b) (4) years of age.

## 2.4 Extrinsic Factors – Not applicable

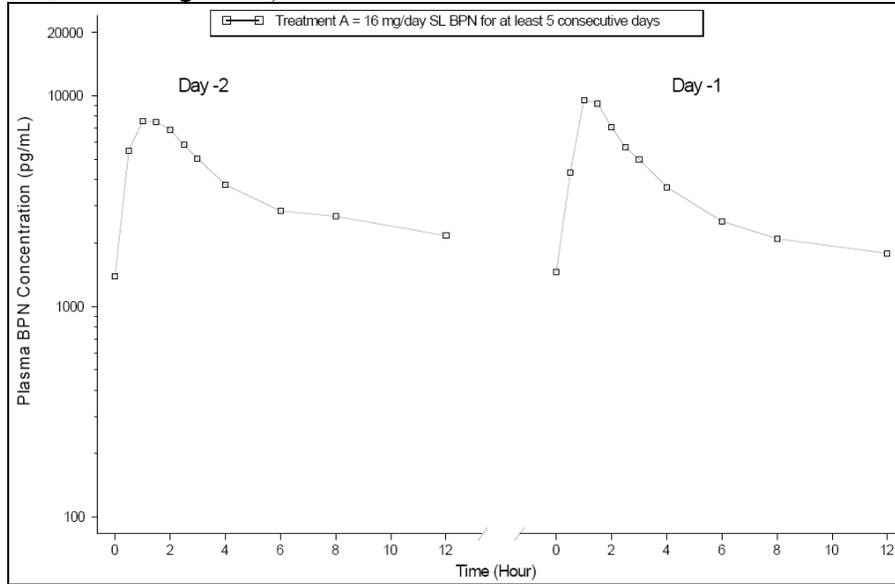
## 2.5 General Biopharmaceutics

### 2.5.1 Relative Bioavailability

**Study PRO-810** was an open-label, planned 26-week, single-center, relative bioavailability PK study comparing the buprenorphine steady state AUC<sub>0-24</sub> of four 80 mg Probuphine implants to the reference drug Suboxone SL tablets (16 mg/day; contains buprenorphine and naloxone, available as 2 mg/0.5 mg and 8 mg/2 mg strengths). Sublingual buprenorphine could be used as rescue medication after Probuphine implant insertion if clinically indicated. Subjects underwent induction period with SL buprenorphine for at least 8 days, with stabilization at 16 mg/day by Day -5. Blood samples were taken from the subjects to measure plasma buprenorphine and norbuprenorphine concentrations during the final 2 days of 16 mg/day SL buprenorphine dosing (Day -2 and Day -1) and the first 2 days (Days 1 and 2) after insertion of 4 Probuphine implants. Subjects were seen on an outpatient basis for collections after Day 2 until Week 4. Additional plasma samples were then collected on an outpatient basis until Week 8 (Day 56), when subjects were admitted to the clinical research unit 1 day prior to removal of the Probuphine implants and had a third round of PK sampling over a 24-hour period that followed implant removal (Day 57). The Applicant stated that the planned 24-week study was terminated by the sponsor after 8 weeks due to lack of funding. Blood samples were collected at the following specific time points for pharmacokinetic assessment: 1) During the last 2 days of induction on Day -2 and Day -1: predose (0 hour) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 hours postdose; 2) Day 1 (day of implant insertion): predose (0 hour) and 2, 4, 6, 9, 12, 16, 20, 24, 30, and 36 hours relative to Day 1 fourth implant insertion; 3) Days 3, 4, 5, 7, and 14: 0 hour (same time relative to Day 1 fourth implant insertion); 4) Week 4: 0 hour (same time relative to Day 1 fourth implant insertion) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours; 5) End of Treatment: prior to implant removal 0 hour (same time relative to Day 1 fourth implant insertion) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours after implant removal. Since the study was terminated early at Week 8, no PK assessments were performed after this time point. Plasma AUC was calculated using noncompartmental methods (WinNonlin® Pro Version 5.0.1 or higher and SAS Version 8.2 or higher). Plasma C<sub>max</sub> and T<sub>max</sub> were determined from the observed concentrations during the respective time intervals.

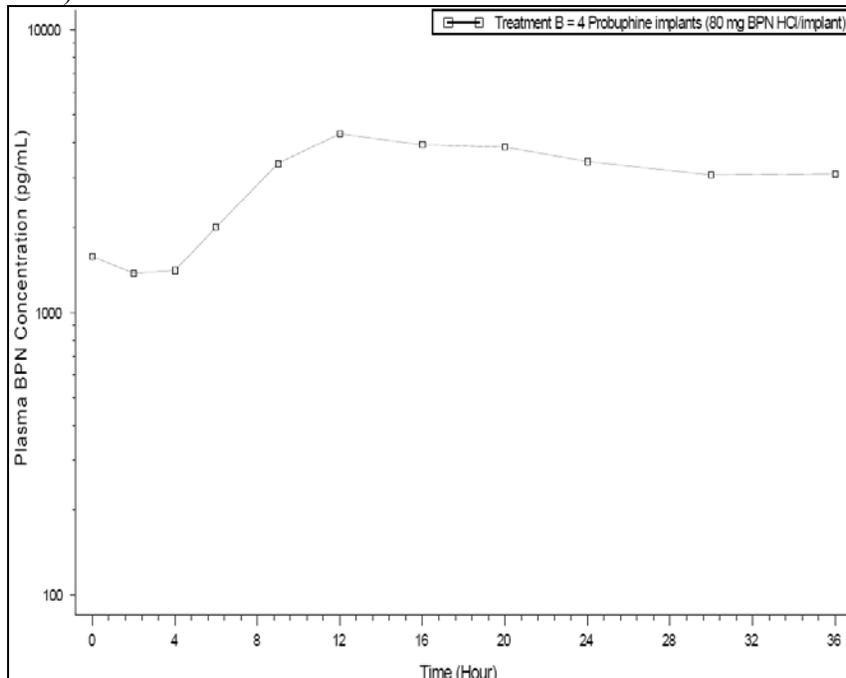
Buprenorphine steady state concentration after SL buprenorphine administration for at least 5 days (Day -2 and Day -1) is presented in the following figure (Figure 3).

Figure 3. Day -2 and Day -1 Mean Plasma Buprenorphine Concentrations Versus Time (All Subjects, Semi-Log Scale)



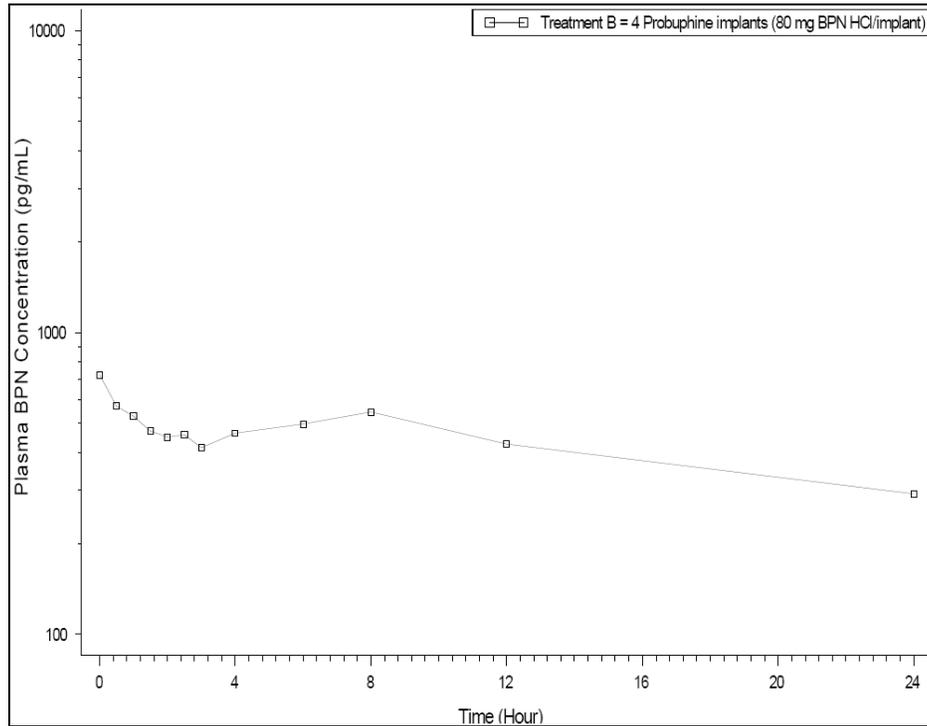
The Day 1 buprenorphine concentration after the Probuphine insertion is presented in the following figure (Figure 4).

Figure 4. Day 1 Mean Plasma Buprenorphine Concentrations Versus Time (All Subjects, Semi-Log Scale)



The Day 57 buprenorphine concentration right after the Probuphine removal is presented in the following figure (Figure 5).

Figure 5. Day 57 (End of Treatment) Mean Plasma Buprenorphine Concentrations Versus Time (All Subjects, Semi-Log Scale)



Overall mean ( $\pm$ SD) plasma buprenorphine concentrations (pg/mL) vs. sampling time points following SL buprenorphine and Probuphine implants are presented in Table 11.

Table 11. Overall mean ( $\pm$ SD) plasma buprenorphine concentrations (pg/ml) following treatment with SL buprenorphine or Probuphine implants

Sampling Time (hour)	Sublingual Buprenorphine		Probuphine Implants		
	Day -2 n = 9	Day -1 n = 9	Day 1 n = 9	Day 28 n = 8	Day 57 <sup>a</sup> n = 6
0	1390 $\pm$ 711	1460 $\pm$ 728	1580 $\pm$ 602	833 $\pm$ 133	724 $\pm$ 143
0.5	5500 $\pm$ 8070	4300 $\pm$ 3220	--	809 $\pm$ 110	571 $\pm$ 104
1.0	7560 $\pm$ 6230	9580 $\pm$ 13600	--	805 $\pm$ 111	528 $\pm$ 94.8
1.5	7530 $\pm$ 4850	9170 $\pm$ 10900	--	813 $\pm$ 112	471 $\pm$ 129
2.0	6920 $\pm$ 3140	7110 $\pm$ 6440	1380 $\pm$ 446	828 $\pm$ 151	451 $\pm$ 94.5
2.5	5850 $\pm$ 2080	5690 $\pm$ 4070	--	811 $\pm$ 127	459 $\pm$ 97.3
3.0	5020 $\pm$ 2210	5000 $\pm$ 3300	--	802 $\pm$ 182	416 $\pm$ 82.3
4.0	3780 $\pm$ 1630	3690 $\pm$ 1660	1410 $\pm$ 523	809 $\pm$ 151	464 $\pm$ 91.2
6.0	2840 $\pm$ 1940	2540 $\pm$ 1400	2000 $\pm$ 1300	829 $\pm$ 183	498 $\pm$ 141
8.0	2670 $\pm$ 1680	2100 $\pm$ 1220	--	756 $\pm$ 176	546 $\pm$ 203
9.0	--	--	3370 $\pm$ 1870	--	--
12.0	2170 $\pm$ 1200	1780 $\pm$ 750	4290 $\pm$ 1570	806 $\pm$ 142	427 $\pm$ 127
16.0	--	--	3920 $\pm$ 1480	--	--
20.0	--	--	3850 $\pm$ 1140	--	--
24.0	--	--	3420 $\pm$ 1040	862 $\pm$ 179	292 $\pm$ 82.9
30.0	--	--	3070 $\pm$ 619	--	--
36.0	--	--	3090 $\pm$ 680	--	--

Sublingual buprenorphine = 16 mg once per day for at least 5 consecutive days including on Days -2 and -1 of induction.  
 Probuphine Implants = 4 Probuphine Implants (80 mg buprenorphine hydrochloride per implant)  
<sup>a</sup> Day 57 sampling time 0 represents plasma concentration values prior to Probuphine implant removal; subsequent sampling times on Day 57 represent plasma concentration values after Probuphine implant removal.

Overall mean plasma buprenorphine PK parameters following treatment with SL buprenorphine and Probuphine implants are presented in Table 12.

Table 12: Study PRO-810 – Overall Mean (SD) Plasma Buprenorphine Pharmacokinetic Parameters Following Treatment with Sublingual Buprenorphine or Probuphine Implants

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

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

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

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

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

The steady state C<sub>max</sub> and AUC<sub>0-24</sub> of buprenorphine following 16 mg sublingual buprenorphine were 10.40±13.40 ng/mL and 62.67±36.40 ng.h/mL, respectively. The steady state C<sub>max</sub> and AUC<sub>0-24</sub> on Day 28 after insertion of 4 x PROBUPHINE implants were 0.91±0.16 ng/mL and 19.6±3.37 ng.h/mL, respectively. The relative bioavailability of Probuphine implants (320 mg total buprenorphine) based on the mean AUC<sub>0-24</sub> values at steady state (Day 28) compared with SL buprenorphine (16 mg once daily) on Day-1 was 31.3%.

With respect to gender difference, both groups appear to be similar. It is noted that the findings are based on a small sample sizes (Table 13).

Table 13: Study PRO-810 – Mean (SD) Plasma Buprenorphine Concentrations (ng/mL) by Gender

	Sublingual Buprenorphine <sup>a</sup>	Probuphine <sup>a</sup>			
	Day -1 (prior to Probuphine Implant Insertion)	Day 7	Day 14	Day 28	Day 57 (prior to Probuphine Implant Removal)
Female	1.480 (1.360) n=3	1.770 (0.530) n=3	1.250 (0.166) n=3	0.731 (0.121) n=2	0.656 (0.142) n=2
Male	1.450 (0.326) n=6	1.610 (0.321) n=6	1.300 (0.398) n=6	0.867 (0.127) n=6	0.758 (0.151) n=4

<sup>a</sup> All data are from sampling hour 0 on the indicated days.

The mean norbuprenorphine  $C_{max}$  values following dosing with SL buprenorphine on Days -2 and -1 (7.980 ng/mL and 8.060 ng/mL, respectively) were higher than the mean norbuprenorphine  $C_{max}$  values on Days 1 and 28 after insertion of Probuphine (3.730 ng/mL and 0.476 ng/mL, respectively) (Table 14).

Table 14: Study PRO-810 – Overall Mean (SD) Plasma Norbuprenorphine Pharmacokinetic Parameters Following Treatment with Sublingual Buprenorphine or Probuphine Implants

Pharmacokinetic Parameter	Sublingual Buprenorphine		Probuphine Implants		
	Day -2 n=9	Day -1 n=9	Day 1 n=9	Day 28 n=8	Day 57 <sup>a</sup> n=6
$C_{max}$ (ng/mL)	7.98 (3.330)	8.06 (2.860)	3.73 (1.620)	0.48 (0.216)	0.32 (0.144)
$T_{max}^b$ (hr)	2.0 (1.5, 12)	1.5 (1.0, 6.0)	0.00 (0.00, 12)	3.3 (0.00, 24)	1.8 (0.00, 8.0)
$AUC_{0-t}^c$ (ng•hr/mL)	126.08 (52.612)	109.70 (40.133)	101.14 (50.866)	8.73 (4.073)	5.23 (2.649)
$AUC_{0-24}$ (ng•hr/mL)	126.08 (52.612)	109.70 (40.133)	69.36 (33.549)	8.73 (4.073)	5.234 (2.649)
$t_{1/2}^b$ (hr)	--	7.51156	--	--	--
$\lambda_z$ (hr <sup>-1</sup> )	--	0.0923	--	--	--

$\lambda_z$  = 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; sublingual buprenorphine = 16 mg once per day for 5 consecutive days; Probuphine Implants = 4 Probuphine Implants (80 mg buprenorphine hydrochloride per implant).

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

<sup>b</sup> Median (minimum, maximum) reported for  $T_{max}$  and  $t_{1/2}$ .

<sup>c</sup> 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.

## 2.6 Analytical Section

### 2.6.1 How are buprenorphine and its metabolites measured in plasma?

An LC/MS/MS method was developed and validated for the determination of buprenorphine and norbuprenorphine in human heparinized plasma. Samples were spiked with internal standard, and the compounds of interest were extracted from alkalized plasma using a liquid: liquid extraction. The samples were then dried down and reconstituted with reconstitution solution before injection onto an LC/MS/MS. The method validation results indicated that the assay is stable over the linearity range of 5 pg/mL to 2000 pg/mL for both buprenorphine and norbuprenorphine. The lower limit of quantitation for both buprenorphine and norbuprenorphine was 10 pg/mL. The quality control values were 30, 200 and 1500 pg/mL. The inter-batch precision (%CV) and accuracy (% bias) ranges were 3.4 to 10% and -5 to 1.3%, respectively.

#### Dose linearity Study TTP-400-02-01

The standard curve concentration range was 25 to 600 pg/mL for both buprenorphine and norbuprenorphine in this study (validation date: 2003). Back-calculated calibration curve standard concentrations showed that accuracy (%Bias) ranged from -2.0% to 3.2% for buprenorphine, and -1.5% to 1.6% for norbuprenorphine. The coefficient of determination (R-squared) was 0.9939 or better for buprenorphine, and, 0.9949 or better for norbuprenorphine. Samples were analyzed without exceeding long-term (-20°C validation freeze thaw %CV range: 2.1 to 6.6 for buprenorphine and 1.6 to 9.6 for norbuprenorphine) and freeze thaw stability (defined as six cycles; validation freeze thaw %CV range: 1.2 to 5.2 for buprenorphine and 1.0 to 5.5 for norbuprenorphine). Quality control (QC) samples were 75, 250 and 450 pg/mL for both analytes. The following tables contain the results for buprenorphine (Table 15) and norbuprenorphine (Table 16).

Table 15. Quality control samples for buprenorphine (Between batch precision (%CV) and accuracy (%Bias) information)

	<b>QC75</b> <b>75.0</b> <b>pg/mL</b>	<b>QC250</b> <b>250</b> <b>pg/mL</b>	<b>QC450</b> <b>450</b> <b>pg/mL</b>
Mean	72.1	239	429
S.D.	4.79	12.4	21.8
%CV	6.6	5.2	5.1
%Theoretical	96.1	95.6	95.3
%Bias	-3.9	-4.4	-4.7
n	46	46	46

Table 16. Quality control samples for norbuprenorphine (Between batch precision (%CV) and accuracy (%Bias) information)

	QC75 75.0 pg/mL	QC250 250 pg/mL	QC450 450 pg/mL
Mean	72.4	243	429
S.D.	14	13.5	31.0
%CV	19.3	5.6	7.2
%Theoretical	96.5	97.2	95.3
%Bias	-3.5	-2.8	-4.7
n	36	36	36

The sample dilution precision (%CV) and accuracy (%Bias) was also explored by diluting QC samples, which dilution factors ranged from 5-fold to 100-fold. Precision (%CV) was less than or equal to 9.2% for buprenorphine, and, less than 14.6% for norbuprenorphine; accuracy (%Bias) ranged from -6.8% to 5.6% for buprenorphine, and -66.0% to 12.0% for norbuprenorphine.

#### Relative Bioavailability Study PRO-810

The standard curve concentration range was 5 to 1000 pg/mL for buprenorphine and 10 to 2000 pg/mL for norbuprenorphine in this study (validation date: 2009).

Back-calculated calibration curve standard concentrations showed that accuracy (%Bias) ranged from -1.8% to 2.0% for buprenorphine, and -1.9% to 2.0% for norbuprenorphine. The coefficient of determination (R-squared) was 0.9916 or better for buprenorphine, and, 0.9926 or better for norbuprenorphine.

Samples were analyzed without exceeding long-term (-20°C validation freeze thaw %CV range: 1.3 to 5.2 for buprenorphine and 2.3 to 16.4 for norbuprenorphine) and freeze thaw stability (defined as six cycles; validation freeze thaw %CV range: 1.8 to 5.9 for buprenorphine and 1.8 to 4.7 for norbuprenorphine).

Quality control (QC) samples were 15, 100 and 750 pg/mL for buprenorphine and 30, 200 and 1500 for norbuprenorphine. The following tables contain the results for buprenorphine (Table 17) and norbuprenorphine (Table 18).

Table 17. Quality control samples for buprenorphine (Between batch precision (%CV) and accuracy (%Bias) information)

	QC A 15.0 µg/mL	QC B 100 µg/mL	QC C 750 µg/mL
Mean	15.0	102	751
S.D.	0.672	5.71	25.2
%CV	4.5	5.6	3.4
%Theoretical	100.0	102.0	100.1
%Bias	0.0	2.0	0.1
n	24	24	24

Table 18. Quality control samples for norbuprenorphine (Between batch precision (%CV) and accuracy (%Bias) information)

	QC A 30.0 µg/mL	QC B 200 µg/mL	QC C 1500 µg/mL
Mean	30.4	199	1510
S.D.	1.68	13.5	49.0
%CV	5.5	6.8	3.2
%Theoretical	101.3	99.5	100.7
%Bias	1.3	-0.5	0.7
n	24	24	24

The sample dilution precision (%CV) and accuracy (%Bias) was also explored by diluting QC samples, which dilution factors ranged from 5-fold to 50-fold. Precision (%CV) was less than or equal to 5.6% for buprenorphine, and, less than 6.8% for norbuprenorphine; accuracy (%Bias) ranged from 0% to 2.0% for buprenorphine, and – 0.5% to 1.3% for norbuprenorphine.

### 3 Detailed Labeling Recommendations

There are changes recommended for the Clinical Pharmacology section of the label, as below. The package insert is modified by strikeouts of the existing texts and addition of new texts, in **RED** fonts, where appropriate.

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#### 8.5 Geriatric Use

Clinical studies of PROBUPHINE did not include subjects over the age of 65. Other reported clinical experience with buprenorphine has not identified differences in responses between the geriatric and younger patients. Due to possible decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in geriatric patients, ~~the decision to prescribe PROBUPHINE should be~~ **administered with caution and monitored appropriately** ~~made cautiously~~ in individuals 65 years of age or older.

## 8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of buprenorphine

(b) (4)

## 8.7 Renal Impairment

Clinical studies of PROBUPHINE did not include subjects with renal impairment. No differences in buprenorphine pharmacokinetics were observed between 9 dialysis dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine.

(b) (4)

## 12 Clinical Pharmacology

### 12.2 Pharmacodynamics

(b) (4)

#### Absorption:

Overall buprenorphine exposures were lower after PROBUPHINE administration compared to sublingual buprenorphine administration. Buprenorphine exposure (AUC) after PROBUPHINE administration (four implants) was approximately 31.3% that of sublingual administration (16 mg daily dose) [see *Clinical Pharmacology, Pharmacokinetics (12.3)*].

### 12.3 Pharmacokinetics

(b) (4)

Buprenorphine exposure increased in a linear manner when administered as two and four PROBUPHINE implants.

After PROBUPHINE insertion, an initial buprenorphine peak was observed and median T<sub>max</sub> (b) (4) at 12 hour after insertion. After the initial buprenorphine peak, the plasma buprenorphine concentrations decreased slowly and steady state plasma buprenorphine concentrations were reached by approximately Week 4. Mean steady-

state plasma buprenorphine concentrations were at approximately 0.5 to 1 ng/mL and were maintained for approximately 20 weeks (Week 4 through Week 24) in a 24-week treatment period.

Overall peak plasma buprenorphine concentrations were lower after PROBUPHINE insertion than after dosing with SL buprenorphine. (b) (4)

In subjects who received 16 mg/day sublingual (SL) buprenorphine for a minimum of five consecutive days followed by four PROBUPHINE implants (80 mg buprenorphine/implant), the steady-state (on Day 5) C<sub>max</sub> and AUC<sub>0-24</sub> values of buprenorphine for the sublingual route were 10400 ± 13400 pg/mL and 62666 ± 36397 pg.hr/mL, respectively. The steady-state (on Day 28 after insertion) C<sub>max</sub> and AUC<sub>0-24</sub> values of buprenorphine for PROBUPHINE were 914 ± 157 pg/mL and 19596 ± 3372 pg.hr/mL, respectively. The mean AUC<sub>0-24</sub> value on Day 28 of PROBUPHINE implants (320 mg total buprenorphine) were approximately 31.3% that of 16 mg/day sublingual buprenorphine on Day 5.

Option of including this table:

Table x. Overall steady-state mean ± SD plasma (unadjusted) buprenorphine PK parameters following treatments with sublingual buprenorphine or PROBUPHINE implants

Parameter	Sublingual <sup>#</sup>	PROBUPHINE <sup>*</sup>
C <sub>max</sub> ss (pg/mL)	10400 ± 13400	914 ± 157
AUC <sub>0-24</sub> (pg.hr/mL)	62666 ± 36397	19596 ± 3372

<sup>#</sup>Sixteen mg/day for minimum of 5 days

<sup>\*</sup>Four 80 mg implants; on Day 28

(b) (4)

## **4 Appendices**

### **4.1 Proposed Package Insert**

22 Page(s) of Draft Labeling have been withheld in Full as b4 (CCI/TS) immediately following this page

**4.2 Individual Study Review - Not applicable****4.3 Consult Review (including Pharmacometric Reviews) – Not applicable****4.4 Cover Sheet and OCPB Filing/Review Form**

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	<b>Information</b>		<b>Information</b>
<b>NDA/BLA Number</b>	204442	<b>Brand Name</b>	Probuphine®
<b>OCP Division (I, II, III, IV, V)</b>	II	<b>Generic Name</b>	Buprenorphine HCl
<b>Medical Division</b>	DAAAP	<b>Drug Class</b>	Opioid
<b>OCP Reviewer</b>	David Lee, Ph.D.	<b>Indication(s)</b>	Main
<b>OCP Team Leader</b>	Yun Xu, Ph.D.	<b>Dosage Form</b>	80-mg buprenorphine Implant
<b>Pharmacometrics Reviewer</b>	-	<b>Dosing Regimen</b>	4 to 5 implants Once every 6 months as needed

Date of Submission	October 29, 2012	Route of Administration	Transdermal
Estimated Due Date of OCP Review	March 15, 2013	Sponsor	Titan Pharmaceuticals, Inc.
Medical Division Due Date	April 6, 2013	Priority Classification	1P
PDUFA Due Date	April 30, 2013		
Clin. Pharm. and Biopharm. Information			
	"X" if included at filing	Number of studies submitted	Number of studies reviewed
<b>STUDY TYPE</b>			
Table of Contents present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies	X		
HPK Summary	x		
Labeling	x		
Reference Bioanalytical and Analytical Methods	x		
<b>I. Clinical Pharmacology</b>			
Mass balance:			
Isozyme characterization:			
Blood/plasma ratio:			
Plasma protein binding:			
Pharmacokinetics (e.g., Phase I) -			
Healthy Volunteers-			
single dose:			
multiple dose:			
Patients-			
single dose:	x		Part of P2 studies
multiple dose:	x		Part of P2 studies
Dose proportionality -			
fasting / non-fasting single dose:	x	1	
fasting / non-fasting multiple dose:	x		
Drug-drug interaction studies -			
In-vivo effects on primary drug:			
In-vivo effects of primary drug:			
In-vitro:			
Subpopulation studies -			
ethnicity:	X		Discussion
gender:	X		Discussion
pediatrics:			
geriatrics:	X		
renal impairment:			
hepatic impairment:			
PD -			
Phase 2:			
Phase 3:			
PK/PD -			
Phase 1 and/or 2, proof of concept:			
Phase 3 clinical trial:	x	4	2 are extension studies
Population Analyses -			
Data rich:			
Data sparse:			
<b>II. Biopharmaceutics</b>			
Absolute bioavailability			
Relative bioavailability -			
solution as reference:			
alternate formulation as reference:	x	1	
Bioequivalence studies -			
traditional design; single / multi dose:			
replicate design; single / multi dose:			
Food-drug interaction studies			
Bio-waiver request based on BCS	x		
BCS class			

<b>In vivo alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>	x			<b>Deferral for (b) (4) y of age; Waiver (b) (4) y of age, based on the Applicant's proposal</b>
<b>Literature References</b>				
<b>Total Number of Studies</b>		6		

On **initial** review of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	X			

12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	X			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	X			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? \_\_\_\_yes\_\_\_\_**

\_\_\_\_\_  
 Reviewing Clinical Pharmacologist Date

\_\_\_\_\_  
 Team Leader/Supervisor Date

Titan Pharmaceuticals, Inc. submitted a New Drug Application (NDA) for Probuphine® (buprenorphine hydrochloride in ethylene vinyl acetate polymer (EVA)) under Section 505(b)(2) of the Food, Drug, and Cosmetic Act. The Applicant has developed an implant

for the maintenance treatment of opioid dependence. Patients must be opioid tolerant and have begun treatment with sublingual buprenorphine at a daily dose range of 12-16 mg over a period of at least 3 days in order to use this product. Prior to insertion of Probuphine, sublingual buprenorphine should be discontinued in order to avoid overdose. The proposed Probuphine dosage strength is 80-mg buprenorphine hydrochloride in (b) (4) mg of EVA polymer. Probuphine, four or five implants per administration, will be administered once every 6 months. At 6 months, the implants must be removed or may be replaced by new implants in the opposite arm, if necessary.

The Applicant requests a priority review status for Probuphine based on the fact that Probuphine offers potential to reduce misuse, abuse, and diversion. Additionally, the Applicant states that Probuphine may prevent and reduce pediatric exposure from ingestion and accidental poisoning, and improve treatment compliance compared with currently marketed buprenorphine products.

The proposed listed drugs by the Applicant are Suboxone® and Subutex®. The clinical program was conducted under IND 70852. The Applicant conducted a relative bioavailability study using Suboxone (Study PRO-810). The Applicant provided buprenorphine exposure information comparing 2 and 4 implants (Study TTP-400-02-01). Additionally, the Applicant submitted buprenorphine concentration information from two Phase 3 studies (Study PRO-805 and 806) and two extension studies (2<sup>nd</sup> administration of four implants in the ‘opposite arm’; Study PRO-807 and 811, respectively). The to-be-marketed formulation was used in all clinical studies.

Conclusion:

From a clinical pharmacology perspective, the application is recommended for filing.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DAVID J LEE  
04/01/2013

YUN XU  
04/01/2013