CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204442Orig1s000

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	May 25, 2016
From	Rigoberto Roca, M.D.
Subject	Deputy Division Director Summary Review
NDA Number	204442
Applicant Name	Titan Pharmaceuticals (Authorized Representative: Braeburn)
Date of Original Submission	October 31, 2012 Complete Response letter issued April 30, 2013
Date of Complete Response Submission	August 27, 2015
PDUFA Goal Date	May 27, 2015 (includes a 3-month clock extension)
Proprietary Name / Established (USAN) Name	Probuphine (buprenorphine HCl / ethylene vinyl acetate) implant
Dosage Forms / Strength	EVA implants, 74.2 mg of buprenorphine (equivalent to 80 mg of buprenorphine hydrochloride)
Proposed Indication	For the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product (i.e., doses of no more than 8 mg/day of Subutex or Suboxone sublingual tablet or generic equivalent). Probuphine should be used as part of a complete treatment program to include counseling and psychosocial support. Prescription use of this product is limited under the Drug Addiction Treatment Act."
Recommended Action	Approval

Material Reviewed/Consulted OND Action Package, including reviews by:	
CDTL	Celia Winchell, MD
Medical Officer	Rachel Skeete, MD
Pharmacology Toxicology	Gary Bond, PhD; Jay Chang, PhD; Dan Mellon, PhD
OTS/OCP/DCP II	David Lee, PhD; Yun Xu, PhD
OTS/OB/DB II	James Travis, PhD and Dave Petullo, MS
ONDQA/DNDQA III	Xiaobin Shen, PhD and Julia Pinto, PhD
OND/ODE III/DBRUP	Catherine Sewell, MD, MPH; Christina Chang, MD, MPH; Audrey Gassman, MD
OSE/OMEPRM/DMEPA	Millie Shah, PharmD; Vicky Borders-Hemphill, PharmD; Irene Chan, PharmD, BCPS; Kellie Taylor, PharmD, MPH
OSE/OMEPRM/DRISK	Donella Fitzgerald, PharmD; Joan E Blair, RN, MPH; Kim Lehrfeld, PharmD; Cynthia LaCivita, PharmD
OSE/OPE/DEPI II	James Trinidad, MPH; Tamra Meyer, PhD
OSI/DCCE/GCPAB	John Lee, MD; Janice Pohlman, MD, MPH; Kassa Ayalew, MD, MPH
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CDRH/OC/DMQ	Viky Verna and Francisco Vicenty
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OMP/DMPP	LaShawn Griffiths, MSHS-PH, BSN, RN; Barbara Fuller, RN, MSN, CWOCN; Morgan Walker, PharmD, MBA, CPH
OMP/OPDP	L Shenee' Toombs, PharmD

CDRH = Center for Devices and Radiological Health
CDTL = Cross-Discipline Team Leader
DAGRID = Division of Anesthesiology, General Hospital, Respiratory, Infection Control, & Dental Devices
DBRUP = Division of Bone, Reproductive, and Urologic Products
DB II = Division of Biometrics II
DCCE = Division of Clinical Compliance Evaluation
DCP II = Division of Clinical Pharmacology II
DEPI II = Division of Epidemiology II
DMEPA = Division of Medication Error Prevention and Analysis
DMPP = Division of Medical Policy Programs
DMQ = Division of Manufacturing and Quality
DNDQA III = Division of New Drug Quality Assessment III
DPMH = Division of Pediatrics and Maternal Health
DRGUD = Division of Reproductive, Gastro-Renal, and Urological Devices
DRISK = Division of Risk Management
GCPAB = Good Clinical Practice Assessment Branch
OB = Office of Biostatistics
OC = Office of Compliance
OCP = Office of Clinical Pharmacology
ODE = Office of Device Evaluation
ODE II = Office of Drug Evaluation II
ODE III = Office of Drug Evaluation III
OMEPRM = Office of Medication Error Prevention and Risk Management
OMP = Office of Medical Policy
OMPQ = Office of Manufacturing and Product Quality
ONDQA = Office of New Drug Quality Assessment
OPE = Office of Pharmacovigilance and Epidemiology
OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSE = Office of Surveillance and Epidemiology
OSI = Office of Scientific Investigations
OTS = Office of Translational Sciences

1. Introduction

The Applicant (Titan Pharmaceuticals, and their legal representative, Braeburn Pharmaceuticals), has submitted a the results of a clinical study in support of their complete response to the Complete Response letter issued on April 30, 2013. During the first review cycle in 2012, the Agency's conclusion was that the data submitted did not support the intended indication, specifically, for patients newly-entering treatment for opioid dependence. In this submission, the Applicant has amended the indication for their new drug application (NDA) to state that the product is intended as maintenance treatment for opioid-dependent patients who have been clinically stable for a sustained period of time on low to moderate doses of transmucosal buprenorphine. An example of a low to moderate dose would be 8 mg/day or less of a Subutex or Suboxone sublingual tablet. Additional examples include the following (and their corresponding generic products):

- Subutex buprenorphine tablets 8 mg
- Suboxone buprenorphine/naloxone tablet, 8 mg/2 mg
- Suboxone buprenorphine/naloxone sublingual film 8 mg/2 mg
- Zubsolv buprenorphine/naloxone sublingual tablet 5.7 mg/1.4 mg
- Bunavail buprenorphine/naloxone buccal film 4.2mg/0.7 mg

This is a 505(b)(2) application and the Applicant references NDA 20732, Subutex (buprenorphine sublingual tablets) and NDA 20733, Suboxone (buprenorphine/naloxone combination tablets), which are approved for the treatment of opioid dependence.

The review clock was extended by 3 months dues to the fact that several components of the Risk Evaluation and Mitigation Strategy (REMS) program needed to be submitted at the time of the original PDUFA goal date.

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling requested by the Applicant.

2. Background

Buprenorphine is a partial agonist at the μ-opiate receptor. Buprenorphine was initially approved in 1981 as a parenteral formulation for the treatment of pain (Buprenex, NDA 18401). Since 1981, there have been seven NDAs containing buprenorphine approved:

- Three sublingual tablet formulations intended for treatment of opioid dependence
  - Subutex (buprenorphine), NDA 20732
  - Suboxone (buprenorphine/naloxone), NDA 20733
  - Zubsolv (buprenorphine/naloxone), NDA 204242
- Sublingual film formulation intended for treatment of opioid dependence
  - Suboxone (buprenorphine/naloxone) film, NDA 22410
- Buccal film formulation intended for maintenance treatment of opioid dependence
  - Bunavail (buprenorphine/naloxone) film, NDA 205637

- Extended-release transdermal film formulation intended for the treatment pain
  - Butrans (buprenorphine), NDA 21306
- Buccal film formulation intended for the treatment of pain
  - Belbuca (buprenorphine hydrochloride), NDA 207932

As noted in Dr. Skeete's and Dr. Winchell's reviews, buprenorphine was developed as a treatment for opioid dependence because of its pharmacological properties. Buprenorphine's activity at the μ-receptor was expected to relieve the patient's urge to use illicit opioids, and its long duration of action would allow a patient to achieve a steady state without the highs and lows associated with illicit opioids. Further, its partial agonist property was expected to result in a "ceiling" effect at moderate doses with respect to its euphorigenic effects. Lastly, at sufficiently high doses, buprenorphine blocks full agonists from achieving their full effects, which, in buprenorphine maintained patients, would result in decreased use of these substances.

As noted by Dr. Winchell in her review, despite these features, buprenorphine sublingual products have been increasingly identified in the illicit drug market, and it is known that they are diverted, abused, and misused. Consequently, a depot injection or an implantable formulation of buprenorphine would have the potential to make it more difficult to divert or abuse. Furthermore, such a formulation would also have the potential of providing sufficient plasma level of buprenorphine that could block the effects of exogenous opioids which, in turn, could ensure compliance because patients would not be able to periodically discontinue use and allow the blocking effect to dissipate in order to experience the effects of their preferred opioid.

Although the last potential advantage was not demonstrated to be true for Probuphine, the other potential advantages were sufficient to grant the application a priority review during the first review cycle.

The results of the review of the original NDA submission are well detailed in Dr. Skeete's and Dr. Winchell's reviews. Only the major points will be summarized here.

October 2012 – Initial NDA Submission

The indication in the initial submission was for the maintenance treatment opioid dependence. Two Phase 3 trials in subjects that were new entrants into treatment were submitted in support of the original application. The subjects were initially treated with sublingual buprenorphine tablets to a target dose of 12 to 16 mg/day for three consecutive days, at which point they were switched to four Probuphine implants. There was an option for dosing with a fifth implant rod, as well as supplemental buprenorphine. The review team found that a very small minority of patients treated with Probuphine at the proposed dose accomplished substantial improvements in their drug use behavior, even after months of treatment. The team concluded that, although the trial met its pre-specified endpoints, the proposed dose was too low to provide effective treatment for patient new to buprenorphine treatment.

March 2013 – Psychiatric Drugs Advisory Committee meeting

The review team's assessment of the results from the two Phase 3 trials was presented to the Psychopharmacologic Drugs Advisory Committee on March 21, 2013. The majority of the committee members voted in favor of approval of the application, indicating that that adequate

data had been submitted in support of the efficacy, safety, and risk:benefit profile of Probuphine. However, there was considerable discussion amongst the committee members that reflected ambivalence about the application, with some members that had voted for approval indicating that additional data were still needed to fully assess the safety and efficacy of Probuphine, and concerns about the proposed REMS.

The following summary about some of the discussion points made during the meeting are reproduced from Dr. Winchell's review.

> Many participants, even some who voted that efficacy had been demonstrated, expressed that their vote reflected the fact that, on the primary endpoint, the drug had out-performed placebo. Several did note concerns about the adequacy of the dose, and five voted that efficacy had not been demonstrated. Panel members noted difficulty reconciling Applicant's claim that the steady-state blood levels were maintained in an efficacious range with the pattern of urine toxicology results, asking "How can I make the claims of robust efficacy jive with the very disappointing results in terms of negative urines?" and "I'm not sure that we're doing anyone a service if we put something on the market that's not the right dose, that doesn't actually optimally achieve what we're trying to accomplish..," and "if there's tons of positives at the 24th week, did that medicine do the right thing, or … what's the purpose of that drug?" One panelist noted that, if he treats a patient with buprenorphine "And if they've got a few months of dirty urine, I'm going to say treatment failed" and refer the patient for other treatment.
>
> Although addiction medicine providers on the panel observed that it was not a requirement or expectation for a patient in treatment to have "totally clean urines," one provider noted that "when we have people who give us urines that are positive for illicit or unauthorized use, it's a signal to us that we need to reevaluate the patient and make some changes in whatever therapy that we're providing." He expressed some concern about the use of supplemental buprenorphine as an indication that the dose was inadequate, and concern that providers would be "stuck with" a dose that would leave providers with "difficulty meeting our patients' needs." Another addiction medicine expert noted that the REMS would need to address the use of supplemental sublingual buprenorphine and that physicians would need to be educated to minimize its use.
>
> An expert appearing on behalf of the Applicant noted that "In thinking about the individuals who were stabilized on 12 to 16 milligrams and then transferred over to the rods, I would look at them as very early responders to the treatment. So they're in the phase 1 and 2, at most, in the six months of study. Her further comments seemed to indicate that patients need to be titrated to the dose of medication that is necessary to help them discontinue illicit drug use, which may be higher than 12-16 mg, and certainly higher than the dose provided by Probuphine (which is 1/3 the AUC of 16 mg/day), noting, "people with mild to moderate disease, being those that you want to capture in the 12 to 16 range. I think that's where we want to induce people, and we want to increase them…until we get them at a place where we can reliably support their desire not to use heroin or prescription drugs while they're on this medication."
>
> One addiction medicine specialist noted, "One of the populations that it has been suggested by several people, and I think it's an appropriate suggestion, is for the patient who's already stable. Half of my stable patients are on less than 12 milligrams. Most of them are on 4 or 8…I frankly think that this is an extremely important product concept, to be able to give a patient six months of medication that will keep them stable and that we would have limited oral or sublingual supplementation on that would decrease that issue with diversion…I've got patients who have been on buprenorphine sublingually now for five to eight years. None of them are on 16. My new patients are generally on 16, but they back off within six months, nine months to a lower dose.
>
> Several participants in the open public hearing were investigators in the clinical trials or individuals with expertise in addiction treatment. Their comments reflected an expectation that the product would be efficacious enough to bring patients' addiction into remission, emphasizing that

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

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

November 2013 – Post-action meeting

The Division met with the Applicant November 19, 2013. Although the Applicant disagreed with the Division's conclusions about the demonstrated efficacy, they did concur that the four Probuphine implants resulted in buprenorphine concentrations that were more comparable with 4 to 8 mg/day of sublingual buprenorphine. With the intent of incorporating some of the comments that were heard during the advisory committee meeting, the Applicant proposed a revised indication for Probuphine – specifically, for the treatment of patients stabilized on sublingual buprenorphine at dose of 8 mg or less.

3. Chemistry, Manufacturing, and Controls (CMC)

The following summary is reproduced from Dr. Winchell's review, which is, in turn, excerpted from the reviews from member of the review staff in the Office of Pharmaceutical Quality (OPQ) and the Office of Device Evaluation in the Centers for Devices and Radiological Health (CDRH).

- General product quality considerations

The drug substance is Buprenorphine Hydrochloride (BPN). It is not a NME. The characterization of this compound has been well documented in the literature, and the applicant has adequately confirmed the structure of the drug substance they produced. The drug substance does not contain structural alert moieties. Only one crystal form of BPN was observed. Neither polymorphism nor [redacted] was observed.

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

The drug product Probuphine® (buprenorphine HCl implant) is a subdermal implant containing 80 mg buprenorphine hydrochloride USP (BPN) coextruded with [redacted] mg of ethylene vinyl acetate copolymer (EVA, the only excipient) as a matrix [redacted] Each implant measures 26 mm in length and 2.5 mm in diameter. The implants are individually packaged into laminated foil pouches. The pouches are terminally sterilized using gamma irradiation. [redacted] The release profile consists of an initial burst followed by a slow steady state drug release over a period of 6 months.

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

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

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

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

- Facilities review/inspection

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

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

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

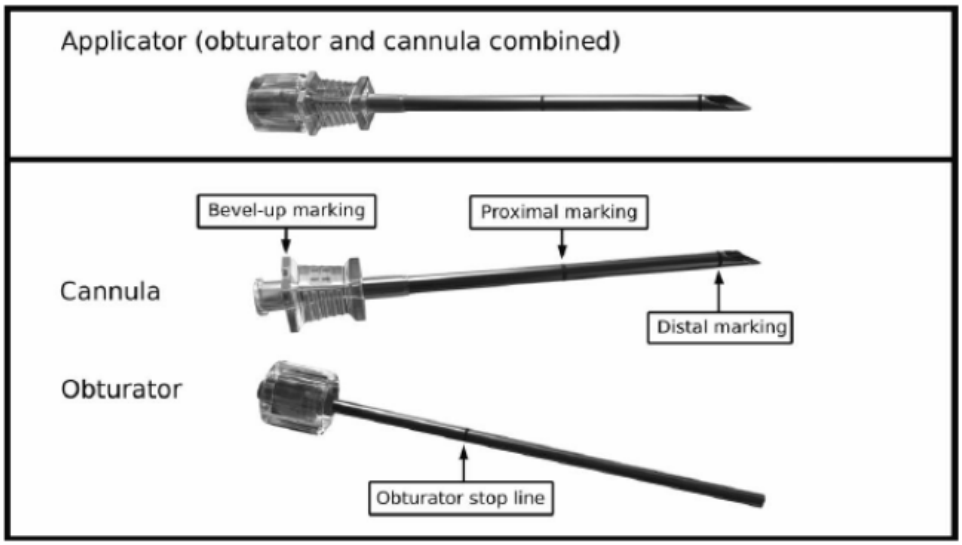
The Probuphine Applicator consists of three parts: (1) an insertable obturator (stylet rod), (2) a cannula needle, and (3) a needle guard which covers the entire cannula from hub to tip. Further descriptions of the device parts are below.

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

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

3. Needle Guard
The Needle Guard for the Applicator consisting of an LDPE sleeve which covers the entire Cannula from the hub to the tip. The Needle Guard protects the Applicator tip during transport and handling and as a safety measure during user handling (removal of the Applicator from packaging). The components of the Applicator are shown in (excluding the Cover). The Cannula and Stylet have interlocking hubs (referred to as Swivel Nuts) manufactured from biocompatible polymeric materials. The Applicator design includes guide and orientation marker visual aids to assist healthcare providers with the proper placement of the Probuphine implants. These markers include orientation markings on both the Cannula and Stylet to facilitate the proper depth of implant placement, and a foil stamp marking on the hub of the Cannula showing the correct" bevel up" position for the cannula which facilitates the correct subdermal insertion of Probuphine.

<u>Packaging of Probuphine Applicator:</u>
The Probuphine Applicator is packaged in a (b) (4) pouch (b) (4) The material has been verified to maintain sterility for up to (b) (4) months.



Probuphine Applicator Components

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

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

- Purported Abuse-Deterrent Features

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

Outstanding or Unresolved Issues

I concur with the conclusions reached by the product quality reviewers that there are no manufacturing issues that would preclude approval of this application.

4. Nonclinical Pharmacology/Toxicology

There had not been any nonclinical issues identified during the first review cycle that would have precluded approval. The Applicant did not submit any new nonclinical data submitted during this review cycle.

However, the review team evaluated the proposed label with respect to the requirements of the Pregnancy and Lactation Labeling Rule (PLLR).

Outstanding or Unresolved Issues

There were no outstanding or unresolved pharmacology/toxicology issues that precluded approval during the first review cycle, and there are none during this review cycle.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology information submitted in support of this application was evaluated during the first review cycle. There were no clinical pharmacology issues that precluded approval during the previous review cycle, and the Applicant has not submitted any new clinical pharmacology information in this submission.

The following table, reproduced from Dr. Lee's review during the first cycle, summarizes key pharmacokinetic parameters for Probuphine.

Pharmacokinetic Parameter	Sublingual Buprenorphine		Probuphine Implants		
	Day -2 n=9	Day -1 n=9	Day 1 n=9	Day 28 n=8	Day 57[a] n=6
C_{max} (ng/mL)	8.61 (6.900)	10.40 (13.400)	4.89 (1.110)	0.91 (0.157)	0.78 (0.128)
T_{max}[b] (hr)	1.5 (0.50, 2.5)	1.5 (1.0, 2.0)	12 (9.0, 36)	10 (0.00, 24)	0.00 (0.00, 12)
AUC_{0-t}[c] (ng•hr/mL)	66.25 (35.878)	62.67 (36.397)	113.13 (27.737)	19.60 (3.372)	10.23 (2.264)
AUC_{0-24} (ng•hr/mL)	66.25 (35.878)	62.67 (36.397)	75.191 (24.443)	19.60 (3.372)	10.23 (2.264)
$t_{1/2}$[b] (hr)	11.42 (11.04, 12.09)	7.63	--	--	--
λ_z (hr^{-1})	0.0604 (0.00231)	0.0908	--	--	--

λz = apparent elimination rate constant; AUC0-24 = area under the plasma concentration-time curve from time 0 to 24 hours; AUC0-t = area under the plasma concentration-time curve from time 0 to t, where t is the last measurable plasma concentration; Cmax = maximum observed plasma concentration; t1/2 = apparent terminal elimination half-life; Tmax = time of maximum plasma concentration; SL buprenorphine = 16 mg once per day for 5 consecutive days; Probuphine Implants = 4 Probuphine Implants (80 mg buprenorphine hydrochloride per implant).

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

[b] Median (minimum, maximum) reported for Tmax and t½.

[c] On Days -1 and -2, AUC0-t represents the AUC from Day -1 or Day -2 Hour 0 through Day 1 or Day -2 Hour 12. On Day 1, AUC0-t represents the AUC from Day 1 Hour 0 through Day 2 Hour 36, relative to the time of insertion.

It is notable that after six months of implantation, approximately 40% of the buprenorphine remains in the implant. This has potential implications with respect to the proper handling of the implants that are removed from patients at the end of the treatment period. This issue has been addressed in the Applicant's proposed Risk Evaluation and Mitigation Strategy (REMS) program.

As noted in Dr. Lee's reviews, based on a steady-state comparison between Probuphine and the approved treatment at 16 mg/day, the plasma buprenorphine exposure associated with Probuphine implants [320 mg total buprenorphine] is 31% of the steady-state plasma level associated with sublingual buprenorphine tablets [16 mg once daily], based on the mean AUC_{0-24}, and provides a level that approximates the trough plasma level associated with sublingual buprenorphine tablets 8 mg/day.

There is the potential for drug-drug interactions if buprenorphine is administered with agents that affect the CYP3A4 activity. The potential implications are summarized in Dr. Winchell's review, and reproduced below.

> Buprenorphine is metabolized to norbuprenorphine primarily by cytochrome CYP3A4; therefore, potential interactions may occur when buprenorphine is given concurrently with agents that affect CYP3A4 activity. Drug-drug interaction considerations are complicated because it is anticipated that the greater role of first-pass metabolism in disposition of sublingual products as compared to subdermal products could result in a different impact of metabolic inhibitors or inducers on buprenorphine clearance. The effects of co-administered inducers or inhibitors have been established in studies using transmucosal buprenorphine; study of transdermal buprenorphine suggests it is not affected by ketoconazole, suggesting that the effects may be dependent on the route of administration.
>
> For this reason, considerations are different for various clinical scenarios:
> 1. Patients transferring from transmucosal buprenorphine taken concomitantly with inhibitors:
>   In these patients, the plasma exposure of their maintenance transmucosal dose is likely to be higher than in patients not on concomitant inhibitors. When switching to Probuphine, which could be less impacted by inhibitors, the result would be that the dose provided by Probuphine would be relatively lower and may not be adequate.
>
> 2. Patients initiating inhibitors for the first time while maintained on Probuphine:
>   In these patients, there is a possibility that the exposure to Probuphine could be increased. These patients should be monitored for over-medication and if the inhibitor cannot be discontinued, they should have Probuphine removed and be treated with a product that allows for dose adjustment. Although a higher-than-intended exposure is a possibility, the relatively low dose provided by Probuphine is unlikely to present significant safety concerns even if the exposure is increased by the addition of inhibitors. (The maximum labeled dose of sublingual buprenorphine is 24 mg/day, and doses as high as 32 mg/day have been studied.)
>
> 3. Patients who are already on inhibitors while taking Probuphine but discontinue them:
>   In this situation, the plasma level before might fall (although this is unknown). These patients should to be monitored for withdrawal/lack of efficacy and could need supplementation through the end of the dosing cycle and then could need to be treated with other options.
>
> 4. Patients transferring from transmucosal buprenorphine taken concomitantly with inducers:

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

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

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

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

Outstanding or Unresolved Issues

There were no outstanding or unresolved clinical pharmacology issues that precluded approval during the first review cycle, and there are none during this review cycle.

6. Clinical Microbiology

Probuphine is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical – Efficacy

The Applicant submitted the results of one clinical trial in support of this submission, Study PRO-814, 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." In addition to the attributes noted in the title of the study, it also included a non-inferiority design, and three phases: a Screening Phase (Weeks -2 to -1), a 24-week Maintenance Phase, and a 2-week Follow-Up Phase. Additional details of the study design are well detailed in Dr. Skeete's, Dr. Travis' and Dr. Winchell's respective reviews, and will only be summarized here.

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

Subjects were to be randomized in a 1:1 ratio to one of the following treatment groups:

1. Treatment as usual with daily sublingual buprenorphine tables (≤8 mg/daily) + four placebo implants.
2. Four 80 mg Probuphine implants + daily sublingual placebo tablets.

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

In order to be enrolled, the subjects need to meet the following inclusion criteria:

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

The following conditions would exclude the subject from the study:

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

The primary efficacy endpoint was designated to be the proportion of responders for each treatment group. The protocol specified that a responder would be defined as a subject with no more than 2 out of 6 months with any evidence of illicit opioid use, and illicit opioid use was defined as either a positive opioid urine toxicology result or self-reported illicit opioid use.

As noted in Dr. Travis' review, the Applicant provided two different definitions for the primary analysis population. In the study protocol, the intent-to-treat (ITT) population was defined as all randomized subjects who received study medication, while the statistical analysis plan and the final study report defined this population to be all randomized subjects who received study medication *and provided some efficacy data* (emphasis added).

There were also several secondary efficacy endpoints identified in the protocol, specifically:

- Measures of desire/need to use:
  - Desire to Use VAS.
  - Need to Use VAS.
- Measures of withdrawal
  - Clinical Opiate Withdrawal Scale (COWS).
  - Subjective Opioid Withdrawal Scale (SOWS).

However, these secondary efficacy endpoints were not evaluated to any significant extent by the review team because there were no statistical adjustments for multiplicity included in the statistical analysis plan

As noted above, the design of the study included an active control, and a non-inferiority design. The following description of the statistical methodologies, including the strategy used by the Applicant to determine the appropriate non-inferiority margin to test, is reproduced from Dr. Travis' review:

> Since this was an active-controlled study the Applicant conducted a test of non-inferiority for the rate of responders between the two treatment arms utilizing a non-inferiority margin of 20%. If πc and πt equal the proportion of responders for the control arm and the experimental treatment arm, respectively, then the null hypothesis of inferiority can be stated as:
>
> $$H0: \pi t \leq \pi c - 0.20.$$
>
> The alternative hypothesis of non-inferiority can then be stated as:
>
> $$HA: \pi t > \pi c - 0.20.$$
>
> The hypothesis of non-inferiority will be concluded if the null hypothesis can be rejected at the 5% level. In order to test this hypothesis the Applicant computed the standard Wald confidence interval for the risk difference. If the lower bound of the 95% confidence interval for the difference between Probuphine and sublingual buprenorphine was greater than -0.20 then noninferiority would be established.
>
> The Applicant provided the following rationale for the 20% non-inferiority margin:
>
> - Previous studies with patients on longer term buprenorphine or methadone treatment found that 18 to 31% of patients remained abstinent following treatment discontinuation.
> - The Applicant also conducted a survey of addition experts and reported that they expected a median of 25% of clinically stabilized patients to remain abstinent if their stable dose were discontinued.
>
> Based on the results of these studies and the assumption that all subjects remaining on sublingual buprenorphine would continue to be stable, a non-inferiority margin of 20% was selected as it would preserve greater than 70% of the estimated effect size. This was considered clinically significant by the Applicant.

> The Applicant stated that since this was an active-controlled study, bias would be introduced if all missing values were replaced with extreme values (i.e., either all replaced with "negative" or all replaced with "positive"). For example, if all missing values are replaced with "positive" then the results will be biased in favor of the group with the smaller dropout rate. Therefore the Applicant proposed imputing missing urines using the average of the within-subject proportion of opioid positive samples. The Applicant made the primary analysis more conservative by applying a 20% relative penalty to the higher of the two positive rates to impute missing data in the Probuphine treatment arm. For example, if the imputation for sublingual buprenorphine used a 15% positive rate then the rate for Probuphine would be 18%.

As noted by Dr. Winchell in her review, the design of this study was unique for the following reasons:

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

In addition, Dr. Winchell noted the following regarding the non-inferiority design:

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

Of note, the assumption that the treatment group of patients who were continued on treatment-as-usual would have 100% response was not consistent with the observed data. Subsequently, the review team performed additional analyses, as described below.

Study Results

The study enrolled 177 subjects from 21 sites in the United States between June 2014 and May 2015. There were several sites that enrolled only a few subjects (e.g., less than 10 subjects); only three sites enrolled 20 or more subjects.

The following table, adapted from the Applicant's clinical study report, summarizes the subject disposition.

	Probuphine N (%)	**Sublingual Buprenorphine** N (%)	**Total** N (%)
Category			
Randomized	87	90	177
Safety population	87	89 (99)	176 (99)
Completed	81 (93)	84 (94)	165 (94)

	Probuphine N (%)	Sublingual Buprenorphine N (%)	Total N (%)
Discontinued	6 (7)	5 (6)	11 (6)
Reason for discontinuation			
Adverse event	1 (1)	0	1 (<1)
Request of Sponsor or regulatory agency	0	1 (1)	1 (<1)
Lost to follow-up	4 (5)	2 (2)	6 (3)
Other (incarcerated)	1 (1)	0	1 (<1)
Subject request	0	2 (2)	2 (1)

The safety population was defined as all subjects who were randomized and who received study medication.

The baseline demographics of the safety population are summarized in the following table, adapted from the Dr. Skeete's review.

	Probuphine N=87	Sublingual Buprenorphine N=89	Total N=176
Age (years)			
Mean (SD)	38 (11.2)	39 (10.8)	39 (11.0)
Min, max	21, 63.0	22, 64.0	21, 64.0
Gender, n (%)			
Male	52 (59.8)	52 (58.4)	104 (59.1)
Female	35 (40.2)	37 (41.6)	72 (40.9)
Race, n (%)			
White	82 (94.3)	85 (95.5)	167 (94.9)
Black or African American	3 (3.4)	2 (2.2)	5 (2.8)
Asian	1 (1.1)	0	1 (0.6)
American Indian or Alaska native	0	1 (1.1)	1 (0.6)
Other	0	1 (1.1)	1 (0.6)
Ethnicity, n (%)			
Hispanic or Latino	3 (3.4)	3 (3.4)	6 (3.4)
Not Hispanic or Latino	84 (96.6)	86 (96.6)	170 (96.6)
BMI (kg/m^2)			
Mean (SD)	28 (6.94)	27 (5.92)	28 (6.47)
Min, max	14, 46.4	19, 50.6	14, 50.6

The Applicant's primary analysis is summarized in the table below, adapted from the Applicant's clinical study report.

	Probuphine N = 84 n (%)	Sublingual Buprenorphine N = 89 n (%)	Proportion Difference (95% CI) Probuphine – Sublingual Buprenorphine	Superiority *P*-Value (2-Sided)
Responder	81 (96%)	78 (88%)	0.09 (**0.01**, 0.17)	0.03
Non-Responder	3 (4%)	11 (12%)		

Based on these results, the Applicant reported that the lower bound of the 95% confidence interval of the difference in the proportion of responders was greater than -0.20 and hence

concluded that Probuphine was non-inferior to sublingual buprenorphine. The Applicant also found a p-value for superiority of 0.03 and also concluded that Probuphine was superior to sublingual buprenorphine.

As noted by the review team in their reviews, there were concerns regarding the conclusions reached by the Applicant about the efficacy results from this study. The concerns revolved around the subject population that was used in the primary efficacy analysis, the procedure for the assumptions made about missing urine test results, the interpretation of the implications of supplemental sublingual buprenorphine use, and the number of positive tests that defined a responder.

Primary Efficacy Analysis Population

The Applicant had excluded from the primary efficacy analysis four subjects that had been randomized. These were three subjects randomized to Probuphine treatment group and one subject randomized to the sublingual buprenorphine treatment group. The review team felt that the exclusion of the subject randomized to the sublingual buprenorphine treatment group was acceptable because that subject did not receive any medication. However, the three subjects that were randomized to the Probuphine treatment group did received medication, and the review team felt that these subjects should not have been excluded from the primary efficacy analysis.

The table below summarizes the results if the primary efficacy endpoint is analyzed with the three subjects in the Probuphine treatment group included as non-responders.

	Probuphine N = 87 n (%)	**Sublingual Buprenorpohine N = 89 n (%)**	**Proportion Difference (95% CI) Probuphine – Sublingual Buprenorphine**	**Superiority *P*-Value (2-Sided)**
Responder	81 (93%)	78 (88%)	0.055 (**-0.03**, 0.14)	0.22
Non-Responder	6 (7%)	11 (12%)		

In this analysis, Probuphine is no longer found to be superior, although it would still be considered non-inferior.

Missing Urine Toxicology Results

As noted by the review team, there were approximately twice as many positive urine samples in the sublingual buprenorphine treatment group. However, there were twice as many urine samples that were either missed or not conclusively analyzed in the Probuphine treatment group. This finding is summarized in the table below, adapted from Dr. Travis's review.

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

Dr. Winchell notes the following about this issue in her review.

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

The review team evaluated the effect of the missing data on the primary efficacy endpoint by conducting two additional analyses. The first analysis considered any missing urine as positive, and the second analysis considered missing urine samples and any sample that was not completely analyzed also as positive. The results of these analyses are summarized in the table below, adapted from Dr. Travis' review.

Imputation Scheme	**Category**	**Probuphine N = 87 n (%)**	**Sublingual Buprenorphine N = 89 n (%)**	**Proportion Difference (95% CI) Probuphine – Sublingual Buprenorphine**
Missing Urine Samples Imputed as Positive	Responder	78 (90%)	76 (85%)	0.04 (**-0.06**, 0.140)
	Non-Responder	9 (10%)	13 (15%)	
Incomplete and Missing Urine Samples Imputed as Positive	Responder	73 (84%)	70 (79%)	0.05 (**-0.06**, 0.17)
	Non-Responder	14 (16%)	19 (21%)	

In both of these analyses, non-inferiority was still demonstrated.

Use of Supplemental Sublingual Buprenorphine

The review team noted that it was the expectation that subjects enrolled in the clinical trial would be clinically stable and on a stable dose of sublingual buprenorphine with no dose adjustments for at least three months prior to randomization. The primary objective of the study was to

demonstrate maintenance of treatment efficacy when transferring adult outpatients from sublingual buprenorphine to the Probuphine, therefore, an additional expectation was also that the subjects would require little, if any, supplemental sublingual buprenorphine.
The results of the trial indicated that approximately 16% of the subjects required supplemental buprenorphine, and subjects in the Probuphine treatment group were dispensed approximately 70% more supplemental buprenorphine than subjects randomized to the sublingual buprenorphine treatment group. This level of use was not anticipated when the protocol was being designed, therefore, it was not incorporated into the definition of a responder.

Furthermore, the establishment of whether a subject was clinically stable may have been affected by the manner in which subjects were identified. As noted in Dr. Skeete's review, although the protocol indicated that patients needed to have been on sublingual buprenorphine for at least 6 months, the Applicant did not include measures in the execution of the protocol to ensure that only patients with at least six consecutive months of buprenorphine treatment would be enrolled.

As the review team evaluated the results of the study, they took into account the Advisory Committee members comments, including the point that some supplemental use of buprenorphine would be acceptable.

Definition of a Responder

In view of the above concerns, the review team conducted sensitivity analyses that evaluated different definitions of responders, taking various factors into account, such as the subject population used in the primary efficacy analysis, the number of months permitted for positive urine results, the imputation strategy for missing and/or incomplete samples, the use of supplemental sublingual buprenorphine, as well as the timepoint during the trial in which the supplemental buprenorphine was used.

The responder rates identified as a result of these analyses are summarized in the table below, adapted from Dr. Travis' review.

Analysis Population	**Number of Allowed Positive Months**	**Value Imputed for Missing Data**	**Value Imputed for Incomplete Samples**	**Rescue Use Permitted**		**Probuphine N (%)**	**Sublingual Buprenorphine N (%)**	**Lower Bound (95% CI)**
				Probuphine	**Sublingual Buprenorphine**			
Applicant's	2	Applicant's	Negative	Yes	Yes	81 (96%)	78 (88%)	0.01
Revised	2	Applicant's	Negative	Yes	Yes	81 (93%)	78 (88%)	-0.03
Revised	2	Positive	Negative	Yes	Yes	78 (90%)	76 (85%)	-0.06
Revised	2	Positive	Positive	Yes	Yes	73 (84%)	70 (79%)	-0.06
Revised	2	Positive	Negative	No	No	63 (72%)	65 (73%)	-0.14
Revised	2	Positive	Positive	No	No	58 (67%)	59 (66%)	-0.14
Revised	2	Positive	Negative	No	Yes	63 (72%)	76 (85%)	-0.25
Revised	2	Positive	Negative	Month 1 and 6	Yes	66 (76%)	76 (85%)	-0.21

Analysis Population	Number of Allowed Positive Months	Value Imputed for Missing Data	Value Imputed for Incomplete Samples	Rescue Use Permitted		Probuphine N (%)	Sublingual Buprenorphine N (%)	Lower Bound (95% CI)
				Probuphine	Sublingual Buprenorphine			
Revised	0	Positive	Negative	Month 1 and 6	Month 1 and 6	57 (66%)	48 (54%)	-0.03
Revised	0	Positive	Negative	Month 1 and 6	Yes	57 (66%)	57 (64%)	-0.13

Revised – Three previously-excluded subjects in the Probuphine treatment group are included as non-responders.

All but one of the analyses conducted by Dr. Travis found Probuphine to be non-inferior to sublingual buprenorphine with the Applicant's prespecified margin of -20%. Superiority of Probuphine to sublingual buprenorphine was not demonstrated in any of the analyses.

In order to understand the impact of the different variables on the responder rates, the review team performed additional analysis that evaluated the presence or absence of positive months, the use of supplemental buprenorphine use, and the timing of that use. The table below, adapted from Dr. Winchell's review, summarizes the results of those analyses. It is noted that, in these analyses, the analysis population and imputation strategy for missing or incompletely/inconclusively analyzed urine samples remained the same.

Analysis Population	Number of Allowed Positive Months	Value Imputed for Missing Data	Value Imputed for Incomplete Samples	Rescue Use Permitted		Probuphine N (%)	Sublingual Buprenorphine N (%)	Lower Bound (95% CI)
				Probuphine	Sublingual Buprenorphine			
Revised	0	Positive	Negative	Yes	Yes	66 (76%)	57 (64%)	-0.02
Revised	2	Positive	Negative	Yes	Yes	78 (90%)	76 (85%)	-0.06
Revised	0	Positive	Negative	Month 1 and 6	Yes	57 (66%)	57 (64%)	-0.13
Revised	2	Positive	Negative	Month 1 and 6	Yes	66 (76%)	76 (85%)	-0.21
Revised	0	Positive	Positive	No	Yes	55 (63%)	57 (64%)	-0.15
Revised	2	Positive	Negative	No	Yes	63 (72%)	76 (85%)	-0.25

Revised – Three previously-excluded subjects in the Probuphine treatment group are included as non-responders.

After additional internal discussions, and taking into account the comments and advice from the Advisory committee members, the review team concluded that the most appropriate interpretation of the efficacy results from this clinical trial would be the following.

Probuphine Only (no supplemental dosing) (N=87)	Treatment as Usual (sublingual buprenorphine) (N=89)	Treatment Difference (95% CI)
55 (63%)	57 (64%)	-1% (-15%, 13%)

This table summarizes the proportion of patients with no evidence of illicit opioid use throughout the 6 months, with missing urine samples imputed as positive for opioid use, and any supplemental buprenorphine use in the Probuphine arm only adjudicated as a non-responder.

The review team also noted that, although the protocol permitted supplemental buprenorphine use for patients in both arms, the use of supplemental dosing in patients assigned to the sublingual treatment arm is consistent with treatment as usual, which includes dose adjustments as needed. Because the use of supplemental buprenorphine in patients on Probuphine, which cannot be titrated, may be interpreted to indicate that the dose of buprenorphine provided by Probuphine was inadequate for that patient (to maintain stability), patients who required supplemental dosing were not included in the table as successfully maintained, even if they did not have evidence of opioid use.

Outstanding or Unresolved Issues

Although the review team was not able to concur with the Applicant's assessment of the treatment effect of the product, the team was able to conclude that the trial provides sufficient evidence of efficacy in a patient population that consists of patients who are responsive to buprenorphine maintenance treatment and require relatively low doses of buprenorphine to maintain this status.

I concur with the review team that there are no outstanding issues or concerns regarding the efficacy of Probuphine that would preclude approval.

3. Safety

The safety database consists of data from three Phase 3 trials (PRO-805, PRO-806, and PRO-814), two Phase 3 extension trials (PRO-807 and PRO-811), and two clinical pharmacology trials (TTP-400-02-01 and PRO-810). All except Study PRO-814, which is the primary study supporting for this submission, have been previously evaluated by the Agency.

As noted by Dr. Skeete in her review, the safety data from the three Phase 3 trials were pooled, and supplemented by safety data from the extension studies. Limited safety data were available for the clinical pharmacology studies.

The systemic safety profile of buprenorphine has been well established, and Probuphine provides a much lower exposure than target doses of approved transmucosal formulations of buprenorphine. Therefore, the primary focus of the safety evaluation by the review team was the safety experience related to the implants and the insertion and removal procedures. This included a consultation request for assistance from the Division of Bone, Reproductive, and Urologic Products (DBRUP), given their experience with implantable contraceptives.

The review team from DBRUP pooled the safety data from five clinical trials (the three efficacy trials and the two extension trials). The number of subjects exposed to procedures is summarized in the table below, reproduced from Dr. Winchell's review.

Number of subjects	Probuphine implants	Placebo implants	Total
Study 805	108	55	163

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

The most commonly reported procedure-related adverse events were noted as mild and self-limited. They were primarily pain, pruritis, and erythema at the incision/implant site.

The team from DBRUP also evaluated the incidence of certain adverse events of interest, such as bleeding, complicated removals, and implant site infections. The table below, adapted from Dr. Winchell's review, summarizes their findings.

	Efficacy Studies			Extension Studies		Total Number of Events of Special Interest	Adverse Event Incidence (based on 654 procedures being performed)
	Study 805 (N = 163)	Study 806 (N = 168)	Study 814 (N = 176)	Study 807 (N = 62)	Study 811 (N = 85)		
Implant expulsion	4 (2.5%)	1 (0.6%)	1 (0.6%)	2 (4.8%)	0	8	1.2%
Implant site infection	9 (5.5%)	3 (1.8%)	6 (3.4%)	4 (6.4%)	4 (4.7%)	26	4.0%
Wound complications	4 (2.5%)	2 (1.2%)	2 (1.1%)	1 (1.6%)	1 (1.1%)	10	1.5%
Complicated Removal, or requiring a 2nd attempt	15 (9.2%)	0	7 (4%)	3 (4.8%)	2 (2.3%)	27	4.1%
Bleeding	30 (18.4%)	19 (11.3%)	1 (0.6%)	16 (25.8%)	5 (5.9%)	71	10.9%

- "Implant expulsion" includes implant expulsion and implant protrusion
- "Implant site infection" includes AE terms of cellulitis, purulent discharge, implant site pruritus, incision site infection, and wound infection, implant site abscess, and subcutaneous abscess
- "Wound Complications" includes AE terms of incision site necrosis, wound dehiscence, incision site complication, postoperative wound complication, suture-related complication, wound complication, impaired healing
- "Bleeding" includes AE terms of implant site bleeding/hematoma/hemorrhage, and incision site hemorrhage

Dr. Winchell noted that Applicant did not consider subjects who required a second attempt to remove all implants as having a "complicated removal," and that DBRUP considered a failure to remove all implants during the first attempt, and therefore, requiring imaging studies to locate all implants and a second removal attempt, to be a complication of the initial implant removal attempt.

QT Prolongation

At the time that Suboxone and Subutex were being developed, it was believed that buprenorphine was not likely to have cardiac conduction effects because of negative in vitro binding studies. In the interim, a thorough QT study has been performed for a transdermal buprenorphine product intended for analgesia, and it demonstrated a signal for QT prolongation that had met the threshold for regulatory significance. This signal was not known at the time the Probuphine trials were being designed, and the Applicant had not been asked to conduct a formal evaluation of the potential for conduction effects. Subsequently, although electrocardiograms were collected during the course of the trials, the timing relative to the dosing of the supplemental sublingual buprenorphine was not standardized, and the electrocardiograms were interpreted on site, rather than at a central site.

Because of the uncertain clinical significance of the signal, and because there are several buprenorphine products currently approved that have not manifested any clear cardiac conduction safety signal, Applicants seeking approval of new buprenorphine products are being permitted to conduct the thorough QT studies as a post-marketing requirement study.

Hepatic Toxicity

The current label for Suboxone and Subutex notes that buprenorphine has been associate with hepatic adverse events, ranging from transient serum transaminase elevations to significant hepatic toxicity. The safety database for Probuphine identified several patients with elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) to more than three times the upper limit of normal, as well as subjects with elevations in serum total bilirubin. However, there were no cases that met the Hy's law criteria of AST or ALT elevations more than three times the upper limit of normal *in conjunction* with total bilirubin elevations greater than or equal to twice the upper limit of normal.

The following overall summary of the safety findings is reproduced from Dr. Winchell's review.

> Because the systemic safety of buprenorphine is fairly well-characterized, the size of the safety database seems adequate to identify systemic safety concerns related to Probuphine and to provide a characterization of the local tolerability of the implant.
>
> The safety database informing an understanding of the risks of the insertion and removal procedures also includes patients who underwent the procedures for insertion and removal of placebo implants. A total of 654 patients underwent at least one insertion procedure. The safety experience in the initial trials in the program indicated that modifications to the procedures were needed to improve procedural safety. Therefore, the size of the safety database collected before modifications to the equipment and procedures do not provide insight into the risks of the current procedures; unfortunately, the Sponsor did not carefully capture the numbers of patients enrolled before and after these changes. Suffice it to say, the numbers of patients who underwent insertions and removals according to the current procedures is not extensive and the understanding of the potential risks of the procedures must be based, in part, on the risks that emerged with Norplant. Further post-marketing collection of information on the procedures and outcomes will be helpful to augment understanding of the risks.
>
> The major safety findings are summarized below. In comparing rates across arms, it is important to note that patients designated as being in a "placebo" arm often received sublingual buprenorphine for part of the time they were participating, making a true placebo comparison difficult. Additionally, in the original clinical trials, many placebo patients discontinued early in the trials, giving less opportunity to report adverse events. Patients designated as "SL

buprenorphine" were enrolled in the open-label comparator arm in Study 806 (no implants) or the double-dummy arm in Study 814 (placebo implants). Patients in the Probuphine arms of the controlled trials were treated with 4 implants initially; some patients in Studies 805 and 806 had a 5th implant added.

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

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

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

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

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

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

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

Outstanding or Unresolved Issues

I concur with the review team that there are no outstanding safety issues that would preclude approval. I also concur with the review team's recommendation that the Applicant be required to conduct a post-marketing clinical study to evaluate the effect of scarring or inflammation at previously implanted sites on the safety of re-implantation/reinsertion into a previously-used site and on the bioavailability of Probuphine and a post-marketing observational study to evaluate insertion-, localization-, and removal-related adverse events associated with Probuphine use, and their sequelae.

4. Advisory Committee Meeting

A meeting of the Psychiatric Drugs Advisory Committee (PDAC) was convened on January 12, 2016. Key issues presented with the intent of getting the panelist's opinion during that advisory committee were:

- Whether the target population—stable patients on lower doses of buprenorphine—is a realistic target that would benefit from Probuphine, and how such patients should be selected.
- What the most clinically-relevant considerations would be in defining a responder to treatment, including what conclusions should be drawn when urine toxicology samples were not provided, when supplemental buprenorphine doses were required, or when patients were lost to follow-up.
- What guidance should be given to the prescriber regarding the use of supplemental buprenorphine doses.
- Whether the proposed training program appeared adequate to ensure the safe insertion and removal of the implants

The following, reproduced from Dr. Winchell's review, summarizes some of the key comments made by the committee members.

> The Committee generally agreed that the consistent finding of non-inferiority across a variety of analyses supported a conclusion that Probuphine was effective in the intended population.
>
> The Committee also generally agreed that the protocol-specified responder definition was not appropriate. They noted that patients who were lost to follow-up should be considered non-responders. They also agreed that use of supplemental buprenorphine in the Probuphine arm on more than one or two occasions could be construed as an indicator that Probuphine was not adequately treating the patient; therefore patients who required ongoing rescue should be adjudicated as non-responders. They recommended that urine samples that were not collected should be assumed to be positive; urine samples that were collected but not analyzed appropriately could be treated as negative if no other indicators of drug use were present. Finally, they generally agreed that, in a stable population, it would be appropriate to adjudicate patients with any evidence of drug use as non-responders.
>
> Regarding the proposed REMS, the Committee expressed some reservations about the adequacy of the training program using a meat model to simulate the insertion procedures, with several participants noting that this might not be sufficient for them as psychiatrists who are not adept at procedures. Some participants advocated for the availability of additional training opportunities or supervised procedures.

The Committee also noted that it would be important for the product's labeling to emphasize that patients should be clinically stable, and not just a pre-specified time period in treatment or time period on a particular dose, prior to commencing treatment with the product. Additionally, the Committee noted that six months of stability would be a minimum time period.

The Committee's vote was 12 to 5 in favor of approval. Dr. Winchell noted in her review "Those voting against included one statistician and the patient representative who identified concerns with the wording of the question, and the consumer representative who provided no

comment. The acting chairman of the committee voted against approval noting concerns with the Applicant's approach to analyzing the data, and one addiction expert voted against approval noting her concerns about the Applicant's responder definition, the use of rescue medication, and the lack of information about how to continue dosing past four treatment cycles. Those voting yes emphasized the need to clearly define the patient population in terms of stability and to make it clear that regular follow-up visits would still be required; they also supported the Division's approach to revising the responder definition."

10. Pediatrics

During the first review cycle, the Applicant had requested a partial waiver for patients between the ages of (b) (4) years of age, and a deferral for patients between the ages of (b) (4) years of age. (b) (4) Therefore, the size of the patient population of treatment-seeking, opioid dependent adolescents would make the conduct of clinical trials infeasible. Although a potential theoretical use of buprenorphine would be in infants exposed to opioids in utero and who may be born with a physiologic dependence to opioids, Probuphine would not be an appropriate therapy due to its invasive nature and lack of dosing flexibility.

Due to these reasons, Division concluded that it would be more appropriate to waive clinical studies in the entire pediatric age range stipulated by PREA. This assessment was presented to the members of the Pediatric Research Committee on April 3, 2013, and they concurred.

(b) (4)

11. Other Relevant Regulatory Issues

Clinical Site Inspections

The Division of Clinical Compliance Evaluation conducted on-site audits of four (of 21) clinical investigator sites, based on site-specific efficacy results (enrollment and effect size) and protocol deviations (rescue medication use and urine sample collection).

The following table, adapted from Dr. Lee's review summarizes the information about the four clinical sites that were inspected.

Clinical Investigator Site	Site Number and Enrollment	Inspection Dates and Outcome
Paul W. Schkolnik, M.D. Maryhaven Institute 1791 Alum Creek Drive Columbus, Ohio	Site 002 6 randomized	Nov 17 – 25, 2015 NAI
John V. Bernard, M.D. Wellness and Research Center 526 Water Street Belvidere, New Jersey	Site 005 29 randomized	Jan 19 – 22, 2016 NAI
Amit K. Vijapura, M.D. 9141 Cypress Green Drive, Suite 1 Jacksonville, Florida	Site 007 26 randomized	Nov 17 – 23, 2015 VAI
James G. Sullivan, M.D. Parkway Medical Center 1160 Huffman Road Birmingham, Alabama	Site 011 20 subjects	Nov 30 – Dec 3, 2015 NAI

NAI = no action indicated (no significant violations)
VAI = voluntary action indicated (minor violations)

Dr. Lee noted the following in the Overall Assessment and Recommendations section of his review:

> No significant GCP deficiencies were observed at all four sites. A Form FDA 483 was issued at Site 007 for deficiencies unlikely to be significant to the study outcome. Study conduct at all inspected sites appeared adequate, including IRB/sponsor oversight of study conduct. All audited data were verifiable among source records, CRFs, and NDA data listings. The data from the four study sites appear reliable as reported in the NDA resubmission.

Risk Evaluation and Mitigation Strategy (REMS)

This product will require the implementation of a REMS. The goals of the proposed REMS are described as follows by the Applicant:

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

The elements of the REMS are a Medication Guide (MG), Elements to Assure Safe Use, Implementation Plan, and a Timetable for Submission of Assessments. The description and

analysis of the proposed REMS is well detailed in the reviews by the Division of Risk Management (DRISK) review team.

Of note, the elements to mitigate the risks are as follows:

- Healthcare providers have particular experience or training, or are specially certified
- Practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients only in certain health care settings
- Each patient using the drug is subject to certain monitoring

The REMS assessment plan must include, but is not limited to, the following:

1. **REMS Program Outreach and Communication**
   a) Number of *Probuphine REMS Prescriber Enrollment forms* sent to prescribers who attempt to order Probuphine or inquire about certification

   b) Number and location of REMS training programs
      i. Number of healthcare providers (HCPs) certified as prescribers, inserters and dually certified to both prescribe and insert at each training program

2. **REMS Program Utilization**
   a) Number of certified HCPs who prescribe
      i. Number of orders per certified prescriber
      ii. Degree, specialty, practice setting, and geographic location
      iii. Number of replacement kit orders shipped.
      iv. Number of times unused implants from replacement kits are returned per certified prescriber.
         1) Number of unused implants from each replacement kit returned.

   b) Number of certified HCPs who insert
      i. Degree, specialty and geographic location
      ii. Number of certified inserters who are re-certified by method of certification (i.e. live training, video)
         1) If recertified by video, number of certified HCP who insert who have operating privileges versus those successfully performing 10 or more procedures

   c) Number of dual-certified HCPs who prescribe and insert
      i. Number of orders per dual-certified prescriber
      ii. Degree, specialty and geographic location
      iii. Number of replacement kit orders shipped and returned per dual-certified prescriber
      iv. Number of dual-certified prescribers that are re-certified by method of certification (i.e. live training, video)
         1) If recertified by video, number of certified HCPs who insert who have operating privileges versus those successfully performing 10 or more procedures

3. REMS Program Infrastructure and Performance

a) Number of non-certified prescribers attempting to prescribe Probuphine and corrective actions

b) Number of orders shipped to non-certified prescribers and corrective actions taken

c) Number of insertions/removals performed by a HCP not certified or dually certified to insert Probuphine and corrective actions taken

d) Summary of results of audits of 10% (or 15, whichever is greater) recertification forms for inserters (beginning at the 24-month assessment)

e) Summary of call center calls; include corrective actions taken for any non-compliance identified through the call center by stakeholder type

f) Number of certified prescribers, inserters, and dual-certified prescribers that have been decertified and a summary of the reasons for decertification

g) Assessment of the distribution and use of the Medication Guide in accordance with 21 CFR 208.24 and the Probuphine REMS Program requirements

h) Report on failures to adhere to distribution requirements, and corrective actions taken to address noncompliance

4. Evaluation of knowledge

a) Healthcare Providers - Results of evaluation of healthcare provider's knowledge of the risk of complications of migration, protrusion, expulsion and nerve damage associated with the insertion and removal of Probuphine, and the risks of accidental overdose, misuse, and abuse if an implant comes out or protrudes from the skin. Results should be stratified by certified prescriber, certified inserter, and dual-certified prescribers

b) Patients – Results of evaluation of patients' knowledge of the risk of complications of migration, protrusion, expulsion, and nerve damage and the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin.

5. Overall REMS evaluation

As required for assessments of an approved REMS under section 505-1(g)(3) the Applicant will include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

Division of Epidemiology II (DEPI II)

The Division of Epidemiology II was consulted to help develop the post-marketing requirement to assess the safety of Probuphine with respect to the assessment of insertion-, localization-, and

removal-related adverse events. Their recommendation was that the Applicant should be required to conduct a prospective descriptive observational cohort study.

Outstanding or Unresolved Issues
There are no outstanding or unresolved regulatory issues that would preclude approval of this application.

12. Labeling

The labeling was reviewed by members of the following review organizations:

- Division of Biometrics II
- Division of Bone, Reproductive, and Urologic Products
- Division of Medical Policy Programs
- Division of Medication Error Prevention and Analysis
- Division of New Drug Quality Assessment III
- Division of Pediatrics and Maternal Health
- Division of Risk Management
- Office of Prescription Drug Promotion

The review team made significant modifications to the package insert, container labels, and carton labeling. The major issues that were addressed were:

1. Placement of a boxed warning in the label, as required whenever a drug product has a REMS. In this case, it contained a warning about the potential adverse consequences associated with the insertion and removal of the implants.
2. Detailed instructions regarding the insertion and removal of the implants.
3. Placement of serial numbers on the kits, in order to permit appropriate documentation of the procedures in the REMS Insertion and Removal Log.
4. Inclusion of language regarding neonatal opioid withdrawal syndrome and medication-assisted treatment for opioid addiction.
5. Guidance on the type of monitoring that should be conducted in patients transferring to Probuphine from a treatment regimen of transmucosal buprenorphine used concomitantly with CYP3A4 inhibitors.
6. Language consistent with the Pregnancy and Lactation Labeling Rule.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Approval.

Risk:Benefit Assessment

As noted by Dr. Winchell and Dr. Skeete in their respective reviews, the data from Study PRO-814 support the conclusion that Probuphine is not unacceptably less effective in maintaining established stability compared to treatment-as-usual in a subset of patients. This subset consists of patients who have been successfully treated and who are clinically stable on daily doses of buprenorphine that are well below the 16 mg/day target dose recommended in

the referenced drug product label. However, these patients will still require appropriate follow-up and monitoring, and possibly the additional supplemental doses of buprenorphine.

Additional benefits of Probuphine treatment include the potential of increased convenience, privacy, and decreased risk of having their medication lost, stolen, or accidentally ingested.

The potential risks of the product are primarily associated with complications associated with the insertion and/or removal of the implants. Ensuring that the clinicians that are performing these procedures are appropriately qualified, as is being proposed in the product's REMS, will help mitigate these risks.

Therefore, I concur with the review team that Applicant has submitted adequate information to support the safety and efficacy of Probuphine when used as proposed in the agreed-upon labeling and REMs.

Recommendation for Postmarketing Risk Management Activities

As noted above, this product will require a REMS.

Recommendation for other Postmarketing Study Requirements

The Applicant will be required to conduct four post-marketing requirements. These requirements and the agreed-upon timelines are identified as follows:

1. A clinical trial to assess the risk of QT prolongation with subdermal buprenorphine.

   Final Protocol Submission: February 2017
   Study/Trial Completion: August 2018
   Final Report Submission: February 2019

2. A clinical trial to evaluate the effect of scarring or inflammation related to a prior implant on the safety of re-implantation/reinsertion, the potential for migration of implants, and the bioavailability of Probuphine when the drug is implanted in a previously used site.

   Final Protocol Submission: November 2016
   Study/Trial Completion: February 2019
   Final Report Submission: August 2019

3. A clinical trial to evaluate the safety, feasibility, and pharmacokinetics of Probuphine implantation at alternate body sites. The trial should also evaluate the safety of other methods of inserting Probuphine into additional locations on the arm.

   Final Protocol Submission: November 2016

Study/Trial Completion: February 2018
Final Report Submission: August 2018

4. A prospective descriptive observational cohort study of insertion-, localization-, and removal-related events and their sequelae associated with Probuphine use.

The data for this study shall be collected from a prospective U.S. registry of Probuphine prescribers and health care providers who performed the insertion and removal procedures and necessary follow-up (e.g., post-operative check-up). Sufficient information shall be collected to enable follow-up of patients and providers through deterministic (e.g., unique identification number on the Probuphine kit) and probabilistic linkage (e.g., patient year of birth, sex, and date of insertion). The insertions that could not be linked to removals shall be reported as loss to follow-up events. The study shall accrue a sufficient sample size to rule out an excess risk of 1.5% or more of clinically significant implant migrations that occur within 6 months of insertion, as determined on removal forms. Clinically significant implant migrations shall include implant migrations greater than 2 cm, implant migration less than 2 cm but of clinical consequence (e.g., associated with nerve damage), and protrusions and expulsions. Annual interim status reports and the final report shall describe the following:

- Numbers of: providers in the study, linked insertion-removal pairs, patients lost to follow-up
- Patient characteristics: for example, age, sex, race/ethnicity, BMI, prior opioid maintenance therapy
- Health care provider characteristics: for example, type of provider (e.g., surgeon), extent of prior experience with Probuphine insertion/removal procedures (e.g., number performed), type of institution (e.g., outpatient)
- Insertion characteristics: for example, site of Probuphine insertion, insertion attempts, number of treatment cycles
- Insertion/removal tools and techniques that differ from marketed tools and techniques
- Insertion-related events, such as:
    - Pain, bruising, scarring, bleeding, infection, nerve damage, altered strength/range of motion, disability
- Localization- and removal-related events, such as:
    - Pain, bruising, scarring, bleeding, infection, nerve damage, altered strength/range of motion, disability
    - Reason for removal (other than completing full treatment cycle)
    - Implant protrusion, expulsion, palpability, damage or tampering (by patient)

- Implant migration; if migration to distant site is identified, document location, sequelae, and intervention (e.g., surgical procedures to remove implants)
  - enumerate implant migrations greater than 2 cm
  - enumerate implant migrations less than 2 cm but of clinical consequence
- Implant fragmentation and documentation of removal of all fragments
- Imaging modalities, if any, used to locate implants (e.g., ultrasound, MRI) prior to removal
- Referral to surgical specialties to complete removal
- Non-localized implants/implants never removed

Draft Protocol Submission: October 2016
Final Protocol Submission: March 2017
Annual Interim Reports: Annually, until final report submission
Study/Trial Completion: May 2021

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

/s/

SWATI A PATWARDHAN
05/25/2016

JUDITH A RACOOSIN on behalf of RIGOBERTO A ROCA
05/25/2016