Zacks Small-Cap Research

March 22, 2013
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Titan Pharmaceuticals, Inc. (TTNP-OTC)

TTNP: FDA Advisory Panel Recommends Approval Of Probuphine By Solid Margin…

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	06/01/2011
Current Price (03/22/13)	$1.66
Target Price	**$3.00**

UPDATE

On March 21, 2013, The U.S. FDA Psychopharmacologic Drugs Advisory Committee voted to recommend approval of Titan Pharmaceuticals Probuphine, a subdermal implant of buprenorphine for the maintenance treatment of opioid dependence. Our report highlights the four questions asked of the panel, provide a recap of the voting, and conclude with some analysis on how the vote may impact the FDA's decision on April 30, 2013 or the market opportunity for Titan's commercial partner, Braeburn Pharmaceuticals.

We have made some significant changes to our financial model following the Advisory Committee vote, namely on the timing for approval and market opportunity for the drug. We see $3.00 per share as fair value. Our rating remains 'Buy'.

SUMMARY DATA

52-Week High	**$2.53**
52-Week Low	**$0.65**
One-Year Return (%)	**2.50**
Beta	**9.79**
Average Daily Volume (sh)	**1,652,272**
Shares Outstanding (mil)	**82**
Market Capitalization ($mil)	**$101**
Short Interest Ratio (days)	**0.25**
Institutional Ownership (%)	**10**
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	3.6 E	6.2 E	57.3 E	6.5 E	73.6 E
2014					34.9 E
2015					47.0 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	-$0.00 E	$0.04 E	$0.66 E	$0.04 E	$0.75 E
2014					$0.27 E
2015					$0.38 E

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

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WHAT'S NEW

FDA Panel Votes To Approve Probuphine

On March 21, 2013, The U.S. FDA Psychopharmacologic Drugs Advisory Committee voted to recommend approval of Titan Pharmaceuticals Probuphine, a subdermal implant of buprenorphine for the maintenance treatment of opioid dependence. Below we highlight the four questions asked of the panel, provide a recap of the voting, and conclude with some analysis on how the vote may impact the FDA's decision on April 30, 2013 or the market opportunity for Titan's commercial partner, Braeburn Pharmaceuticals.

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 16mg 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, 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 wanted 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).

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.

We do not see this as an issue. In fact, it simplifies the entire process in our view. However, this new REMS needs to be vetted more by the FDA, and perhaps even Titan and Braeburn. Thus, we are not sure all can be accomplished by April 30, 2013. In fact, during the committee meeting, FDA Director, Bob Rappaport, MD, hinted at the fact that there was still significant work to be done with respect to the REMS and that the combination of a priority review and REMS presented a challenge to the agency to complete by the PDUFA date. We would not be surprised to see a 3 month extension of the PDUFA from April 30, 2013 to July 30, 2013. That's not to say the agency will require the entire 3 months extension, but final approval on April 30, 2013 seems a daunting task.

Discussion: Please discuss whether the absence of any information on each of the following matters should be considered a critical deficiency in the application:

a) The potential for removal of the implants by non-medical personnel for the purpose of diversion.

The majority of panel members felt this was only a minor concern, and certainly did not meet the standard for a critical deficiency warranting denial of approval.

b) The potential for long-term exposure to the components of the rods if an individual never has the implants removed.

Similar to above, the panel expressed little concern here.

c) The potential for patients to require implantation into an arm which has received an implant previously in order to remain on treatment, which would necessitate identification of multiple implantation sites per arm, or use of previously implanted sites.

Several panel members did express concern with respect to this issue, although all stopped short of calling the lack of information on implant location and re-insertion into the same area critically deficient. Several members would like to see post-approval studies on this topic, including alternative locations around the body for the implant, re-insertion of the implant into the same locations, and the impact of fibrosis and scarring on the pharmacokinetics. Two members of the committee, Judith M. Kramer, MD, MS, Professor of Medicine at the Duke University Medical Center and Robert Steinbrook, MD, Professor Adjunct of Internal Medicine at the Yale School of Medicine, suggested that the drug should not be approved without this information.

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. However, we note two panel members who voted YES on questions #1 and #2, , Laura F. McNicholas, MD, PhD and Edward C. Covington, MD, Director of the Cleveland Clinic Foundation - Neurological Center for Pain, vote NO on question 4, which seems awful contradictory. Conversely, patient representative, Michael L. Yesenko, MDiv, voted NO on questions #1 and #2, but in the end voted to recommend approval of the drug – again, highly perplexing.

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. However, work still needs to be done with respect to the REMS and the dosing range / titration of the product. 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. We believe none of the dissenting opinions felt this is an un-approvable product; they simply wanted to see more data.

Titan Licenses Probuphine To Braeburn Pharma

On December 17, 2012, Titan Pharma announced the signing of a license agreement with Braeburn Pharmaceuticals Sprl, wholly owned by Apple Tree Partners. As per terms of the agreement, the license grants Braeburn exclusive commercialization rights to Probuphine in the U.S. and Canada. In return, Titan has 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, 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 a tiered royalty ranging from "mid-teens" to "low-twenties" on sales of Probuphine at Braeburn. In addition, Braeburn has allocated in excess of $75 million to launch, commercialize and continue the development of Probuphine.

…Meaningful Market Opportunity…

We see a meaningful market opportunity for Probuphine. 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 (Figure-1).

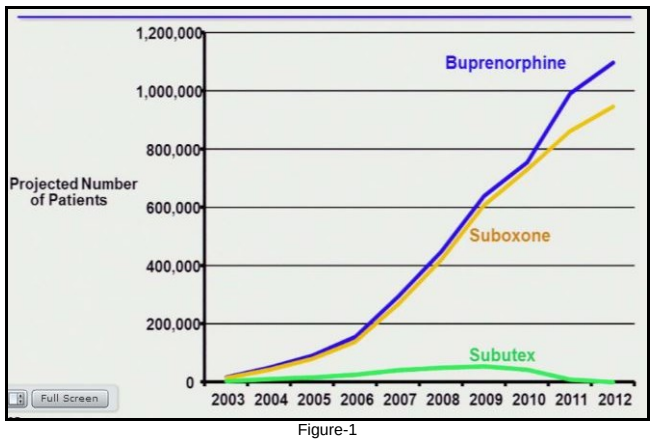

Figure-1

The majority of Suboxone prescriptions are written by general practitioners, family medicine doctors, doctors of osteopathy, psychiatrists, and internal medicine specialists. During the FDA advisory panel, the FDA was concerned that none of the high Suboxone prescribers were surgeons or OB/GYNs with significant experience implanting devices such as Probuphine. The FDA was concerned that the addiction medicine physician, who will be DATA-2000 waived, would refer out the implantation procedure to a surgeon, who may not be DATA-2000 waived and have no experience with either buprenorphine or in treating opioid addicts. The FDA proposed REMS mandates that the implantation procedure must take place at a DATA-2000 waive 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.

We think the FDA's proposed model makes sense. We do not see favorable enough economics for a surgeon to implant Probuphine, the reimbursement for the procedure simply will not afford for a dual-physician model, nor does the FDA want to see a dual-physician model. We believe high prescribing DATA-2000 waived centers may have the economics to hire a specialist, nurse practitioner / physician's assistant, to train under the REMS program. 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 physiatrist 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. We estimate that around two-thirds of the Suboxone market is on stable doses of 12-16mg. These are the patients that can be transitioned over to Probuphine without dose-slippage or a need for titration. Thus, from a modeling standpoint, it make sense to eliminate another one-third of the market.

Above we note approximately 1 million subjects per year on buprenorphine. Our market assumption is that Braeburn can capture approximately 10% 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 12mg 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 by 2019. 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 $350 million (100,000 patients x $2,000 x 1.75). We have $0 revenues in our model for chronic pain indications at this time.

A Whole New Ballgame For Titan

Titan exited 2012 (December 31, 2012) with $18.1 million in cash and investments. We note that Titan has a $2.5 million scheduled installment payment to Deerfield in early April 2013. However, if Probuphine is approved, either in late April 2013 or late July 2013, Titan will receive up to $50 million from Braeburn Pharmaceuticals. This would be a transformational event for the company, and allow management to continue to expand upon the novel delivery of the ProNeura technology platform. We remind investors that Titan is seeking to generate proof-of-concept data using the ProNeura delivery platform and a dopamine agonist for the treatment of Parkinson's disease.

We believe risk still exists prior to the scheduled PDUFA on April 30, 2013. Firstly, the agency may ask for a three month extension to finalize the REMS. We remind investors that the DEA needs to get involved here as well. The second risk we see is on the inspection of the manufacturing facility. Although we have no insight into any potential issues, a complete response letter based on CMC deficiencies is a quite common event.

Regardless, we think Titan's stock has some meaningful upside left given the big pull back earlier in the week. The stock is still trading well below its 52-week high of $2.53. We remind investors that Titan will receive $50 million upon approval from Braeburn. The current market capitalization (on basic shares) is only $135 million. At some point, Titan plans to seek regulatory filings in Europe as well, which could allow for additional out-licensing opportunities in the coming quarters as Braeburn holds only the U.S. and Canadian rights to the drug. Our target is now $3.00 per share based on DCF. Announcement of a 3 month extension to the PDUFA could create a nice entry point for shareholders. A complete response letter (CRL) on an easily fixable CMC issue could also present a nice entry point. Nevertheless, with the stock trading 75% below our target price, we'd be buyers today.

PROJECTED FINANCIALS

Titan Pharmaceuticals, Inc.
Income Statement

Titan Pharma	2011 A	2012 A	Q1 E	Q2 E	Q3 E	Q4 E	2013 E	2014 E	2015 E
Probuphine Royalty	**$0**	**$0**	**$0**	**$0**	**$1.0**	**$2.7**	**$3.7**	**$9.9**	**$24.5**
YOY Growth	-	-	-	-	-	-	-	*165.1%*	*147.5%*
Fanapt Royalty	**$3.6**	**$4.8**	**$1.1**	**$1.2**	**$1.3**	**$1.3**	**$4.9**	**$5.0**	**$2.5**
YOY Growth	*42.7%*	*32.5%*	*-10.4%*	*-11.8%*	*5.9%*	*39.2%*	*3.2%*	*2.0%*	*-50.0%*
Licensing & Grant Revenue	**$0.5**	**$2.4**	**$2.5**	**$5.0**	**$55.0**	**$2.5**	**$65.0**	**$20.0**	**$20.0**
Total Revenues	**$4.1**	**$7.1**	**$3.6**	**$6.2**	**$57.3**	**$6.5**	**$73.6**	**$34.9**	**$47.0**
YOY Growth	*-59.7%*	*75.0%*	-	-	-	-	*934.5%*	*-52.6%*	*34.6%*
CoGS	$0	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	*100.0%*	*100.0%*	-	-	-	-	*100.0%*	*100.0%*	*100.0%*
R&D	$11.2	$10.6	$2.5	$2.0	$1.8	$2.0	$8.3	$7.5	$8.0
% R&D	*275.5%*	*149.1%*	-	-	-	-	*11.3%*	*21.5%*	*17.0%*
SG&A	$3.4	$4.9	$1.3	$1.1	$1.2	$1.3	$4.9	$5.2	$5.5
% SG&A	*82.8%*	*68.5%*	-	-	-	-	*6.7%*	*14.9%*	*11.7%*
Operating Income	($10.5)	($8.4)	($0.2)	$3.1	$54.3	$3.2	$60.4	$22.2	$33.5
Operating Margin	*-258.3%*	*-117.6%*	-	-	-	-	*82.1%*	*63.6%*	*71.2%*
Total Other Income	($4.7)	($1.5)	$0.1	$0.5	$0.4	$0.4	$1.4	$1.0	$1.0
Pre-Tax Income	($15.2)	($9.9)	($0.1)	$3.6	$54.7	$3.6	$61.8	$23.2	$34.5
Taxes & Other	$0	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*5%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	($15.2)	($9.9)	($0.1)	$3.6	$54.7	$3.6	$61.8	$23.2	$34.5
Net Margin	*-373.7%*	*-138.7%*	-	-	-	-	*84.0%*	*66.5%*	*73.4%*
Reported EPS	**($0.26)**	**($0.15)**	**($0.00)**	**$0.04**	**$0.66**	**$0.04**	**$0.75**	**$0.27**	**$0.38**
YOY Growth	*171.5%*	*-42.1%*	-	-	-	-	*-606.1%*	*-63.7%*	*40.4%*
Weight Ave. Shares Out	59.3	66.5	81.8	82.0	82.5	83.0	82.3	85.0	90.0

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

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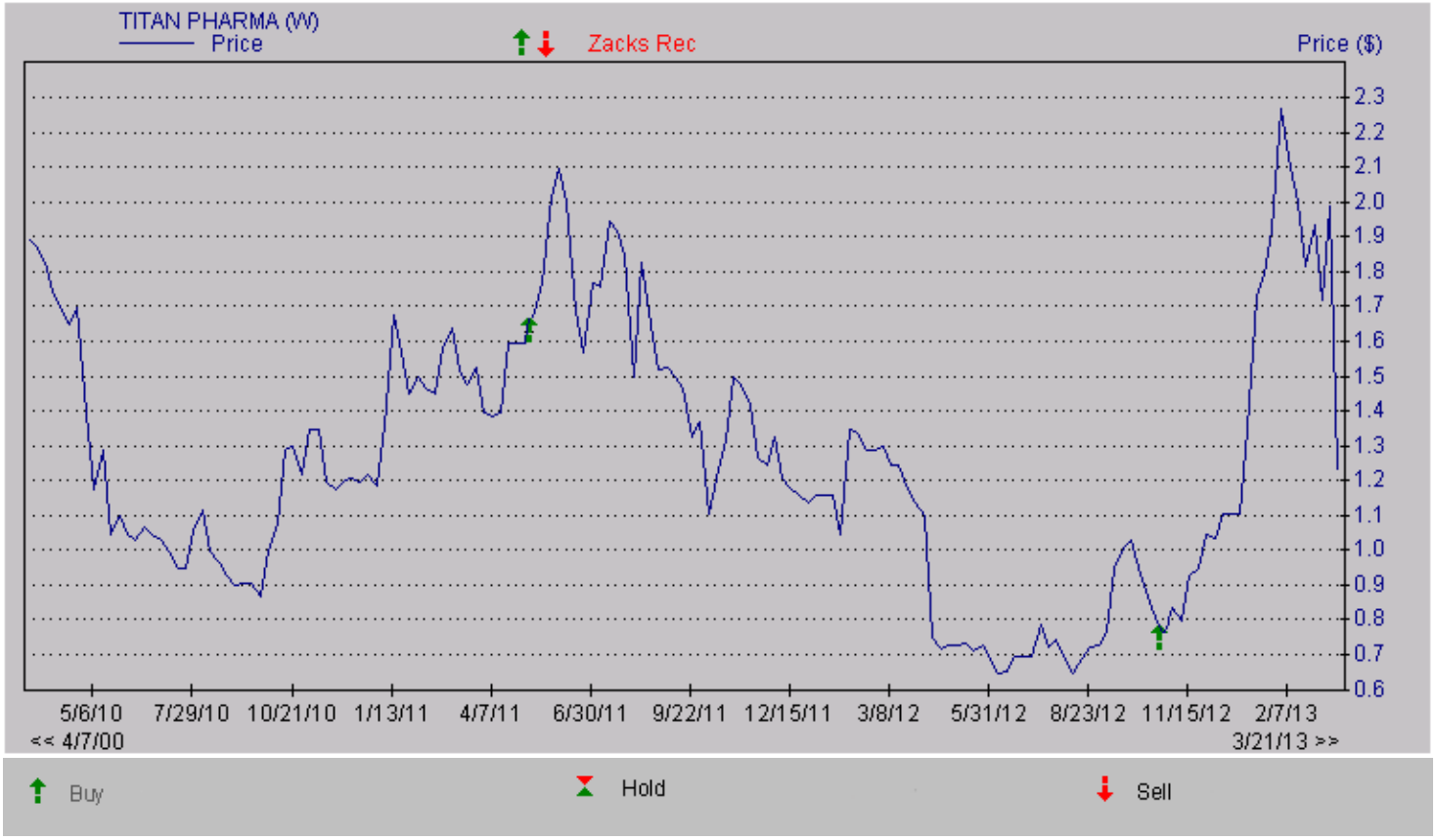
HISTORICAL RECOMMENDATIONS



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