Zacks Small-Cap Research

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Titan Pharmaceuticals, Inc. (TTNP-OTC)

TTNP: Focus Turns To FDA Meeting…

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	06/01/2011
Current Price (08/15/13)	$0.56
Target Price	**$1.00**

UPDATE

On April 30, 2013, The U.S. FDA issued a complete response letter to Titan Pharmaceuticals with respect to the new drug application for Probuphine, the company's subdermal implant for the maintenance treatment of opioid dependence in adult patients. The CRL states the FDA cannot approval the application in its present form, and requests additional data supporting the efficacy or use of Probuphine. Concerns mainly revolve around dosing, dosage, and human factors testing associated with the insertion and removal. The CRL also included recommendations regarding product labeling and the implementations of the Risk Evaluation and Mitigation Strategy (REMS). We expect Titan and commercial partner Braeburn to push forward with Probuphine, although it could be tough sledding for the next several months.

SUMMARY DATA

52-Week High	**$2.48**
52-Week Low	**$0.43**
One-Year Return (%)	**-16.30**
Beta	**9.70**
Average Daily Volume (sh)	**219,372**
Shares Outstanding (mil)	**83**
Market Capitalization ($mil)	**$47**
Short Interest Ratio (days)	**0.25**
Institutional Ownership (%)	**1**
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 2013 Estimate	**N/A**
P/E using 2014 Estimate	**N/A**

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)
2012	1.3 A	1.4 A	1.2 A	3.3 A	7.1 A
2013	5.2 A	2.2 A	2.2 E	2.2 E	11.8 E
2014					4.5 E
2015					0 E

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

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2012	-$0.09 A	-$0.03 A	-$0.12 A	-$0.01 A	-$0.15 A
2013	$0.07 A	$0.06 A	-$0.01 E	-$0.02 E	$0.10 E
2014					-$0.10 E
2015					-$0.11 E

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WHAT'S NEW

Shares of Titan Pharmaceuticals (TTNP) have been suck in a narrow trading range between $0.45 and $0.65 for the past 4+ months following the surprise decision from the U.S. FDA to issue a complete response letter (CRL) for Probuphine back in late April 2013. We call this decision by the FDA a "surprise", because only five weeks prior to the decision, in March 2013, the FDA's Psychopharmacologic Drugs Advisory Committee (PDAC) voted to recommend approval of the product. Titan plans to request a meeting with the FDA to discuss the issued raised in the CRL in the next few weeks. We strongly believe, based on the success of two phase 3 trials and the recommendation of the PDAC, that Probuphine should have been approved back in late April 2013. Below we provide investors with a detailed history of the data from Titan's pivotal trials, rehash the outcome of the PDAC meeting, and provide some potential guidance on timelines for the re-filing of approval.

Part-1: Background On Opioid Addiction & Probuphine

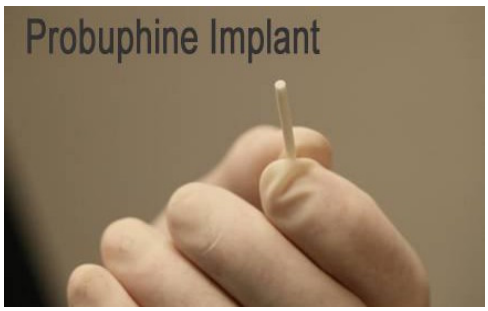
Buprenorphine is a synthetic derivative of opium, chemically similar to both morphine and codeine, but has stimulatory rather than depressant effects. Buprenorphine is 25-50X more potent than morphine and is sometimes used recreationally by insufflations (crushing and inhaling the powder). Buprenorphine is a Schedule III controlled substance under the United Nations' Convention on Psychotropic Substances.

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 2.2 million people addicted to opioids in the U.S., over 80% of which are prescription drugs. The statistics are quiet staggering - more information is available on the CDC's website.

Buprenorphine was first marketed in 1980 by British firm, Reckitt & Colman as an analgesic. In October 2002, the U.S. FDA approved Subutex as high-dose (2 mg & 8 mg) sublingual pill preparations and 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. As a result, Suboxone is now predominantly used for this purpose.

In October 2009, the FDA approved a generic preparation of sublingual 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. Additional supply is now online. To counter the generic pressure, Reckitt Benckiser began marketing a Suboxone Film, first approved in August 2010. In September 2012, Reckitt notified the FDA that it was voluntarily discontinuing supply of Suboxone tablets due to increasing concern with pediatric exposure; but we all know that Reckitt clearly had ulterior motives for its decision.

Titan's Probuphine is a novel, subcutaneous implantable formulation of buprenorphine designed using the company's ProNeura technology. Probuphine delivers six months of buprenorphine without risk of accidental pediatric exposure, overdose, or misuse. Patients undergo a simple 10 minute procedure to receive the Probuphine implant, after which buprenorphine is slowly released in continuous fashion over the next six months. Besides the obvious zero risk of accidental exposure or potential for abuse, we see Probuphine as a meaningful improvement in compliance. Heroin and other opioid addicts, as well as the treating physician, knows Probuphine is always working to curb the addictive craze.

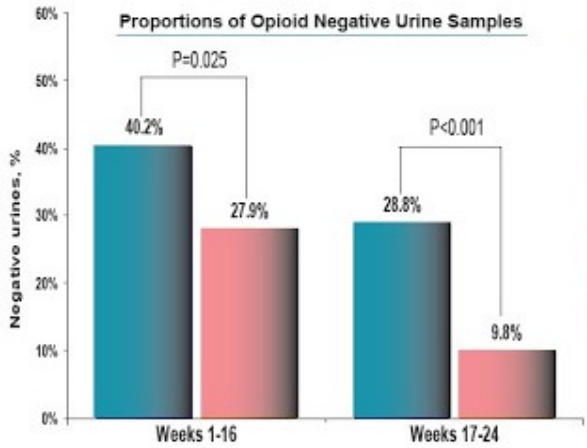


Part-2: The Phase 3 Data

Prior to filing the new drug application (NDA) for approval, Titan completed two Phase III trials and two long-term safety analyses with Probuphine. The two Phase III trials were called PRO-805 and PRO-806. The company also enrolled two open-label extension studies called PRO-807 and PRO-811.

Data from the first Phase III trial, PRO-805, was published in JAMA in October 2010 (Ling MD, W., 2010). A poster of the data has been presented at the American College of Neuropsychopharmacology in December 2009 (ACNP Poster). Data from the second Phase III trial, PRO-806, was just recently published in Addiction (Rosenthal MD, R.N., 2013). Data has also been presented in poster form at the International Society of Addiction Medicine in September 2011 (ISAM Poster), and the American Society of Addiction Medicine in April 2012 (ASAM Poster).

Data from PRO-805 showed that Buprenorphine implants (Probuphine) were clinically and statistically superior to placebo in the treatment of opioid-dependent patients on the primary and key secondary endpoints. Probuphine was found to be safe and well-tolerated in this study. Below shows Probuphine (BPN) vs. placebo on the primary endpoints of weeks 1-16 and 17-24, as well as key secondary endpoints assessed during the study.



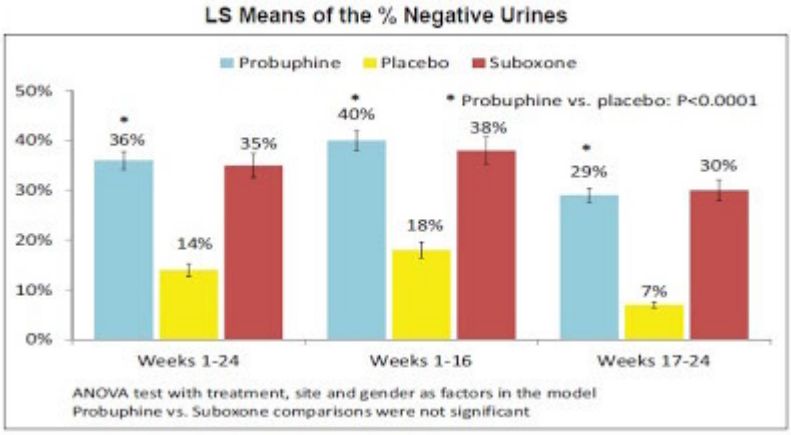
Secondary and Exploratory Efficacy Measures

	BPN Implants N=108	Placebo N=55	P-value
Proportion of study completers, N (%)	71 (65.7)	17 (30.9)	<0.0001
Clinician-rated opioid withdrawal scale (COWS), mean (SE)	2.3 (0.2)	3.4 (0.3)	0.0004
Subject-rated opioid withdrawal scale (SOWS), mean (SE)	4.1 (0.5)	6.5 (0.7)	0.0039
CGI-Improvement, Responders, N (%)*	73 (80.2)	24 (51.1)	0.0003
CGI-Severity, borderline-to-no symptoms, N (%)*	52 (57.2)	16 (34.0)	0.0086
VAS-opioid craving, LS mean (SE)	9.9 (1.1)	15.8 (1.6)	0.0009

*CGI-I and CGI-S evaluated at Visit 15 or End-of-Treatment

BPN implants (n=108) Placebo implants (n=55)

Data from PRO-806 showed the efficacy of Probuphine for the treatment of opioid dependence was confirmed, and statistically significant efficacy was demonstrated on the primary endpoint of negative urine samples at weeks 1-24 vs. placebo. The data show showed non-inferiority to Suboxone. Secondary endpoint data from PR-806 confirmed efficacy of opioid withdrawal, drug craving, and treatment retention, as well as safety and tolerably.



We view the data as impressive. Probuphine works, and the concept is ideally suited for curbing addictive behavior without risk of accidental exposure or misuse / abuse. We base our opinion on the strong clinical data, the thoughtful and rational design for the product, and various conversations we've had with management and lead investigators from the two Phase III studies. For example, in August 2011, Titan hosted a call with Dr. Walter Ling, M.D., Professor of Psychiatry and Director, Integrated Substance Abuse Programs at the David Geffen School of Medicine at UCLA and Dr. Richard N. Rosenthal, M.D., Chairman of Psychiatry at St. Luke's-Roosevelt Hospital

Center, a teaching hospital of Columbia University, past president of the American Academy of Addiction Psychiatry. You will notice Dr. Ling it the lead author on the JAMA paper from 2010 and Dr. Rosenthal is the lead author on the Addiction paper from 2013. Both doctors expressed their enthusiasm for Probuphine and why they believe it will see meaningful commercial uptake.

Part-3: The NDA & A Partnership

In late October 2012, Titan filed the NDA on Probuphine. The company asked for Priority Review given the high unmet medical need for new treatment options targeting opioid addiction and the potential for meaningfully less abuse or miss-use with Probuphine versus current generic buprenorphine / naloxone. The NDA was been submitted under Section 505(b)(2) of the Food, Drug and Cosmetic Act and references the approved sublingual tablet formulations of buprenorphine. Priority review was granted by the U.S. FDA on January 3, 2013.

On December 17, 2012, Titan announced the signing of a license agreement with Braeburn Pharmaceuticals Sprl, wholly owned by Apple Tree Partners. The agreement granted Braeburn exclusive commercialization rights to Probuphine in the U.S. and Canada. In return, Titan received $15.75 million in an up-front payment and will receive up to $50 million upon the approval of Probuphine by the FDA for the treatment of opioid dependence. Additionally, Titan is eligible to receive up to $130 million upon achievement of sales milestones and up to $35 million in regulatory milestones for additional contemplated indications, including chronic pain. Finally, Titan will receive tiered, double digit percentage royalties on net sales of Probuphine in the U.S. and Canada.

In addition to the potential milestone payments, Apple Tree Partners noted that it had allocated in excess of $75 million to launch, commercialize and continue the development of Probuphine. Upon the signing of the deal, we noted the terms of the agreement were superior to our predictions, which we believe was a testament to the potential for the drug.

	Our Expectations	Actual Braeburn Deal
Upfront Payment	$15 million	$15.75 million
Approval Milestone	$15 – 20 million	"Up to $50 million"
Sales Milestones	$100 million	$130 million
New Indications	-	$35 million
Royalties	~20%	"Tiered Double-Digit"

Part-4: The Advisory Committee

On March 21, 2013, The U.S. FDA Psychopharmacologic Drugs Advisory Committee (PDAC) voted to recommend approval of Probuphine. The FDA asked PDAC four key questions asked:

Question # 1: Please comment on whether the Applicant conducted adequate dose exploration in the development program to determine the most effective dose. Do the data from the clinical trials provide substantial evidence of effectiveness of Probuphine for the maintenance treatment of opioid dependence?

VOTE: 10 YES, 5 NO

The panel spent a significant amount of time discussing the dose of Probuphine, the plasma concentration of four rods vs. sublingual Suboxone, and the lack of a true "dosing-finding" study or maximum tolerated dose. One panel member, Laura F. McNicholas, MD, PhD, a Clinical Associate Professor of Psychiatry at the University of Pennsylvania School of Medicine Center for Studies of Addiction, was particularly concerned about how many rods to implant in stable patients on less than 16 mg of Suboxone given that Titan did not really provide information on dose titration in its application for approval. However, in the end, the discussion on dose exploration was separate from the actual question on effectiveness. Although several panel members questioned the lack of dose ranging studies (and options for dosing) and use of sublingual Suboxone as a rescue medication, the majority believed that Titan did demonstrated substantial evidence of efficacy versus placebo.

Question # 2: Please comment on the Applicant's assessment of the safety aspect of Probuphine in general, as well as on safety concerns specific to the placement and removal of the implants. Has the Applicant adequately characterized the safety profile of Probuphine in this patient population?

VOTE: 12 YES, 2 NO, 1 ABSTAIN

The panel concluded that the procedure, especially implantation, seems simple and there should be little issue in training physicians on both implantation and remove. The question remains, will physicians, specifically psychiatrists that may not have any surgical background, office setting, and required certifications under the proposed REMS, bother to enter the training program; and is this a big enough market opportunity that addiction medicine clinics, which are Drug Addiction Treatment Act of 2000 (DATA-2000) compliant, will hire a nurse practitioner or physician's assistant to handle the procedures under supervision of the attending physicians. The panel also seemed to have an issue with DATA-2000 centers warehousing the product, as proposed under the FDA's REMS, believing that it could create security and liability issues, but that the product itself, once implanted, presents low risk for adverse events or serious adverse events.

Question # 3: Is the Risk Evaluation and Mitigation Strategy (REMS) proposed by the Applicant, which consists of restricted distribution and a training/certification program for healthcare professionals who will implant the product, adequate to address the risks of potential complications associated with the implantation procedure and abuse, misuse, and accidental overdose. Include in your deliberations any concerns related to the proposed model of care and training / certification program?

VOTE: 5 YES, 4 NO, 6 ABSTAIN

The FDA had significant issues with Titan's original proposed REMS, specifically with respect to the model of care and closed distribution system. The FDA wants to bring the entire process under the roof of one DATA-2000 compliance center. A DATA-2000 compliant center allows the waiver from the registration requirement of the Controlled Substance Act (CSA) to prescribe and dispense opioid medications in Schedule III for the treatment of opioid additional outside of an opioid treatment program (OTP). For example, in a DATA-2000 Office Based Opioid Treatment (OBOT) center, both the physician and designated person doing the implantation / removal must complete the REMS certification. The FDA wants the product distributed from the wholesaler to an OBOT or OTP to a REMS certified physician. The OBTP or OTP will maintain Probuphine on sight for administration instead of using a specialty pharmacy model as previously suggested by Titan.

Question # 4: Based on the data presented and discussed today, do the efficacy, safety, and risk benefit profile of Probuphine support the approval of this application?

VOTE: 10 YES, 4 NO, 1 ABSTAIN

The voting went pretty much as we expected given that 10 of 15 found the drug to be effective and 12 of 15 found the drug to be safe. Most panel members seemed to be sitting on the fence, in the end concluding that Probuphine seems to offer utility for the maintenance treatment of opioid addiction, and that the product does have some unique characteristics with respect to reducing the potential for diversion and improving compliance to recommend approval. Dissenting opinions (Kramer, Covington, McNicholas, and Steinbrook) felt that without improvement in the REMS and adequate understanding of the dosing, the product should not be approved at this time.

Following the granting of Priority Review and the signing of an impressive partnership for the commercialization of Probuphine, Titan's stock experienced an impressive run during the first quarter 2013. The FDA clearly felt as though Probuphine offered some meaningful improvement to the standard-of-care or else why grant Priority Review? And, although not an over-whelming endorsement, PDAC did recommend approval in late March 2013. It looked as though Probuphine was heading toward final FDA approval in late April 2013.

Part-5: The Surprise Rejection

To our surprise, on April 30, 2013, Titan announced the U.S. FDA had issued a complete response letter (CRL) for Probuphine. The CRL states that the FDA cannot approve the application in its present form. The CRL notes concerns with the efficacy and use of Probuphine and requests additional data before approval can be granted. Below we highlight the four issues noted in the CRL.

Issue – 1: The ability of Probuphine to provide opioid blockade of relevant doses of agonists.

The FDA is clearly throwing a curveball at Titan with this request. Buprenorphine is not a new molecule to the FDA with a curious mechanism of action. Buprenorphine is a mixed agonist / antagonist, blocking the activity of other opiates and inducing withdrawal in opiate dependent individuals who are currently physically dependent on another opiate like heroin or oxycodone. Data shows that buprenorphine binds strongly to receptors in the brain compared to other opioids such as heroin, making it more difficult for addicts to experience a euphoric high.

This effect is present even at low dosages, with as little as 2 mg enough to produce a blocking effect. High doses of buprenorphine, at >32 mg, is enough for the drug to become a full agonist; i.e., it not only completely blocking or reversing opiate effects from other opioids, but also itself. None of this information should be new to the FDA.

Titan's responsibility with its new drug application (NDA) for Probuphine should be to show clear signs of clinical efficacy and safety. We believe it did that with PRO-805, -806, -807, and -811. The FDA held an Advisory Committee meeting in March 2013 to discuss this exact issue, and the panel voted to recommend approval. What the FDA wants to know now seems tied to the dosing of Probuphine and the plasma levels of the drug given the six month implant vs. daily peak and trough plasma levels with Suboxone. This issue ties directly into the second issue which we discuss in greater detail below.

Issue – 2: The effect of higher doses of Probuphine, ideally doses more closely approximating the blood plasma levels associated with sublingual doses of buprenorphine of 12 to 16 mg / day.

The FDA is asking Titan to study higher doses of Probuphine that more closely approximate the blood plasma levels associated with 12 to 16 mg / day of buprenorphine. This is a surprising request considering Titan designed the Probuphine implant so that 4 rods is roughly equivalent in efficacy to 16 mg / day. PRO-806 confirms this design. Now the FDA wants to know how it compares on a plasma level (see the first issue noted above).

Probuphine was designed so that each rod delivers 20 mg of buprenorphine over six months with controlled release. However, according to the data from Titan's two phase 3 studies (PRO-805 and PRO-806), a good percent of Probuphine patients both required supplemental sublingual buprenorphine and / or a fifth rod implant. Below is a snap-shot of the data from the clinical study, which includes data from the two open-label extension studies (PRO-807 and PRO-811).

Study	Treatment Group	Subjects Requiring Supplemental SL Buprenorphine	Subjects Requiring A Fifth Implant of Probuphine
PRO-805	Probuphine	62.0%	20.4%
	Placebo	90.9%	58.2%
PRO-806	Probuphine	39.5%	21.9%
	Placebo	66.7%	38.9%
	Suboxone	5.9%	N/A
PRO-807	Probuphine	41.9%	9.7%
PRO-811	Probuphine	20.0%	11.0%

The data above clearly show that more patients on placebo required supplemental buprenorphine than patients on Probuphine; but, perhaps that is not a fair comparison? The FDA asks that companies run randomized, placebo-controlled clinical trials. But in this case, there is an existing product on the market, Suboxone, from which Titan is attempting to capture market share. Clearly far more patients on Probuphine required "help" than those on Suboxone. Titan has responded publicly to this issue noting that the majority of supplemental buprenorphine use was very early in the study and was not materially different from Suboxone only a few weeks into the 24 week PRO-806 study.

Based on the data from PRO-806, Probuphine is as effective as Suboxone over a 24 week period, but patients may still require supplemental Suboxone help in the first two to three weeks. Is this is a viable drug then? Absolutely, but the FDA seems to want clarity on how to get around this issue. For example, the Probuphine implant is 2.5 mm thick x 26 mm long. We note that is smaller than the Norplant birth control implant at 2.4 mm x 34 mm, or the Norplant II (Jadelle) implant 2.5 mm x 43 mm. Perhaps instead of testing a fifth implant, Titan can extend the length of each Probuphine implant by 6 to 8 mm.

Although this sounds like an easy fix, extending the length of the implant would require additional clinical testing. Nevertheless, it seems as though this is what the FDA wants. Titan's stance is that constant (stable) buprenorphine delivered via the six month implants from Probuphine is equivalent to daily Suboxone, even though the plasma levels are far less. Management believes the peaks and troughs of daily dosing for Suboxone is what limits its efficacy. So what the FDA seems to be asking Titan about here is – what kind of efficacy results can be obtained if the dose of Probuphine is increased to plasma levels equivalent to 12 – 16 mg? This could potentially limit the need for patients to require supplemental Suboxone altogether.

Bulls can interpret this request as a signal that the FDA likes the data they've seen on Probuphine, and now wants more. The FDA is swinging for the fences. Imagine what kind of results we can get IF… However, Bears can clearly argue, the FDA is not satisfied with the data, and thinks this product falls short of truly effective at the doses Titan proposed in the NDA. We tend to agree with the Bulls here, although the path forward is the same, regardless.

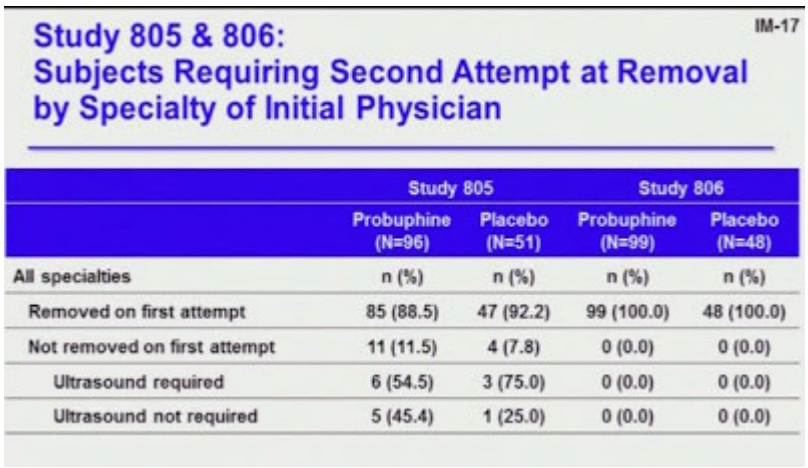
The FDA is asking this question despite the fact that it essentially asked the Advisory Committee the same thing. Question # 1 to the committee asked, *"Please comment on whether the Applicant conducted adequate dose exploration in the development program to determine the most effective dose."* The committee voted 10 YES to 5 NO in response to this question. That was not enough for the FDA. It seems as though the FDA would like Titan to conduct additional efficacy studies with Probuphine to provide an adequate response. If that's the case, generating the data to address issue 1 and 2 could take as much as $10 million and 12 to 18 months. Unless Titan already has this data on hand?

Issue – 3: Human factors testing of the training associated with Probuphine's insertion and removal.

Of all the issues outlined in the CRL, this is the most surprising to us. During the FDA's Psychopharmacologic Drugs Advisory Committee meeting on March 21, 2013, some of the panel members voiced concerns on the ability of psychiatrists and addiction medicine physicians being able to insert and remove the Probuphine implant without significant training. IMS Health data from January 2003 to December 2012 shows that 70% of all Suboxone (sublingual buprenorphine HCl + naloxone HCl) prescriptions (some 40+ million prescriptions) were written by general practice / family medicine doctors, doctors of osteopathy, psychiatrists, and internal medicine specialists. However, the FDA presented data noting that primarily only surgeons and OB/GYNs have significant experience with rod insertion and / or removal.

A major concern during the panel was the potential that an addiction medicine specialist would out-source the implantation and removal of Probuphine to a surgeon. Panel members noted two potential issues here: The first is the lack of reimbursement and economics associated with such a simple procedure, meaning that surgeons are not going to take the time to come down to an opioid treatment center just to do a quick implant or removal of Probuphine; and the second issue, even if a surgeon did decide to do the procedure for a psychiatrist or addiction medicinal specialist that surgeon would not be DATA-2000 compliant. The Drug Addiction Treatment Act of 2000 allows for a waiver from the registration requirements of the Controlled Substance Act (CSA) to prescribe and dispense opioid medications in Schedule III, IV, and V for the treatment of opioid addiction, outside of an opioid treatment program, provided such medications are approved by the FDA. A non-DATA-2000 physician implanting Probuphine creates issues for the FDA and the CSA.

Interestingly enough, in Titan's two phase 3 studies (PRO-805 and PRO-806) and the two open-label extension studies (PRO-807 and PRO-811), the most common physician use was a family medicine (29%), followed by OB/GYNs (24%), and anesthesiologists, surgeons, and psychiatrists (12% each). Despite this high use of so called "physicians without significant rod insertion and/or removal", the procedure was a non-issue once Titan re-vamped the training procedure after PRO-805 and before PRO-806. Below is a slide from the FDA's Advisory Committee meeting showing 100% success on first-attempt removal for PRO-806 after the revised training and insertion / removal improvements Titan made following PRO-805.


IM-17

Study 805 & 806:
Subjects Requiring Second Attempt at Removal by Specialty of Initial Physician

	Study 805		Study 806	
	Probuphine (N=96)	Placebo (N=51)	Probuphine (N=99)	Placebo (N=48)
All specialties	n (%)	n (%)	n (%)	n (%)
Removed on first attempt	85 (88.5)	47 (92.2)	99 (100.0)	48 (100.0)
Not removed on first attempt	11 (11.5)	4 (7.8)	0 (0.0)	0 (0.0)
Ultrasound required	6 (54.5)	3 (75.0)	0 (0.0)	0 (0.0)
Ultrasound not required	5 (45.4)	1 (25.0)	0 (0.0)	0 (0.0)

Nevertheless, the FDA has asked for some additional data on this procedure and Titan and Braeburn will push forward with a simple human factors study to address the FDA's concern. We believe this study can be conducted parallel to the new clinical studies required to address issues 1 and 2 noted above.

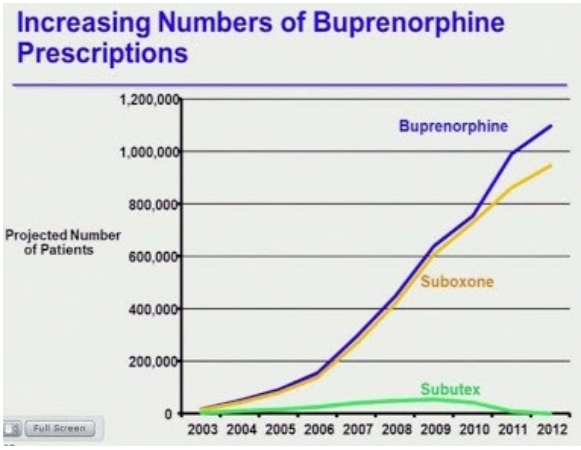
With respect to the commercial plans, Titan and Braeburn plan to create a Probuphine steering committee to oversee the training and roll-out program. Step-1 of the program is to train 50 Master Trainers, 20 of which have already been identified from the clinical programs. These 50 Master Trainers will then train an additional 2,000 physicians over the next 12 months. Training will take place at 20-30 regional meetings with 50-100 trainees per meeting (goal of 1 trainer per 10 trainees). If Titan and Braeburn can convince each of these 50 Mater Trainers to participate in 4 meetings over the subsequent 12 months following approval, they should have no problem meeting this goal. It remains to be seen if the planned human factors study Titan plans to conduct changes the commercial training plans. The potential exists that Titan will have far more than 50 Master Trainers by the time the NDA is re-submitted to the U.S. FDA given the need to enroll the human factors study.

Issue -4: The CRL also included recommendations regarding product labeling and the implementation of the Risk Evaluation and Mitigation Strategy (REMS).

We do not see much issue here. Titan and Braeburn will take into consideration the FDA's recommendations and revise the proposed label and REMS for Probuphine to satisfy the agency. End of discussion.

Part-6: The Market

The market is currently dominated by Suboxone, a combination buprenorphine and naloxone tablet, indicated for the maintenance treatment of opioid dependence. The drug is most commonly used by oxycodone and heroin addicts looking to kick their habit. Between Suboxone tablets and Suboxone sublingual film, Reckitt took in over $1.3 billion in sales from the franchise in the U.S in 2012. There were an estimated 10.7 million prescriptions for opioid addiction in 2012, the majority Suboxone or another combination of buprenorphine / naloxone. Data from the FDA suggests there are over 1 million patients currently being treated for opioid addiction in the U.S., with an estimated 900,000 on Suboxone (below).



Source: FDA ADCOM, March 21, 2013

The majority of Suboxone prescriptions are written by general practitioners, family medicine doctors, doctors of osteopathy, psychiatrists, and internal medicine specialists. The FDA proposed REMS mandates that the implantation procedure must take place at a DATA-2000 waived center, which keeps both the prescriber and person doing the implantation (may be the same person) under one roof. Given that Titan believes general practitioners and family medicine physicians can be easily trained to implant and remove Probuphine, this does not see limiting to the uptake of the drug.

Titan's plan is to create a steering committee that will oversee the training of physicians for the implantation / removal procedure. The plan is to have the 20 certified implanters from Titan's clinical trials and 30 new physicians trained to act as master trainers upon the launch of the product. The goal is to have 2,000 implanters trained over the first 12 months after the launch. The training sessions will take place at 20-30 regional meetings with approximately 50-100 trainees per meeting.

We think the challenge for Titan and Braeburn will be getting physicians to show up to the training session (approximately 8 hours) and get certified to prescribe Probuphine under the REMS. Roughly 30% of Suboxone prescriptions are written by psychiatrist who both lack the surgical background and may not have the office setting or capabilities to implant the device. From a modeling standpoint, it might make sense to eliminate half of these doctors from any forecast. Dosing, or the lack of dosing flexibility, will eliminate another chunk of the market.

Above we note approximately 1 million subjects per year on buprenorphine. Our market assumption is that Braeburn can capture approximately 5% of the market five years after launch. This seems reasonable given the characteristics of the product and the potential for improved compliance and less diversion, but also takes into account some of the prescribers that we've peeled away, such as half the psychiatrists and around one-third of the market that is on less than 12 mg of Suboxone.

We suspect that the price of Probuphine will run roughly the cost of 7-8 months of what it cost for Suboxone, or around $1,500 on launch, with price increases taking the product to $2,000 five years after launch. We assume the average patient will have 1.75 procedures per year (assumes one implant for six months with about 75% of the patients receiving re-implantation during removal of the first implants). Accordingly, we see peak sales of Probuphine at approximately $175 million (50,000 patients x $2,000 x 1.75). We have $0 revenues in our model for chronic pain indications at this time.

Part-7: Braeburn Hedges, Then Takes Over

On May 28, 2013, Titan announced an amendment to the agreement with Braeburn. The original agreement provided the right for Braeburn to terminate the licensing agreement if Titan received a CRL from the FDA. We provide the relevant information from the Form 8K SEC filing in the picture below:

(ii) in the event (A) Titan receives from the FDA a complete response letter advising that the Product NDA as filed by Titan for the Initial Indication will not be approved and that additional clinical studies and/or other development will be required to be performed prior to receipt of Regulatory Approval of Product for the Initial Indication (" **Additional Registration Studies** ") and (B) such Additional Registration Studies would materially adversely impact the timing or cost required to be incurred by Braeburn for such Regulatory Approval such that Braeburn reasonably believes in good faith either (x) that that the NDA Transfer Date will occur on or after January 1, 2015 or (y) that the costs of such Additional Registration Studies would exceed ***, then within thirty (30) days after receipt of such complete response letter, Braeburn shall, in its sole discretion, have the right and shall notify Titan in writing of its decision either to (xx) terminate this Agreement upon thirty (30) days written notice to Titan, or (yy) continue to proceed to obtain FDA Approval despite the foregoing, in which case, Braeburn shall have the right to set-off against the required milestone payment set forth in Section 6.1(b)(i) an amount equal to the amount by which the actual costs of the Additional Registration Studies exceeds *** up to a maximum set-off of *** (the " **Milestone Set-off** "), it being understood that there is no right of termination in the event that Additional Registration Studies are required other than as specifically set forth above;

The Amendment gives Braeburn the right to terminate the agreement in the event that (A) after May 28, 2013, based on written or oral communications from or with the FDA, Braeburn reasonably determines either that the FDA will require significant development to be performed before approval of the Probuphine NDA can be given, such as, but not limited to, one or more additional controlled clinical studies with a clinical efficacy endpoint, or substantial post-approval commitments that may materially impact the products financial returns or that the FDA will require one or more changes in the proposed label, which change(s) Braeburn reasonably determines will materially reduce the authorized prescribed patient base, or (B) the NDA has not been approved by the FDA on or before June 30, 2014. The Amendment also provides that we will share in legal and consulting expenses in excess of a specified amount prior to approval of the NDA.

On July 2, 2013, Titan and Braeburn again amendment the agreement. This time the amendment establishes the parameters for a committee comprised of representatives of both companies to make all decisions regarding the development and implementation of a strategic plan to seek U.S. approval for Probuphine (and handle all such written and oral communication with the FDA). The second amendment also makes Braeburn the primary contact for FDA communications regarding the Probuphine NDA.

This is an interesting turn of events. First Braeburn hedges, establishing clear parameters around which it could terminate the agreement - e.g. the requirement for new trials, material costs, delays, and timelines for approval. Then, only five weeks later, Braeburn agrees to a joint steering committee and becomes the primary contact for all FDA communications.

Part-8: Conclusion

We think the U.S. FDA should have approved Probuphine back in April 2013, or at the very least, notified Titan of a three-month delay in the review cycle to enhance and implement the new REMS. Some of the above issues noted in the CRL, specifically the questions on opioid receptor blocking or blood plasma levels seem to ask the company above-and-beyond what should be necessary for a 505(b)(2) application. Titan conducted two successful pivotal registration studies on Probuphine. The data has been presented and published for peer-review. The company followed-up these studies with two open-label safety extension studies, provided the FDA with adequate minimum patient data, adequate manufacturing and controls information, and seemed clearly amenable to the proposed changes to the REMS outlined in late March 2013. The goal-post for approval was moved.

That being said, what's done is done. Titan has to figure out a way to move forward based on the guidance that the U.S. FDA provides. The earnings press release issued on August 14, 2013 states, "*Effort continues with preparation of material that is necessary to support the NDA and Titan expects, in the next several weeks, the submission of a request for a meeting with the FDA to discuss the company's response to the CRL and obtain further regulatory process clarification.*"

We are optimistic that a path forward can eventually be found for Probuphine, but how long and at what cost remains to be seen. That being said, at $0.55 / share, downside seems limited while we wait. After all, the market value of Titan on a fully-diluted basis is around $50 million. Braeburn was willing to write a check for $50 million to Titan for Probuphine approval alone back in late April 2013.

If Titan can meet with the FDA in a month or two, and come back to investors with a positive path forward, the stock could have a nice recovery back to the $1 / share range. The biggest risk we see to owning the stock at $0.55 / share today is Braeburn terminating the licensing agreement. That would hit the shares hard. We see that decision from Braeburn as unlikely until after they meet with the FDA. It's clear based on the July 2013 amendment that both companies are working together.

Several investors have asked us why Titan and Braeburn have taken so long before responding to the FDA. It's already the middle of August and a meeting with the FDA hasn't even been requested yet. We believe the duo are preparing a full and complete response for the FDA prior to requesting the meeting. On Titan's second quarter call, Chairman Marc Rubin noted the company expects this respond to be "full and formal". The goal is to go into that meeting armed with enough information that they can re-file quickly after the meeting. Titan agreed to an amendment providing Braeburn with the right to walk unless the FDA grants approval before June 30, 2014. The only way to accomplish that goal would be to re-file the NDA before year-end 2013.

If Titan and Braeburn can pull that off, this is stock that will be significantly higher in a year. Titan exited the second quarter with $11.2 million in cash and investments. Management sees that as sufficient to fund operations until the end of April 2014. It will be a very interesting next 4-5 months given the crunch in time frame for re-filing, raising cash, and potentially approval. Stay tuned!

PROJECTED FINANCIALS

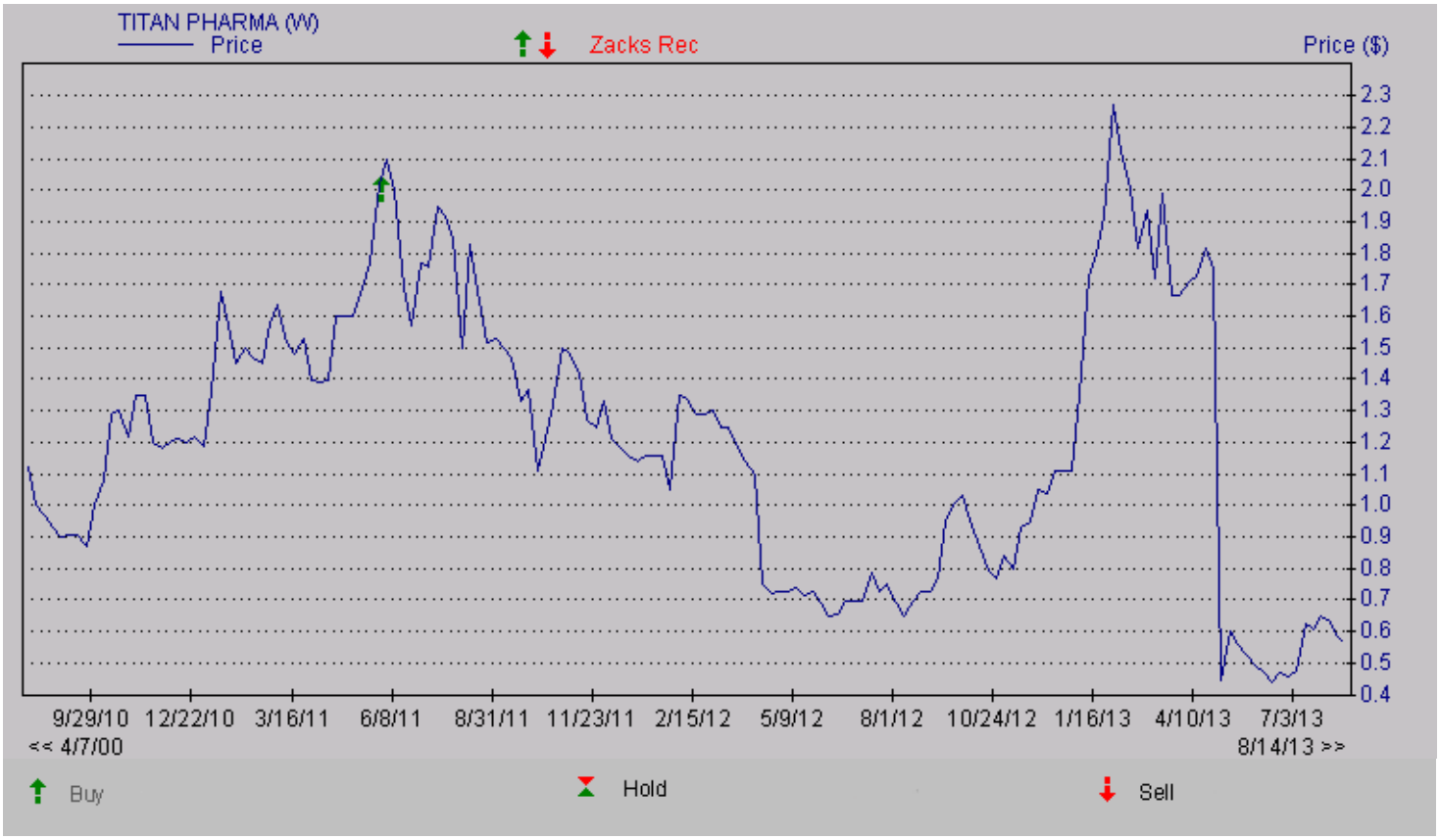
Titan Pharmaceuticals, Inc.
Income Statement

Titan Pharma	2012 A	Q1 A	Q2 A	Q3 E	Q4 E	2013 E	2014 E	2015 E
Probuphine Royalty	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-
Fanapt Royalty	**$4.8**	**$1.4**	**$0**	**$0.0**	**$0.0**	**$1.4**	**$0**	**$0**
YOY Growth	*32.5%*	*16.0%*	*-100.0%*	*-100.0%*	*-100.0%*	*-70.0%*	-	-
Licensing & Grant Revenue	**$2.4**	**$3.8**	**$2.2**	**$2.2**	**$2.2**	**$10.3**	**$4.5**	**$0**
Total Revenues	**$7.1**	**$5.2**	**$2.2**	**$2.2**	**$2.2**	**$11.8**	**$4.5**	**$0**
YOY Growth	*75.0%*	-	-	-	-	*65.4%*	*-61.8%*	*-100.0%*
CoGS	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	*100.0%*	-	-	-	-	*100.0%*	*100.0%*	*100.0%*
R&D	$10.6	$3.9	$1.8	$2.5	$3.0	$11.2	$10.0	$7.5
% R&D	*149.1%*	-	-	-	-	*95.1%*	*222.2%*	*#DIV/0!*
SG&A	$4.9	$1.1	$0.7	$1.2	$1.3	$4.3	$5.2	$5.5
% SG&A	*68.5%*	-	-	-	-	*36.5%*	*115.6%*	*#DIV/0!*
Operating Income	($8.4)	$0.2	($0.3)	($1.5)	($2.1)	($3.7)	($10.7)	($13.0)
Operating Margin	*-117.6%*	-	-	-	-	*-31.6%*	*-237.8%*	*#DIV/0!*
Total Other Income	($1.5)	$5.8	$5.4	$0.4	$0.4	$12.0	$1.0	$1.0
Pre-Tax Income	($9.9)	$6.0	$5.1	($1.1)	($1.7)	$8.3	($9.7)	($12.0)
Taxes & Other	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*5%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	($9.9)	$6.0	$5.1	($1.1)	($1.7)	$8.3	($9.7)	($12.0)
Net Margin	*-138.7%*	-	-	-	-	*70.2%*	*-215.6%*	*#DIV/0!*
Reported EPS	**($0.15)**	**$0.07**	**$0.06**	**($0.01)**	**($0.02)**	**$0.10**	**($0.10)**	**($0.11)**
YOY Growth	*-42.1%*	-	-	-	-	*-166.2%*	*-198.7%*	*12.5%*
Weight Ave. Shares Out	66.5	86.8	82.6	83.0	84.0	84.1	100.0	110.0

Source: Zacks Small-Cap Research, Inc. *Jason Napodano, CFA*

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