Zacks Small-Cap Research

June 17, 2011
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Titan Pharmaceuticals, Inc. (TTNP-OTC)

TTNP: Buying Opportunity on Titan Pharma! We Are Still Positive on Phase 3 Outcome.

Current Recommendation	**Outperform**
Prior Recommendation	N/A
Date of Last Change	06/01/2011
Current Price (06/17/11)	$1.54
Target Price	**$4.50**

FULL REPORT

We believe the new today on the statistical analysis plan (SAP) guidance from the FDA is a minor event with only a minimal delay. We do not believe this will change the outcome of the confirmatory phase 3 trial. We were optimistic when we initiated coverage of Titan two weeks at $1.98, so today at $1.54 we like it even more.

Our valuation incorporates a sum-of-parts (NPV) analysis on the royalties from Fanapt ($1 per share) and the risk-adjusted market potential for Probuphine at this stage in its development ($3.50 per share). We are making an aggressive call to buy Titan shares ahead of the data and the many catalysts we see coming later in 2011.

SUMMARY DATA

52-Week High	**$2.16**
52-Week Low	**$0.87**
One-Year Return (%)	**86.11**
Beta	**10.76**
Average Daily Volume (sh)	**299,592**
Shares Outstanding (mil)	**59**
Market Capitalization ($mil)	**$119**
Short Interest Ratio (days)	**0.25**
Institutional Ownership (%)	**2**
Insider Ownership (%)	**15**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2011 Estimate	**N/A**
P/E using 2012 Estimate	**N/A**
Zacks Rank	**1**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2010	2.4 A	1.3 A	3.6 A	2.7 A	10.1 A
2011	0.9 A	1.5 E	1.6 E	1.8 E	5.8 E
2012					27.6 E
2013					45.2 E

Earnings per Share
(EPS is operating earnings before non-recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2010	-$0.01 A	-$0.03 A	-$0.01 A	-$0.05 E	-$0.09 E
2011	-$0.08 A	-$0.06 E	-$0.04 E	-$0.03 E	-$0.21 E
2012					$0.23 E
2013					$0.40 E

Zacks Projected EPS Growth Rate - Next 4 Years % **N/A**

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WHAT'S NEW

FDA Guidance On Statistical Analysis Plan

This morning, Titan Pharmaceuticals announced that the U.S. FDA has provided the company with a revised protocol for the statistical analysis plan (SAP) to analyst the confirmatory phase 3 trial, PRO-806. The change in the SAP will cause Titan to miss its previous guidance of "data in June 2011" by several weeks.

Titan noted that all clinical sites have completed in PRO-806 and the blinded data set is ready for analysis. Titan has not unblinded the database nor analyzed any findings of PRO-806, and will not do so until final agreement on the SAP has been reached with the FDA.

…A Little History…

The SAP for the confirmatory phase 3 study of Probuphine was submitted to the FDA in the Q3-2010. It included statistical analyses similar to those previously agreed upon with the FDA and performed in the first controlled phase 3 study, PRO-805 (results on page-8 of this report). As a reminder, the PRO-805 study showed a clinically and statistically significant difference over placebo in illicit opioid use as measured by urine testing performed three times per week, for the entire duration of the 6 month treatment (p=0.0117).

The statistical analysis was an evaluation of the Cumulative Distribution Function (CDF) of the percent negative urines analyzed using the Wilcoxon Rank Sum Test conducted twice, specifically, the primary endpoint compared the CDF of percent negative urines for weeks 1-16 (p=0.0361) and the key secondary endpoint compared the CDF of the percent negative urine samples for weeks 17-24 (p=0.0004).

In late March 2011, Titan received comments from the FDA on the study protocol as a whole that included a comment on the primary analysis which needed further clarification. Following this letter, Titan immediately requested a meeting with the FDA to obtain further clarification. In early May 2011, Titan and FDA met via teleconference to clarify the letter and come to an understanding on the type of additional analysis necessary. Our understanding is that the FDA may be interested in seeing a composite endpoint that includes some of the secondary analysis, including treatment retention, patient-reported opioid withdrawal, and patient-reported opioid use, merged into the primary urine analysis endpoint.

Titan completed this work and submitted the revised SAP to the FDA in May 2011, which included the SAP as an additional secondary endpoint. Titan also provided to the FDA an analysis conducted retrospectively using the new SAP on the data from PRO-805. The data supported the previously reported positive results.

On June 16, 2011, Titan received a letter from the FDA essentially agreeing with the new proposed SAP methodology, but the FDA noted they would like to see this as part of the primary endpoint analysis. Titan is seeking a meeting with the FDA to obtain clarity regarding their request and to finalize the SAP so they can get onto analyzing PRO-806 expeditiously.

We expect an update from management following this next (telephone) meeting with the FDA. We believe this meeting should take place in the next two weeks, and top-line data from PRO-806 should become available in August 2011.

Buying Opportunity

We believe this is a minor event with only a minimal delay. We do not believe this will change the outcome of the confirmatory phase 3 trial. We were optimistic when we initiated coverage of Titan two weeks at $1.98, so today at $1.54 we like it even more.

OVERVIEW

Titan Pharmaceuticals, Inc is a biopharmaceutical company focused in the development of products for the treatment of central nervous system (CNS) diseases. Titan's first out licensed product, Fanapt (iloperidone) is an atypical antipsychotic approved in the U.S. in May 2009 for the treatment of schizophrenia in adult patients. It is currently marketed in the U.S. by Novartis Pharma, AG, and Titan is entitled to receive 8-10% of global annual sales as royalty revenue for the term of the licensed patents. Titan's second product, Probuphine, is nearing completion of the Phase 3 clinical development program in the treatment of opioid addiction. Probuphine is a novel, subcutaneous implant formulation of buprenorphine designed to deliver six months of medication following a single treatment. This product has already demonstrated strong positive results in the first controlled Phase 3 study for the treatment of opioid addiction. The confirmatory Phase 3 study is currently being conducted at 20 sites in the U.S., and the results of this study are expected in June 2011.



Fanapt

Fanapt (iloperidone) is an atypical antipsychotic (mixed dopamine D2 / serotonin 5HT2A receptor antagonist) approved by the U.S. FDA on May 6, 2009 for the treatment of schizophrenia. The commercialization rights to Fanapt in the U.S. and Canada have been acquired by Novartis AG. The product is currently available (launched in the first quarter 2010) in an oral tablet, and work continues on a long-acting injectable depot formulation.

Fanapt competes in the highly competitive atypical antipsychotic market, going up against mega-blockbuster drugs such as J&J's Risperdal (risperidone) and Lilly's Zyprexa (olanzapine). Both these drugs are now available as generics. Other branded atypicals such as Seroquel (quetiapine), Geodon (ziprasidone), and Abilify (aripiprazole) also produce sales in excess of $1 billion, but will also lose exclusivity shortly. There are an estimated 25 million schizophrenics in the world, about 2.5 million of which are in the U.S. The total branded atypical antipsychotic market eclipsed $16 billion worldwide in 2010, about half of which we estimate was sales for schizophrenia. Yet, despite this massive number, atypicals carry significant side effects and tolerability issues. The class is associated with weight gain, hyperglycemia, and sexual dysfunction, and potentially serious metabolic, cardiovascular, and neurological side effects such as stroke, diabetes, dystonia, akathisia, and tardive dyskinesia.

Fanapt's unique binding profile to dopamine and serotonin receptors provides a highly differentiated treatment for patients suffering from schizophrenia. Clinical studies show reduced incidence of extrapyramidal symptoms and weight gain. The product is generally well tolerated up to 32 mg per day, with the standard therapeutic doses at 12 mg and 24 mg per day. Additionally, schizophrenics often switch atypicals several times over the course of a few years, even trying combinations of products together. Fanapt could even see use off-label in bipolar or other CNS disorders. Therefore, despite the stiff competition from blockbuster generics, we believe the opportunity exists for Novartis to capture niche market share before the patent expires in 2017.

Titan acquired Fanapt from Hoechst Marion in 1997, then turned around and out-licensed worldwide development and commercialization rights to Novartis AG in 1998, in return for milestones and royalties on sales. Vanda subsequently acquired the development rights from Novartis in 2004, and licensed U.S and Canadian rights back to Novartis in 2009. Titan is entitled to receive royalties on global net sales of Fanapt equal to 8% on annual net sales up to $200 million, and 10% on annual net sales above $200 million for the life of the licensed patents (April 2017 with pediatric extension). Titan Pharmaceuticals incurs no ongoing expenses associated with its royalty, although Titan has agreed to pay Deerfield Management 2.5% (of net sales) in connection with a $20 million credit facility financing completed in March 2011.

...Royalties Set To Grow In 2011…

Novartis reported sales of Fanapt of $31.4 million in 2010, the majority of which came in the first quarter 2010 on inventory stocking at wholesalers. The total royalty payment to Titan in 2010 was $2.5 million. Fanapt sales in the first quarter 2011 were $9.0 million, resulting in a $0.7 million royalty payment to Titan. Based on comments made by Vanda on their first quarter conference call, we expect Fanapt sales to accelerate throughout 2011 now that the majority of the initial inventory stock has been worked through. Novartis is still running patient assistance programs that will keep reported sales below actual IMS prescription data, but we believe the trend is clearly improving and sales should start to track end-user demand by the end of 2011.

We forecast sales in 2011 will be roughly $57 million, which will provide $4.6 million in cash to Titan. The product provides non-dilutive cash that helps Titan reduce operating burn and fund the ongoing phase 3 program with Probuphine, as well as fund general corporate expenses.

...What's Fanapt Worth…

We see Fanapt peak sales around $250 million with the current oral formulation. Assuming 8% royalty on these sales to the patent expiration in April 2017, with 2.5% going to Deerfield for the next 5 years, and a 10% discount rate, we see the franchise worth $59 million to Titan. Based on 59.3 million shares outstanding, Fanapt alone is worth about $1 per share. We note the opportunity exists for Titan to monetize the remaining portion of this royalty later in 2011 or 2012. As a reminder, in March 2011, Titan secured $20 million from Deerfield at 8.5% interest rate + 2.5% of the net Fanapt sales royalty payment. Assuming sales of Fanapt do not eclipse $200 million until 2015 or beyond, Titan has the potential to monetize the remaining net 5.5% royalty payment on Fanapt sales at Novartis for an estimated $30 to 40 million in cash. We see upside to the Fanapt royalty value if Novartis can gain approval for a long-acting injectable formulation of iloperidone. Phase 3 trials are expected to start on this formulation in 2012.

Probuphine

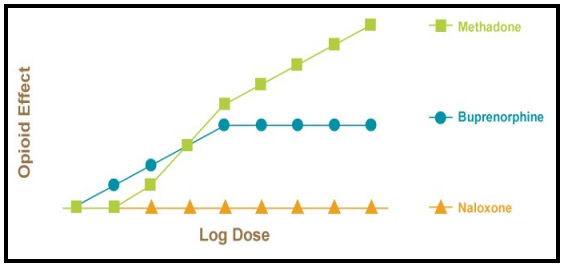
Probuphine is Titan's novel, subcutaneous, implant formulation designed using its ProNeura technology to deliver six months of buprenorphine.

…Background on buprenorphine…

Buprenorphine is a synthetic derivative of opium, chemically similar to both morphine and codeine, but has stimulatory rather than depressant effects. Buprenorphine is 25-50X more potent than morphine and is sometimes used recreationally by insufflations (crushing and inhaling the powder).

Buprenorphine is commonly used to treat addiction to heroin, and has proven superior in its efficacy and convenience to methadone. Withdrawal from buprenorphine after short-term use is generally far milder than other potent opioids, but can have a longer duration of abuse. The drug has a pharmacologic ceiling effect, which provides an increased safety margin when compared to methadone. As a result, the drug is now generally recognized as the gold standard for the treatment of opioid addiction. There are an estimated 3.7 million people addicted to opioids in the U.S., over 80% of which are prescription drugs.

	U.S.	EU
All Opioid Addiction	**3.7M**	**1.8M**
Heroin	0.6M	1.6M
Prescription Drugs	3.1M	0.2M



The product was first marketed in 1980 by British firm, Reckitt & Colman as an analgesic, available as Temgesic 0.2 mg sublingual tablets, and as Buprenex in a 0.3 mg/ml injectable formulation. In October 2002, the U.S. FDA approved Subutex as high-dose (2 mg & 8 mg) sublingual pill preparations indicated for detoxification and long-term replacement therapy in opioid dependency. As a result, the drug is now predominantly used for this purpose. Approval in France first came in 1997, and has since followed to the majority of the EU. Buprenorphine is a Schedule III controlled substance under the United Nations' Convention on Psychotropic Substances.

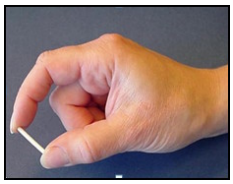
In October 2002, the U.S. FDA also approved Suboxone, a novel formulation of buprenorphine and naloxone, to increase the deterrence of abuse through intravenous injection. Naloxone is an opioid antagonist that blocks the high or euphoric effects for opioids such as heroine that leads to withdrawal symptoms. In October 2009, the FDA approved a generic preparation of 2 mg and 8 mg sublingual dosages of buprenorphine. Demand was so high that pharmacies began to run out of supply and Roxane Labs, the first generic filer, was unable to meet demand. In April 2010, the FDA approved a second supplier in Teva Pharmaceutical. Reckitt is now marketing a Suboxone Film, approved in August 2010, to counter generic the pending availability to the sublingual tablet.

In 2001, Grunenthal introduced Transtec (buprenorphine transdermal patch) in Europe for the treatment of chronic pain. The product is available as a 35, 52.5 and 70 ug (micrograms) per hour transdermal patches that deliver the dose over ninety-six hours. It is also used for the treatment of moderate to severe cancer pain and severe non-cancer pain not responding to non-opioids. Purdue Pharma markets Butrans in the U.S., a 5, 10, and 20 ug, 7-day transdermal patch for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. A similar transdermal product is marketed by collaboration between Mundipharma and Grunenthal in Australia under the name Norspan. We note that buprenorphine is not administered orally due to very high first-pass metabolism. The transdermal patch products can typically be worn for 3 to 7 days.

BioDelivery Sciences is currently in phase 3 trials with BEMA buprenorphine. The company's BEMA technology utilizes a small, bioerodible polymer film for application to the mucosal membranes (inner lining of cheek). BEMA films were designed to rapidly deliver a dose of drug across the mucous membranes for time sensitive conditions or to facilitate administration of drugs with poor oral (pill) absorption. BEMA buprenorphine is being designed to eliminate abuse potential by crushing sublingual tablets, a similar concept to Titan's Probuphine. However, BDSI's BEMA product requires daily dosing whereas Probuphine is a six month implant.

…ProNeura Technology…

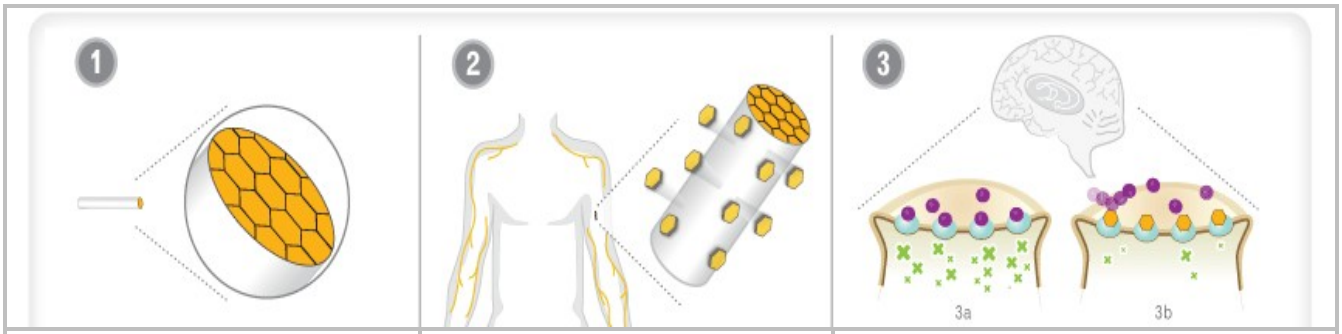
ProNeura is a novel, implantable delivery system technology Titan has exclusively licensed from the Massachusetts Institute of Technology (MIT) to be used in developing products for the treatment of chronic conditions where maintaining consistent and stable, round the clock blood levels of a drug can benefit the patient and improve medical outcomes. The technology is designed to eliminate the peaks and troughs associated with daily oral / sublingual and injectable dosing.



Probuphine (buprenorphine hydrochloride + ethylene vinyl acetate) is a polymeric matrix composed of inert biocompatible copolymer ethylene vinyl acetate (EVA) and the active ingredient buprenorphine HCl in the shape of match-stick sized implants (26 mm long x 2.5 mm diameter) that are implanted subcutaneously in the upper arm in a simple 15-20 minute office procedure.

When opioids such as oxycodone or heroin attach to the mu opioid receptor in the brain, dopamine is released, which results in pleasurable feelings or euphoria. However, in patients with opioid addiction, once the opioid exits the mu receptor, they begin to experience withdrawal symptoms and have drug “cravings”.

…How Probuphine Works…

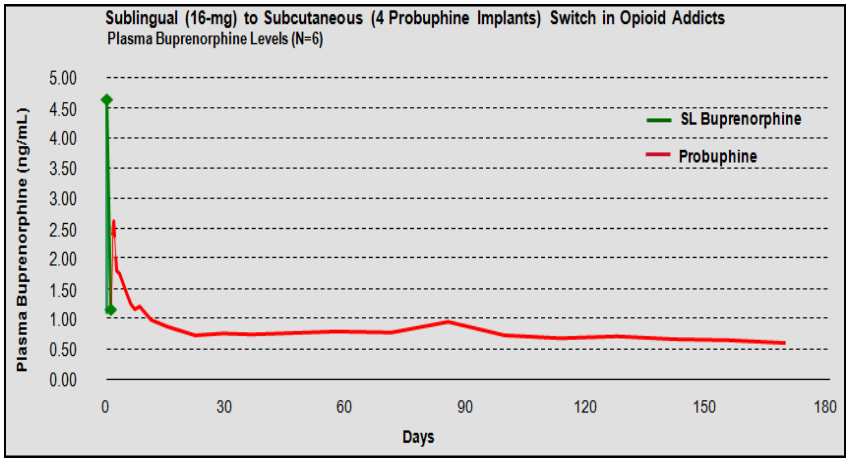


Probuphine is a subdermal implant of buprenorphine HCl, embedded with an EVA polymer matrix. The product provides discrete, long-term delivery of buprenorphine.	Probuphine is designed to release sustained buprenorphine continuously into the circulating blood in patients with Opioid addiction for up to six months.	Buprenorphine is a partial mu opioid receptor agonist/antagonist that binds tightly to the receptor in the brain, blocking other opioids from attaching to them in an attempt to reduce addictive behavior and cravings.

…Probuphine Advantages…

We see several advantages of Probuphine over the standard 16 mg per day sublingual formulation found in Subutex and Suboxone, two drugs with cumulatively over $1.2 billion in global sales, roughly $1 billion of which is in the U.S.

- ✓ Convenient six month dosing
- ✓ Improved compliance
- ✓ Reduce diversion
- ✓ Constant blood plasma levels
- ✓ No “peaks” and “troughs”
- ✓ Lower total opioid exposure
- ✓ Low withdrawal potential



…Early-Stage & Phase 2 Data…

Titan commenced clinical development of Probuphine in 2003 with a phase 2 trial in Australia. This was followed by the acceptance of the U.S. investigational new drug (IND) application in 2005. Probuphine is following a 505(b)(2) pathway that relies heavily on previous safety data on buprenorphine. Early-stage programs were designed to show bioavailability and the pharmacokinetic profile of the drug. Because of the extensive non-clinical and clinical safety database supporting the use of buprenorphine in the treatment of opioid addiction and chronic pain, as well as the previous pharmacokinetic and toxicology studies with ProNeura, the FDA has confirmed that additional non-clinical studies are not necessary in support of an NDA for Probuphine.

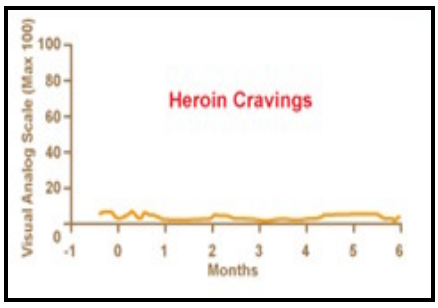
…Strong Historic Safety Profile…

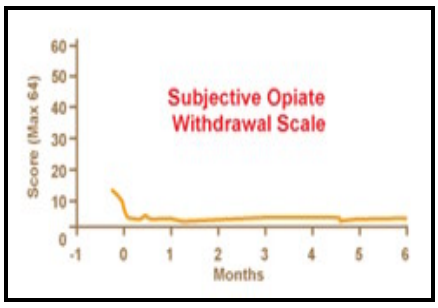
Opioid	Respiratory Depression		
	Increased Arterial $PaCO_2$, ED_{50} (mg/kg)		
	30%	55%	Safety Margin
Buprenorphine*	0.18	6.65	x37
Fentanyl	0.035	0.061	x2
Oxycodone	0.95	3.81	x4
*Ceiling effect			

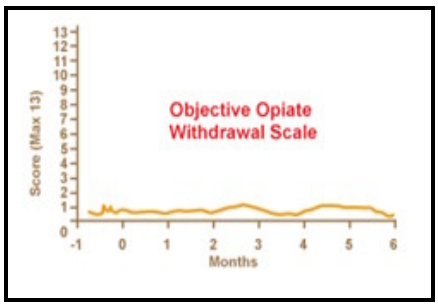
Opioid	Abuse Frequencies Among Primary Prescription Opioid Abusers
Buprenorphine	1%
Oxycodone	79%
Hydrocodone	67%
Methadone	40%
Morphine	29%
Hydromorphone	16%
Heroin	13%
Fentanyl	9%

Titan's phase 2 study evaluated treatment with 2 or 4 implants in 12 heroin addicted patients who had been maintained on sublingual buprenorphine therapy. These patients were switched to treatment with Probuphine for 6 months. The data demonstrated that stable, non-fluctuating, low level plasma buprenorphine concentrations were maintained for up to 6 months after implantation of Probuphine. In the opinion of the Investigators, all patients were considered to be successfully treated with Probuphine for the entire duration of 6 months, as demonstrated by the measurement of opioid craving and withdrawal symptoms of these patients. Probuphine was well-tolerated with minor, transient AEs observed following implantation and removal procedures. Other AEs observed were consistent with the known effects of buprenorphine.

…Phase 2 Data…





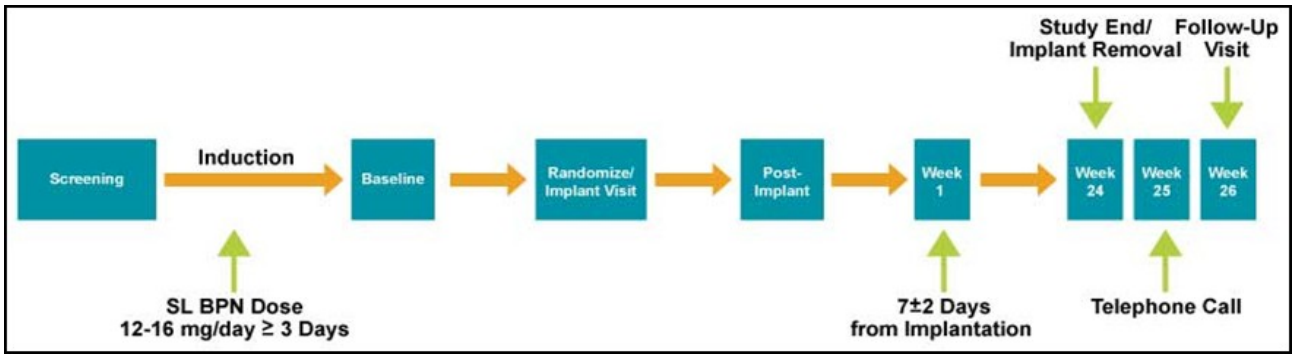


Following the completion of the phase 2 study in Australia, Titan began discussions with the U.S. FDA focusing on the phase 3 program. The trial would take place in patients first diagnosed with opioid addiction and initially treated for a brief period (3-7 days) with sublingual buprenorphine and maintained at a dose of 12-16 mg/day. The FDA requested 2 placebo controlled studies to support efficacy along with a safety data base of 500 patients treated for 6 months and 100 patients treated for a year to be included in the new drug application (NDA).

…First Phase 3 Trial…

Titan successfully completed the first phase 3 study (Study Pro-805) and presented the data at U.S. and international scientific meetings held during 2008 and 2009. Pro-805 was a placebo-controlled, multi-center study which meets the FDA requirements, and incorporates rescue therapy with sublingual buprenorphine for all patients if required (as determined by the physician) with predefined criteria for treatment failure as defined in the protocol. A total of 163 subjects (2-1 randomization) from 18 clinical sites all in the U.S. participated in the program.

…Pro-805 Design…



In this study, Probuphine showed a clinically and statistically significant difference over placebo in illicit opioid use as measured by urine testing performed three times per week, for the entire duration of the 6 month treatment (p=0.0117). As agreed with the FDA, the statistical analysis was an evaluation of the Cumulative Distribution Function (CDF) of the percent negative urines analyzed using the Wilcoxon Rank Sum Test conducted twice, specifically, the primary endpoint compared the CDF of percent negative urines for weeks 1-16 (p=0.0361) and the key secondary endpoint compared the CDF of the percent negative urine samples for weeks 17-24 (p=0.0004).

We note that approximately 66% of the Probuphine patients completed the study vs. only 31% on the placebo. There is often a mixed bag of reasons why patients discontinue, from lack of response to such a great response that patients opted out of the return visits prior to the trials completion. We think it is important to note, however, that there were no treatment failures in the test group, vs. approximately 31% on the placebo. We believe this evaluation demonstrates the effectiveness of Probuphine compared to placebo for the entire treatment period, as well as emphasizes that patients who are compliant to treatment with Probuphine show even better results (compared to placebo) over time.

Treatment retention (24 weeks)	✓ p < 0.0001
Patient-rated opioid withdrawal (24 weeks)	✓ p = 0.0005
Clinician-rated opioid withdrawal (24 weeks)	✓ p = 0.0008
Opioid craving (24 weeks)	✓ p = 0.0006
Global Severity of Opioid Addiction *(Patient Rated)* (24 weeks)	✓ p < 0.0021
Global Severity of Opioid Addiction *(Physician Rated)* (24 weeks)	✓ p < 0.0086

Additional secondary analysis demonstrated things like, comparison of the mean percent negative urines, retention in treatment, patient and clinician opioid withdrawal, opioid craving, and patient and clinician rated improvement and disease severity all showed highly statistically significant differences in favor of Probuphine.

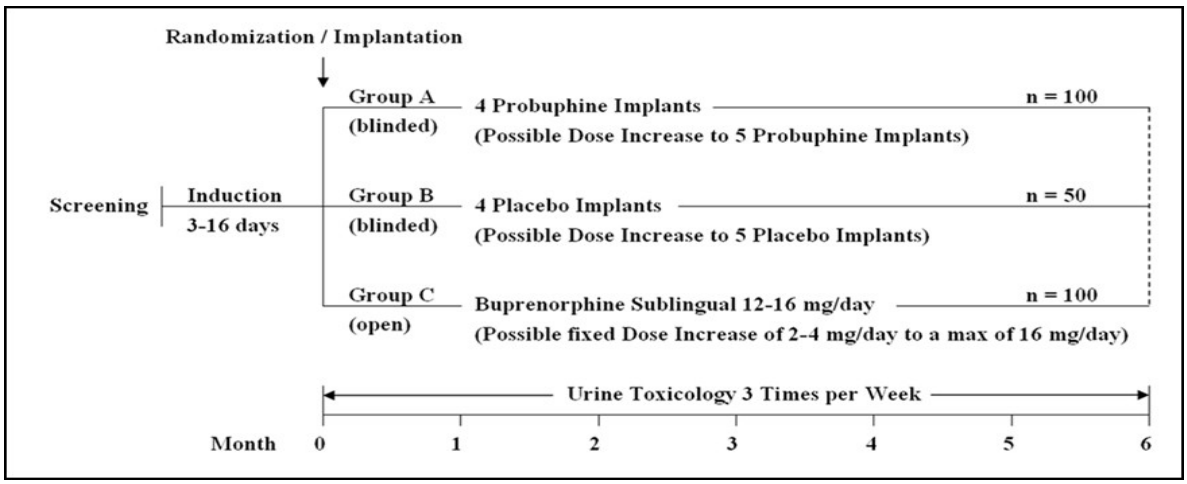
We believe this emphasizes the clear effectiveness of the product, and should help drive sales in the real-world setting. Safety parameters including adverse events, vital signs, and clinical laboratory testing demonstrated that Probuphine was generally well tolerated in this patient population. Data from this study has been published in the Journal of American Medical Association (JAMA) in October 2010.

Following completion of the Pro-805 program, patients were eligible to enroll into a six-month, open-label, multi-center retreatment trial, dubbed Pro-807. This trial was completed in the second quarter 2009. We note that 70% of the eligible test subjects from Pro-805 elected to participate in the open-label safety extension. Approximately 74% of these patients completed the 6 month follow-up. Results show that Probuphine was safe and well-tolerated. During Pro-805 and Pro-807, implant insertion and removal procedures were safe and well-tolerated. Results from these studies have been presented at the American Society of Addiction Medicine (ASAM), the California Society of Addiction Medicine (CSAM), and the American College of Neuropsychopharmacology (ACNP) meeting all in 2009.

…Second Phase 3 Trial…

Titan is currently conducting a second confirmatory phase 3 trial on Probuphine, dubbed Pro-806. A total of 286 subjects have been enrolled in a 2-1-2 randomization at approximately 20 sites around the U.S. The third arm includes an open-label active comparator of sublingual 12-16 mg buprenorphine (Suboxone). The goal of including this arm is to show an overall lower drug exposure that may reduce systemic adverse events, improve retention and compliance, and show non-inferiority in efficacy and patient satisfaction. It also works to satisfy European regulatory authorities where active comparators are required prior to approval.

…Pro-806 Design…

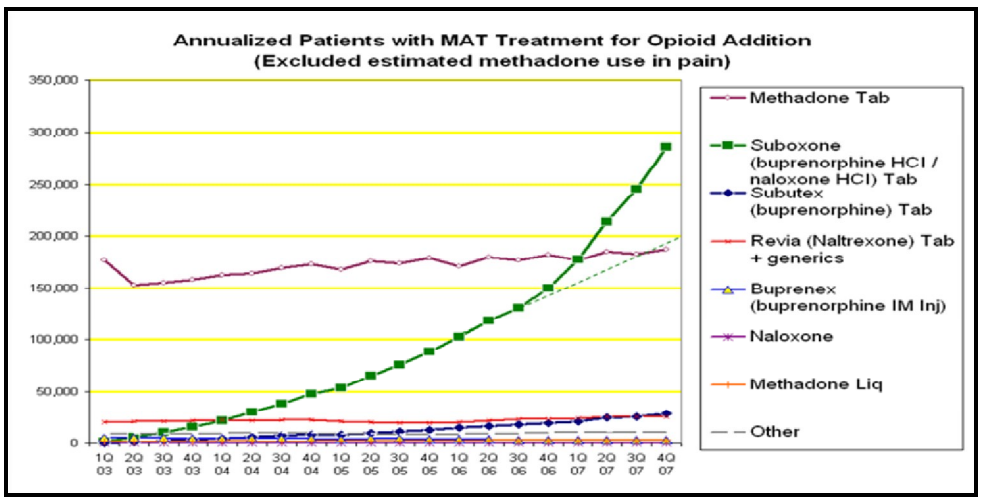


The trial is in progress, with data expected in August 2011. Titan was awarded a $7.6M grant by the National Institutes of Health (NIH) in support of this confirmatory study, which will complete the efficacy evaluation requested by the FDA. This grant covers about half of the expenses and it is being administered by the National Institute on Drug Addiction (NIDA). Clinical development plans also include a second open-label study similar to the Pro-807 program, dubbed Pro-811. Pro-811 has completed enrollment (n around 75) and data is expected late in 2011.

We expect Titan to meet with the U.S. FDA to discuss the entire phase 3 program in the fourth quarter 2011. We believe if all is successful, Titan will be in position to file the NDA on Probuphine around the first quarter 2012. This puts potential regulatory action on Probuphine early 2013.

…Market Potential…

Sublingual buprenorphine sales are estimated to be over $1 billion in the U.S. As noted above, we see Probuphine as having several key advantages over Subutex and Suboxone. These include a convenient six month dosing, improved compliance, a constant blood plasma levels with no “peaks” and “troughs”, and low withdrawal potential.



Opioid addiction is a major health and social issue, especially in the U.S. An estimated 7 million people worldwide, nearly 4 million of which are in the U.S., are abusing or addicted to opioids. In the U.S. alone, opioid abuse has increased 140% from 1992 to 2003. It's a $10+ billion burden to the U.S. healthcare market.

We note the number of patients in the U.S. receiving methadone treatment in the last several years has remained fairly constant at about 200,000, whereas the number of patients in the U.S. receiving buprenorphine has grown to over 500,000 in 2010. It is clear the market is shifting from methadone to buprenorphine thanks to its improved characteristics. We believe Titan's Probuphine can capture conservatively 20% of the market from the sublingual formulation. We also believe that Titan can charge a premium price to oral Suboxone and Suboxone film, both which cost around $4,000 for a six month treatment, because of the superior characteristics of the drug. Probuphine is easily a $500 million opportunity in our view.

We note there is upside to this figure if Probuphine is used for the treatment of chronic pain. Millions of patients require opioids for chronic pain, including around 1 million patients for back pain, 3 million for arthritis pain, and almost a million for cancer pain and breakthrough cancer pain. Chronic pain is an enormous market with sales in excess of $5 billion per year in the U.S. alone. Key issues remain with current therapies for chronic pain, including insufficient pain control, intolerable side effects, the need for repetitive dosing, poor safety, diversion, addiction, under treatment, and physician liability.

As noted above, we believe that Probuphine could address many of these issues. Buprenorphine is an established and approved analgesic for the treatment of acute and chronic pain. We estimate approximately 20% of buprenorphine sales are for chronic pain vs. opioid addiction. The drug is approximately 25-50X more potent than morphine, while also having a pharmacologic ceiling effect that provides an increased safety margin. Buprenorphine is available as a transdermal patch formulation (3-7 days) approved for treatment of chronic pain. We expect that Titan, or it's commercialization partner, will seek to conduct a phase 3 program in chronic pain following the U.S. FDA's approval in opioid addiction.

…Intellectual Property & Manufacturing…

Titan has an exclusive worldwide license from the Massachusetts Institute of Technology to patents covering this implant technology that expire during 2010 through 2014. In June 2003, Titan filed a method of use patent application for Probuphine with claims covering opioid addiction and chronic pain in the US and other regions of the world. A patent was issued in the US in June 2010 for claims related to treatment of opioid addiction which will expire in April 2024. Patents have been issued in Australia, India, Mexico and New Zealand as well, while prosecution of this patent application in other countries continues, including the application in the US for claims covering treatment of chronic pain. At time of launch market exclusivity for 10 years is also anticipated in the EU. Titan will owe a small royalty (2%) to MIT on global sales of the product until the MIT patents expire in 2014.

Titan uses a proprietary, elegant and simple manufacturing procedure to produce Probuphine. Titan employs contract manufacturing services of a large U.S. based company specializing in this area. The buprenorphine API is sourced from a fully licensed, GMP compliant, drug substance manufacturer that meets all necessary specifications. Back-up API sources have also been identified. Titan has acquired sufficient GMP supply of ethylene vinyl acetate to meet clinical and initial commercial requirements, and is also qualifying a proprietary source of GMP supply of this material. The company plans to use the current Contract Manufacturing Organization (CMO) for future clinical and commercial production of Probuphine. The CMO has been audited for GMP compliance relative to both FDA and EMEA requirements, and they are registered as a controlled substance manufacturer with the Drug Enforcement Agency (DEA) which is a requirement for handling of buprenorphine. Product stability studies currently support a 30+ month shelf life at room temperature prior to use in treatment. We estimate the cost of goods sold as a fraction of revenues is expected to be a high single digit percentage, which will be covered by Titan's commercialization partner.

…The Ideal Partner…

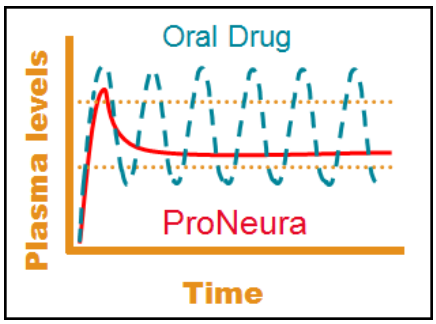
As noted above, we believe that Probuphine is a $500+ million product. Upside exists if management can gain approval outside the U.S. We believe the ongoing phase 3 Pro-806 program will qualify as a pivotal registration study in for European registration purposes, and that only minor safety follow-up studies are necessary before Titan may look to file in the EU. In our view, the ideal time to partner Probuphine is after the pre-NDA meeting in the fourth quarter 2011 and before the actual NDA filing in the Q1-2012. This allows potential partners time to review all the phase 3 data and see the correspondence with the FDA on the NDA filing, while still being able to participate in the actual preparation of the application.

At this point it is difficult to say whether Titan will form one global commercialization partner or look to strike regional alliances. Regional deals may make more sense given differences in how opioid addiction is treated in the U.S. vs. the EU, as well as physician comfort with implantable technology like Titan's ProNeura. Either way, we except a deal for the U.S. and Canadian rights to the drug will come in the fourth quarter 2011. We believe Titan is looking for a partner with a strong commercial presence in addiction medicine, chronic pain, or specialty CNS disorders.

An upfront payment on Probuphine could bring significant cash to Titan. Management will be looking for upfront cash, along with regulatory and sales-related milestones, and royalties on worldwide sales. Probuphine should be a very profitable drug for Titan's partner. Gross margin should be above 90%. Roughly 80% of the market can be effectively targeted by a small sales force of only 40-50 representatives. We think management will look for a royalty rate in the twenties, which should allow Titan to become profitable shortly after the Probuphine launch.

Parkinson's Program

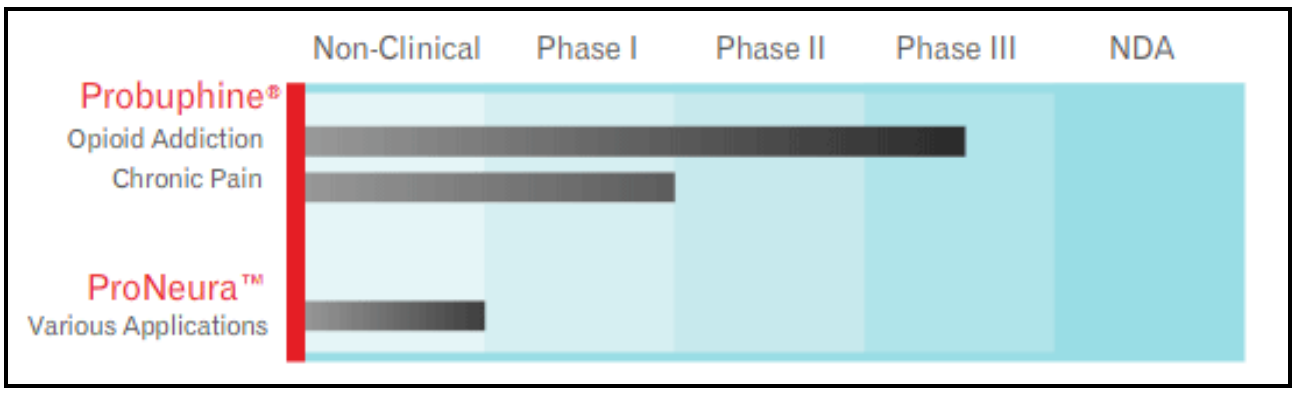
In August 2010, Titan was awarded a $0.5 million grant by the NIH under the Small Business Innovation Research (SBIR) program to conduct non-clinical studies in a model of Parkinson's disease using previously approved dopamine agonists and the ProNeura drug delivery technology. ProNeura has the potential to be used in developing products for the treatment of other chronic conditions where maintaining stable, round the clock blood levels of a drug can benefit the patient and improve medical outcomes. This could be the case in the treatment of Parkinson's disease were short-acting drugs like oral dopamine agonists required dosing several times per day, potentially as often as every 4 hours. This is a major convenience and compliance issue for Parkinson's patients, especially at night when the patient is sleeping an unable to dose for 6 to 8 hours.



Use of ProNeura should smooth out blood level fluctuations and achieve more consistent efficacy, as well as reduce dosing frequency. Maintaining constant blood levels of dopamine agonists could result in a reduction of side effects (dyskinesia, uncontrolled movements when levels are too high) and symptoms (akinesia, lack of initiation of movement when levels are too low) that are caused by current therapy.

The non-clinical studies are in progress and results are expected by year end 2011. Titan recognized approximately $42,000 in revenues related to this grant during 2010.

PIPELINE



Source: Titan Pharmaceuticals, Inc.

MANAGEMENT

Marc Rubin, M.D. – Executive Chairman

Dr. Rubin was appointed Executive Chairman in May 2009. Previously, Dr. Rubin has served as Titan Pharmaceutical's President and Chief Executive since October 2007, and. has been a Director of Titan Pharmaceuticals since November 2007. Until February 2007, Dr. Rubin served as Head of Global Research and Development for Bayer Schering Pharma, as well as a member of the Executive Committee of Bayer Healthcare and the Board of Management of Bayer Schering Pharma. Prior to the merger of Bayer Pharmaceuticals and Schering AG in June 2006, Dr. Rubin was a member of the Executive Board of Schering AG since joining such company in October 2003, as well as Chairman of Schering Berlin Inc. and President of Berlex Pharmaceuticals, a division of Schering AG. From 1990 until August 2003, Dr. Rubin was employed by GlaxoSmithKline where he held positions of responsibility in global clinical and commercial development overseeing programs in the United States, Europe, Asia and Latin America. From 2001 through 2003, he was Senior Vice President of Global Clinical Pharmacology & Discovery Medicine. Dr. Rubin holds an M.D. from Cornell University Medical College. Dr. Rubin currently serves on the Board of Directors of Curis, Inc.

Sunil Bhonsle, MBA – President, Secretary

Mr. Bhonsle was appointed as President in May 2009. Previously, Mr. Bhonsle has served as Titan Pharmaceutical's Executive Vice President and Chief Operating Officer since September 1995 and has been a Director of Titan Pharmaceuticals since February 2004. Prior to joining Titan, Mr. Bhonsle served in various positions at Bayer Corporation from July 1975 until April 1995 including most recently as Vice President and General Manager-Plasma Supply. Mr. Bhonsle holds an M.B.A. from the University of California at Berkeley and a B.Tech. in chemical engineering from the Indian Institute of Technology.

Katherine L. Beebe, Ph.D. – Executive Vice President / Chief Development Officer

Dr. Beebe was recently appointed as the company's Chief Development Officer in May 2011. Dr. Beebe joined Titan in February 2009 as the company's Senior V.P. of Clinical Development. Dr. Beebe's career has spanned more than 20 years as both an academic and industry researcher, focusing primarily on addiction, post-traumatic stress, and anxiety and depression. She has extensive experience leading global clinical development programs, and has contributed substantially to the preparation and approval of 4 new drug applications (NDAs). Her research has been published in peer-reviewed medical journals such as The American Journal of Psychiatry, Drug and Alcohol Dependence and, most recently, in the Journal of the American Medical Association. She holds a Ph.D. in Clinical Neuropsychology from George Mason University in Fairfax, Virginia, and completed predoctoral training in New Haven, Connecticut at Yale University and her post-graduate training at Graduate Hospital and the University of Pennsylvania, in Philadelphia, Pennsylvania.

VALUATION & RECOMMENDATION

Our Thesis

…Optimistic on Probuphine…

We are initiating coverage of Titan Pharmaceuticals with an Outperform rating and $4.50 price target. The biggest catalyst we see for the shares is the impending release of data from Titan's second, confirmatory, phase 3 trial on Probuphine, dubbed Pro-806. Based on the impressive data from the phase 2 and previous phase 3 study, Pro-805, we fully expect the data to be positive. Management expects this data to become available in the next few weeks. An important aspect of this second phase 3 trial will be the direct comparison of Probuphine with an open-label 12 mg and 16 mg sublingual buprenorphine tablet (Suboxone). We note that management is attempting to show an overall lower drug exposure and reduced systemic adverse events, improve retention and compliance, and non-inferiority in efficacy and patient satisfaction. Another goal of this trial is to satisfy European regulatory authorities, which often require active comparators prior to approval.

Opioid addiction is a major health and social issue, especially in the U.S. An estimated 7 million people worldwide, nearly 4 million of which are in the U.S., are abusing or addicted to opioids. We note the number of patients in the U.S. receiving methadone treatment in the last several years has remained fairly constant at about 200,000, whereas the number of patients in the U.S. receiving buprenorphine has grown to over 500,000. It is clear the market is shifting from methadone to buprenorphine thanks to its improved characteristics, such as a lower pharmacologic ceiling effect, increased safety margin, and superior therapeutic window of efficacy.

We believe Titan's Probuphine can capture over 20% of the market from the sublingual formulation. We also believe that Titan's commercialization partner can charge a premium price to Suboxone and Subutex because of the superior characteristics of the drug. This is easily a $500 million opportunity. We also note there is significant upside to this figure if Probuphine is used for the treatment of chronic pain, a multi-billion dollar market in the U.S. We believe that Probuphine could address many of the issues that limit opioid use and encourage opioid abuse today. Buprenorphine is an established and approved analgesic for the treatment of acute and chronic pain. It is approximately 25-50X more potent than morphine, while also having a pharmacologic ceiling effect that provides an increased safety margin.

We see the ideal time to strike a deal for the U.S. and Canadian rights to Probuphine in the fourth quarter 2011. By that time, Titan would have presented top-line data from the Pro-806 program, submitted the full data for publication in a peer-review journal, met with the U.S. FDA for a pre-NDA meeting, and be on track to file the NDA in the first quarter 2012. Our thesis is that partners will want to be involved in the preparation of the application, so a deal will come before the actual filing. At this point it is difficult to say whether Titan will form one global commercialization partner or look to strike regional alliances. Regional deals may make more sense given differences in how opioid addiction is treated in the U.S. vs. the EU, as well as physician comfort with implantable technology like Titan's ProNeura. We believe Titan is looking for a partner with a strong commercial presence in addiction medicine, chronic pain, or specialty CNS disorders.

An upfront payment on Probuphine could bring significant cash to Titan. Management will be looking for upfront cash, along with regulatory and sales-related milestones, and royalties on worldwide sales. Probuphine should be a very profitable drug for Titan's partner. Gross margin should be in the 90%. Roughly 80% of the market can be effectively targeted by a small sales force of only 40-50 representatives. We think management will look for a royalty rate in the twenties, which should allow Titan to become profitable shortly after the Probuphine launch.

…Fanapt Royalties Set To Accelerate…

Besides our bullish stance on Probuphine, we are also starting to see signs that the initial inventory stocking on Fanapt from the first quarter 2010 has been worked through, and we expect that reported sales at Novartis will start to track end user demand by the third quarter 2011. As a reminder, Titan is eligible to receive 8-10% royalty on sales of Fanapt. Novartis paid Vanda Pharmaceuticals $200 million upfront to license the product in October 2009. Vanda is eligible to receive up to an additional $265 million in backend milestones. The hefty deal terms re-enforce our belief that Fanapt is a $250 million product worldwide, and that Titan's royalty will begin to substantially accelerate in the coming quarters as the product takes hold.

Valuation

We see Titan shares as meaningfully under-valued today. We believe that Fanapt alone is worth $1 per share based on the future cash royalty payments. As a reminder, Titan has no ongoing costs associated with these royalties besides the credit facility payment to Deerfield Management, so the net amount is pure cash income to the company. The cash from Fanapt royalties helps management pay for the Probuphine phase 3 program and fund general corporate expenses. We see Fanapt royalties at $4.6 million in 2011, growing to over $16 million per year around the time of the patent expiration in April 2017. The cumulative net present value of these cash flows, assuming a modest 10% discount rate, is $58.9 million. Based on 59.3 million shares outstanding, the Fanapt royalty is worth approximately $1 per share.

Our "optimistic" scenario for Probuphine includes positive phase 3 data from the Pro-806 trial, positive meetings with the FDA later in the year, a new drug application (NDA) in early 2012, and approval in late 2012 with a launch in early 2013. We expect a U.S. deal in the fourth quarter 2011, which should bring upfront cash in the area of $20 to $25 million, a similar approval milestone in late 2013, backend milestone totaling $200 million, and a 20-22% royalty on sales. Under this scenario, we see the net present value (NPV) of Titan's cash from a deal, risk-adjusted backend milestones, and royalties on sales worth $206 million, or $3.50 per share. To account for the risk of this "optimistic" scenario, we are using an aggressive 17.5% discount rate. This is similar to the company's cost of capital based on the March 2011 financing.

Titan should exit the second quarter 2011 with an estimated $8 million in cash. We forecast this will be enough to fund operations into the first quarter 2012. Therefore, a deal with upfront cash is important for later this year. If not, Titan may need to raise $10 million or so to keep timelines on track, as well as continue to negotiate with partners from a position of strength. We believe the company only needs an estimated $10 million to make it to cash flow positive operations based on Fanapt and Probuphine royalty payments.

Titan Pharma Sum-Of-Parts Value	
Fanapt Royalties	$59 Million
Probuphine Value	$206 Million
ProNeura Technology	$10 Million
Cash To Breakeven	($10) Million
Total Firm Value	**$265 Million**
Shares Outstanding	59 Million
Price Per Share	**$4.50**

Recent Financing & Cash Position

In March 2011, Titan Pharmaceuticals entered into an agreement with Deerfield Management that provides Titan with $20 million in financing through a five year senior secured credit facility. Interest will accrue on the outstanding balance until maturity at a rate of 8.5% per annum, which is payable on a quarterly basis. The facility is repayable over five years, with 10% of the principal amount due on the first anniversary, 15% on the second anniversary, and 25% of the principal amount on each of the next three anniversaries. Management can elect to pre-pay the outstanding balance at any time at 110% of the remaining principal amount. Deerfield Management has a repayment right at 110% of the principal amount upon a major transaction (which includes but is not limited to the sale of Fanapt or Probuphine). In conjunction with the financing, Titan has agreed to issue six year warrants to purchase 6 million shares of common stock at an exercise price of $1.57 per share. Deerfield Management will also receive 2.5% of the global net sales of Fanapt subject to a repurchase right by Titan.

In April 2011, Titan repaid its current outstanding loan with Oxford Finance Corp totaling roughly $8 million. Management used the proceeds from the Deerfield credit facility to payback Oxford. We estimate the cash balance at the end of the second quarter 2011 will be around $8 million. We project this is enough cash to fund operations into the first quarter 2012. This is right around the time of the NDA filing on Probuphine. We expect Titan to secure a commercialization partnership on Probuphine later in 2011 to generate additional non-dilutive cash.

Risks

The biggest risk we see is the potential failure of the second, confirmatory phase 3 trail on Probuphine. If this trial were to fail to meet statistical significance, or match the positive data from the first trial, our valuation of the stock would be meaningfully impacted to the downside, and our recommendation would be under review.

Upcoming Events

EVENTS TO WATCH	TIMING
Data presentation at NIDA International Forum	June 2011
Top-line data from phase 3 (confirmatory) Pro-806 trial	August 2011
Meet with U.S. FDA for pre-NDA meeting	Q4-2011
Data presentation at International Society of Addiction Medicine	September 2011
Data from open-label Pro-811 safety re-treatment study	Q4-2011
Sign commercialization partnership on Probuphine	Q4-2011
Data presentation at American Academy of Addiction Psychiatry	December 2011
File U.S. NDA on Probuphine	Q1-2012
U.S. FDA NDA acceptance	Q2-2012
U.S. FDA PDUFA on Probuphine	Q4-2012 / Q1-2013
Launch Probuphine in the U.S.	Q1-2013

Source: Zacks Investment Research, Inc.

PROJECTED FINANCIALS

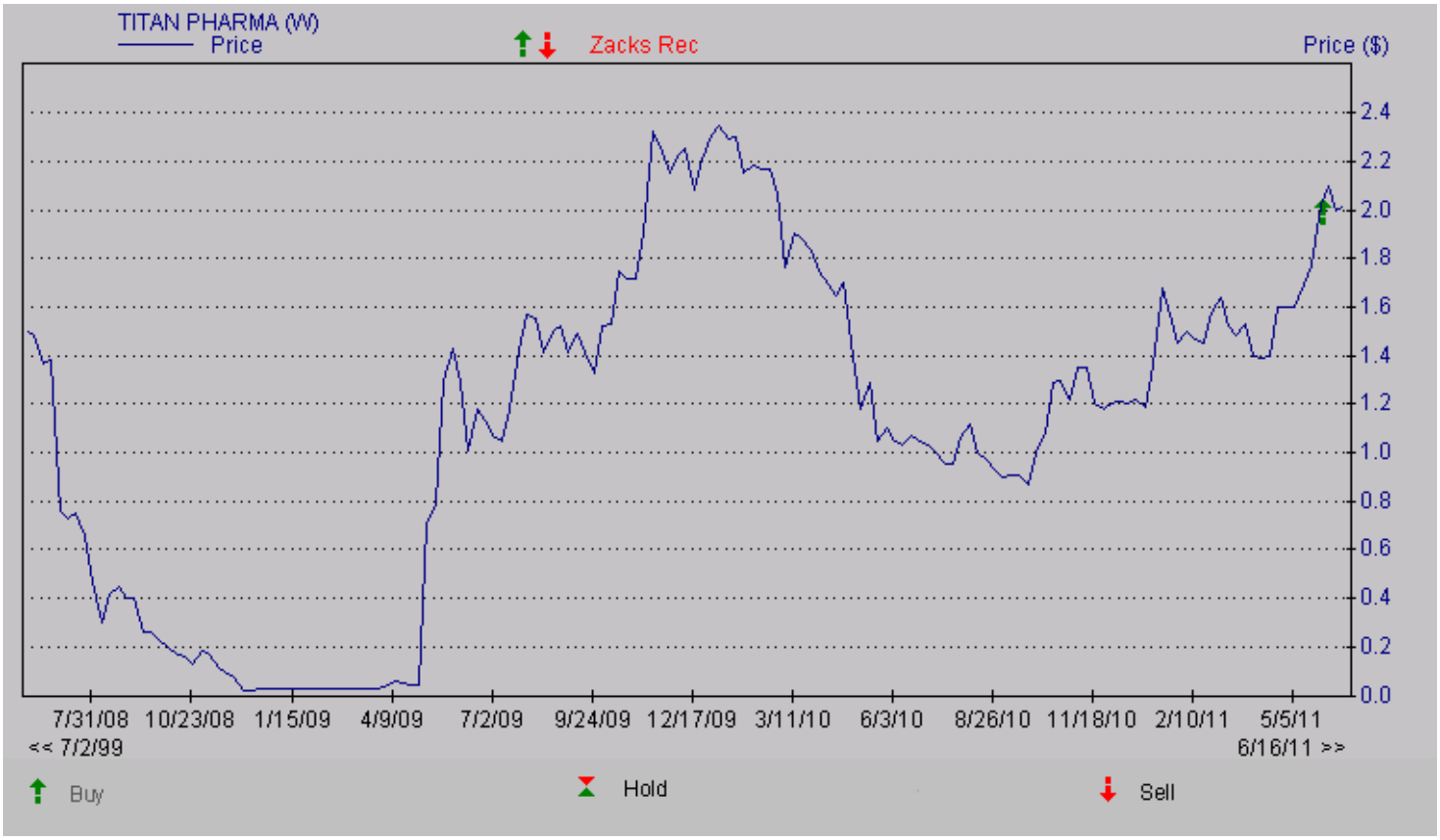
Titan Pharmaceuticals, Inc.
Income Statement

	2009 A	2010 E	Q1 A	Q2 E	Q3 E	Q4 E	2011 E	2012 E	2013 E	2014 E
Probuphine Royalty	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$9.0**	**$18.0**
YOY Growth	-	-	-	-	-	-	-	-	-	*100.0%*
Fanapt Royalty	**$0**	**$2.5**	**$0.7**	**$1.0**	**$1.3**	**$1.6**	**$4.6**	**$7.6**	**$11.2**	**$14.0**
YOY Growth	-	-	*-56.7%*	*1645.5%*	*223.2%*	*292.2%*	*81.4%*	*66.8%*	*47.4%*	*25.0%*
Licensing & Grant Revenue	**$0.1**	**$7.6**	**$0.2**	**$0.5**	**$0.5**	**$0.5**	**$1.7**	**$20.0**	**$25.0**	**$10.0**
Total Revenues	**$0.1**	**$10.1**	**$0.9**	**$1.5**	**$1.8**	**$2.1**	**$6.3**	**$27.6**	**$45.2**	**$42.0**
YOY Growth	-	-	-	-	-	-	*-37.7%*	*338.9%*	*63.8%*	*-7.1%*
CoGS	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	*100%*	*100.0%*	-	-	-	-	*100.0%*	*100.0%*	*100.0%*	*100.0%*
R&D	$2.5	$12.9	$3.7	$4.0	$3.0	$2.5	$13.2	$8.0	$10.0	$10.0
% R&D	-	*127.4%*	-	-	-	-	*210.5%*	*29.0%*	*22.1%*	*23.8%*
SG&A	$3.4	$3.3	$0.8	$0.8	$0.9	$0.9	$3.4	$3.6	$4.0	$4.5
% SG&A	-	*32.3%*	-	-	-	-	*54.0%*	*13.0%*	*8.8%*	*10.7%*
Operating Income	($5.8)	($6.0)	($3.6)	($3.3)	($2.1)	($1.3)	($10.3)	$16.0	$31.2	$27.5
Operating Margin	*0%*	*0.0%*	-	-	-	-	*-164.5%*	*58.0%*	*69.0%*	*65.5%*
Total Other Income	($0.1)	($0.8)	($0.9)	($0.3)	($0.3)	($0.4)	($1.9)	($1.5)	($1.0)	$1.0
Pre-Tax Income	($5.9)	($6.8)	($4.5)	($3.6)	($2.4)	($1.7)	($12.3)	$14.5	$30.2	$28.5
Taxes & Other	$0	($1.2)	$0	$0	$0	$0	$0	$0	$4.5	$8.6
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*5%*	*15%*	*30%*
Net Income	($5.9)	($5.6)	($4.5)	($3.6)	($2.4)	($1.7)	($12.3)	$14.5	$25.7	$20.0
Net Margin	*0%*	*0.0%*	-	-	-	-	*-195.2%*	*52.5%*	*56.8%*	*47.5%*
Reported EPS	**($0.10)**	**($0.09)**	**($0.08)**	**($0.06)**	**($0.04)**	**($0.03)**	**($0.21)**	**$0.23**	**$0.40**	**$0.30**
YOY Growth	-	*-6.2%*	-	-	-	-	*119.1%*	*-212.2%*	*72.9%*	*-24.6%*
Weight Ave. Shares Out	58.5	59.2	59.2	59.3	59.3	59.5	59.3	62.5	64.0	66.0

Source: Zacks Investment Research, Inc. *Jason Napodano, CFA*

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HISTORICAL ZACKS RECOMMENDATIONS



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