Probuphine®: A Sub-dermal Buprenorphine Implant for Treating Opioid Dependence

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ABSTRACT SUMMARY
Probuphine®, a novel implantable formulation of buprenorphine using a sustained-release polymer matrix technology has been developed to provide long-term treatment for opioid dependence while minimizing risks of patient noncompliance to daily oral dosing and illicit diversion of medication.

INTRODUCTION
Probuphine is a sub-dermal matchstick-sized implant capable of continuously delivering therapeutic levels of buprenorphine for up to six months with minimal fluctuations in the steady-state plasma concentration. Probuphine offers potential treatment advantages over daily dosed sublingual buprenorphine formulations by ensuring patient compliance, and its subdermal placement greatly reduces the risk of misuse and diversion. Buprenorphine is a mixed partial agonist at the mu opioid receptor and antagonist at the kappa opioid receptor. Due to this mixed agonist-antagonist quality there is a dose ceiling effect to its activity; making it safer to use compared to other opioids like methadone or fentanyl. In the U.S. buprenorphine has replaced methadone as the gold standard in treating opioid dependence, and it is approved for treating acute and chronic pain as well. The Probuphine implant (26 mm long, 2.5 mm diameter) polymeric matrix is composed of ethylene vinyl acetate (EVA), a copolymer approved by FDA for other implant applications, and 80 mg of buprenorphine HCL. Following an initial pulse release of the drug following subdermal implantation, a continuous therapeutic level of buprenorphine is released for over 6 months, avoiding the plasma peaks and troughs observed with sublingual modes of administration. Probuphine was evaluated in multiple nonclinical studies and clinical studies, over 300 human subjects.

Figure 1. Buprenorphine implant, 26mm long and 2.5mm diameter. Each implant contains 80mg of buprenorphine HCL which has been blended and extruded with EVA copolymer.

EXPERIMENTAL METHODS
The nonclinical safety and pharmacokinetics of drug release of Probuphine implants was conducted in beagle dogs. Four cohorts were treated with 2, 8, 16, or 24 Probuphine implants, respectively, which were placed under the skin in the dorsal region with a trocar. Blood samples were collected from the jugular vein at various times for up to 12 months post-implantation. Plasma concentrations of buprenorphine were quantified by liquid chromatography/mass spectrometric bioanalysis (figure 2).

The clinical evaluation of Probuphine consisted of two pivotal double-blind, randomized, placebo-controlled, 6 month phase III studies and multiple open label studies. One pivotal study consisted of a two-arm double-blind randomized, placebo-controlled, 6-month trial conducted at 18 sites in the U.S. One hundred sixty-three adults, diagnosed with opioid dependence were randomized 2:1 to receive Probuphine implants (108 subjects) or placebo implants (55 subjects). The second pivotal study was a three-arm double-blind randomized, placebo-controlled and open-label active study. This was a 6 month confirmatory efficacy and safety study of 287 adults, at 20 sites in the U.S, and compared Probuphine implants versus placebo implants versus sublingual buprenorphine tablets (Suboxone®).

RESULTS AND DISCUSSION
The in-vivo pharmacokinetic study in beagle dogs demonstrated an early, brief pulse of buprenorphine release (within the first week following implantation) in all the treated animals, followed by a slow decrease to steady state release at approximately 6 weeks post-implantation. Steady state BPN plasma, concentrations (Css) were maintained for up to 8 months post-implantation, and were proportional to the number of implants (Figure 2). The use of 8, 16, or 24 Probuphine implants were carried out to measure the safety exposure of these implants, and therefore sought to show up to a 15-fold higher exposure than will be utilized in man. No signs of infection at the sites of treatment were observed in any of the implanted dogs, while minor irritation at the treatment sites and encapsulation of some implants at removal were observed in some dogs. No behavioral adverse effects on long-term buprenorphine administration were found. The clinical studies with Probuphine, monitored patients vital signs, blood, and urine samples for illicit opioid use during the 24 week trial. The primary outcome measure was the percentage of the urine samples that were negative for illicit opioids during the first through 16-week of the trial. This 16-week period was selected because of the interest in examining early-treatment response in the context of this long term
treatment. The secondary outcome measure was assessed as the percentages of the urine samples that were negative for illicit opioids during weeks 17-24. The study demonstrated that Probuphine implants were effective in the treatment of opioid dependence over a 24-week period following implantation. There was good patient retention with 65.7% of subjects who received the Probuphine implants completing 24 weeks of treatment without experiencing craving or withdrawal symptoms that necessitated removal from the study. Additional outcomes measured included the proportion of treatment failures, the proportion of study completers, the patient-report and clinician-report withdrawal scales, a craving scale, and clinician severity and improvement ratings. The assessment protocol also required that study investigators visually inspect the surgical implant location of each participant during each study visit. Levels of plasma buprenorphine were obtained and analyzed from blood samples taken at baseline and monthly thereafter.

Probuphine was clinically and statistically superior to placebo implants in the treatment of opioid-addicted patients and demonstrated non-inferiority to Suboxone, the approved sublingual buprenorphine product for the treatment of opioid addiction. Adverse events were mild to moderate in severity and generally consistent with the patient population and the known safety profile of buprenorphine in all studies. The implant procedure was generally well tolerated in all studies and there was no evidence of implant diversion or misuse.

Probuphine, thus, delivers an efficacious, low level of buprenorphine continuously for at least six months following a single treatment (Figure 3), and offers several advantages over other current formulations of buprenorphine for the treatment of opioid addiction. Through all of the studies, Probuphine delivered continuous, around-the-clock medication which is well suited for treating disorders such as opioid dependence that require strict compliance, and may also prove useful for maintaining stable plasma levels of drugs for treating a variety of long-term disabilities. A long-term delivery system could be a significant improvement in treating chronic diseases by enhancing compliance, reducing adverse effects associated with fluctuating blood levels, providing constant therapeutic drug levels and improving long-term outcome.

CONCLUSION
Probuphine implants for the treatment of opioid dependence offers a steady therapeutic level of buprenorphine for over 6 months following a single treatment that enhances compliance, reduces adverse effects associated with fluctuating blood levels of drug, lowers the risk of misuse of drug and illicit diversion, and can improve the long-term outcome of patients.

REFERENCES

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