

# Titan Pharmaceuticals Presents Phase 3 Data for Probuphine® at the 2008 International Society of Addiction Medicine Congress

## Press Release

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SOUTH SAN FRANCISCO, Calif & CAPE TOWN, South Africa--(BUSINESS WIRE)--Titan Pharmaceuticals, Inc. (AMEX:TTP) today presented detailed data from its positive Phase 3 placebo controlled study of Probuphine in the treatment of opioid addiction. Titan also presented new data from an ongoing open-label Phase 3 trial of Probuphine. Probuphine is a novel, subcutaneous implant formulation of buprenorphine using Titan's ProNeura™ technology to deliver six months of medication after a single administration. These findings were presented today at the 2008 annual meeting for the International Society of Addiction Medicine (ISAM) Congress which began on November 16, 2008 and continues through November 20, 2008 in Cape Town, South Africa.

The data were presented during a special symposium session entitled, "An Implantable, Six-Month, Sustained-Release Formulation of Buprenorphine: Phase 3 Efficacy and Safety Results." The session included three presentations given by leading clinicians and researchers in the field of opioid addiction treatment:

- "Phase 3 Results Evaluating the Safety and Efficacy of Probuphine: a Six-Month, Sustained-Release Formulation of Buprenorphine," Dr. Paul Casadonte, Clinical Associate Professor, Department of Psychiatry, New York University's Langone Medical Center
- "History and Use of Buprenorphine for Opioid Addiction," Dr. Walter Ling, Professor-in-Residence of Psychiatry and Director of the Integrated Substance Abuse Programs (ISAP) at UCLA
- "Pharmacokinetic Analyses of Plasma Buprenorphine in Patients Treated for 6 Months With Probuphine," Dr. Alan Bye, an independent pharmacology expert and consultant to Titan Pharmaceuticals

"We are pleased to have three presentations at the ISAM meeting which discuss these positive Probuphine data supporting the product's potential to be an important advance in the treatment of opioid addiction," said Marc Rubin, M.D., President and CEO of Titan. "We believe that Probuphine can become a treatment option that addresses the growing concerns regarding potential abuse and poor compliance associated with existing treatments. Further, we are encouraged by the positive patient responses seen across these trials and believe that this is indicative of Probuphine's potential to serve unmet needs in the patient and physician communities."

## **PRO-805: A Phase 3 placebo controlled study of Probuphine**

Dr. Casadonte presented detailed results from Titan's positive Phase 3 placebo controlled study of Probuphine in the treatment of opioid addiction. Top-line results for this study were initially released in July 2008. These data indicated that Probuphine showed a clinically and statistically significant difference over placebo by consistently meeting the primary and secondary endpoints as highlighted below:

- Cumulative distribution function of % negative urines:
  - weeks 1-16: Probuphine>placebo; p= 0.0361 (primary endpoint)
  - weeks 17-24: Probuphine>placebo; p= 0.0004

- weeks 1-24: Probuphine>placebo; p= 0.0.0117
- Difference in mean % negative urines:
  - weeks 1-16: Probuphine>placebo; p= 0.0253
  - weeks 17-24: Probuphine>placebo; p= 0.0006
- Treatment retention over 24 weeks: Probuphine>placebo; p< 0.0001
- Patient-rated opioid withdrawal over 24 weeks: Probuphine>placebo; p= 0.0005
- Clinician-rated opioid withdrawal over 24 weeks: Probuphine>placebo; p= 0.0008
- Opioid craving – 24 weeks: Probuphine>placebo; p= 0.0006
- Global severity of opioid addiction:
  - Patient rated: Probuphine>placebo; p=0.0021
  - Physician rated: Probuphine>placebo; p=0.0086

### **PRO-807: An ongoing open-label Phase 3 trial of Probuphine**

Dr. Casadonte also presented interim safety data from Titan’s six-month re-treatment study, where all patients received active Probuphine implants. Approximately 80% of the eligible patients who had completed the placebo controlled study signed informed consent for this re-treatment study and of those, 62 patients have been treated. A total of 26 patients have completed the full six-month re-treatment study at this time. The main objectives of the re-treatment study are to assess the safety and tolerability of Probuphine in patients treated for one year. Interim analysis of the data indicates that there have been no serious adverse events, and that Probuphine is safe and well-tolerated. Adverse events were mild to moderate in severity and generally consistent with the patient population and the known safety profile of buprenorphine.

“Interim analyses of data from PRO-807 are promising and indicate that buprenorphine implants were generally well-tolerated and adverse events were mild to moderate in severity,” stated Dr. Casadonte. “With its novel delivery mechanism, Probuphine can support a greater level of compliance and minimize the potential to divert and misuse this medication. Based upon all of these characteristics, I believe that Probuphine could become a meaningful new treatment option for patients looking to adopt an effective treatment regimen that may be more effectively incorporated into their day-to-day lives.”

### **Additional Data & Analyses Presented**

Dr. Ling presented the pharmacology of buprenorphine and the history of its development as a treatment for opioid addiction. Dr. Ling added, “While the sublingual formulation of buprenorphine has been widely studied and is known to be safe and efficacious, issues with diversion and compliance present challenges for an addiction treatment program. Based upon the clinical data to date, Probuphine has been shown to be a well-tolerated and efficacious treatment. Probuphine’s ability to deliver buprenorphine around the clock and maintain effective non-fluctuating steady-state levels of buprenorphine for six months makes it a very promising potential treatment for opioid addiction.”

Dr. Bye’s presentation examined the characteristics of Titan’s ProNeura long-term delivery technology demonstrated by Probuphine for treating opioid addiction. He reviewed data from the analysis of plasma samples from subjects from the initial clinical pilot study and the Phase 3 study of Probuphine.

Key pharmacokinetic findings include:

- Probuphine delivered buprenorphine continuously to maintain low, non-fluctuating plasma levels of buprenorphine at steady state which was reached within 3-4 weeks, and this was maintained for 6 months
- These pharmacokinetic findings were consistent across nonclinical studies, a pilot clinical study, and a placebo-controlled Phase 3 study

### **About Probuphine**

Probuphine, which is currently in development for the treatment of opioid addiction, is a small solid rod made from a mixture of ethylene-vinyl acetate (EVA) and buprenorphine that is designed to provide continuous, non-fluctuating, long-term therapeutic levels of the drug buprenorphine for six months after a single administration. Buprenorphine, an approved agent for the treatment of opioid addiction, is sold mainly in the form of a daily dosed, sublingually delivered tablet under the brand names Suboxone® (buprenorphine HCl/nalaxone HCl dehydrate) and Subutex® (buprenorphine HCl) with worldwide sales estimated at \$0.5 billion.

### **About Titan Pharmaceuticals**

Titan Pharmaceuticals, Inc. (AMEX: TTP) is focused primarily on the late-stage development and commercialization of Probuphine, which utilizes Titan's proprietary ProNeura long term drug delivery technology, and has demonstrated positive results in Phase 3 testing for treatment of opiate addiction. Products based on ProNeura technology can provide controlled drug release on an outpatient basis over extended periods of up to 6-12 months and may be useful for other potential treatment applications in which conventional treatment is limited by variability in blood drug levels and poor patient compliance. Titan also has two other products, gallium maltolate and DITPA, in earlier stages of development. For more information, please visit the Company's website at [www.titanpharm.com](http://www.titanpharm.com).

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