Zacks Small-Cap Research

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Titan Pharmaceuticals, Inc.

(TTNP-NASDAQ)

TTNP: FDA Advisory Panel Recommends Approval of Probuphine By Solid Margin for Second Time…

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	06/01/2011
Current Price (1/26/16)	$3.09
Target Price	**$8.25**

UPDATE

On January 12, 2016, The Psychopharmacologic Drugs Advisory Committee (PDAC) of the U.S. Food and Drug Administration (FDA) voted 12-to-5 to recommend approval of Probuphine, the first long-acting, subdermal buprenorphine implant for the maintenance treatment of opioid addiction in stable patients receiving 8 mg or less per day of buprenorphine. The PDUFA date is set for February 27, 2016. Our report provides a recap of the voting question and highlights the discussion questions asked of the panel.

As a reminder, Titan was uplisted to the NASDAQ in October 2015, and the company continues to move forward with the ProNeura in Parkinson's Disease program. Titan recently added an implantable product for hypothyroidism to its pipeline, and it continues to evaluate other chronic disease settings for potential ProNeura platform expansion.

With both late and early-stage programs utilizing the ProNeura platform under way, we continue to re-iterate our "Buy' rating and maintain our $8.25 price target.

SUMMARY DATA

52-Week High	**$5.29**
52-Week Low	**$2.63**
One-Year Return (%)	**8.72**
Beta	**1.85**
Average Daily Volume (sh)	**407,290**
Shares Outstanding (mil)	**20**
Market Capitalization ($mil)	**$61**
Short Interest Ratio (days)	**17.97**
Institutional Ownership (%)	**0**
Insider Ownership (%)	**6**
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 2015 Estimate	**N/A**
P/E using 2016 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)
2014	0.9 A	0.9 A	0.9 A	0.9 A	3.6 A
2015	0.9 A	0.8 A	0.0 A	0.0 E	1.7 E
2016					19.1 E
2017					21.3 E

Earnings per Share

(EPS is operating earnings before non-recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	-$0.11 A	-$0.05 A	$0.04 A	-$0.02 A	-$0.14 A
2015	-$0.24 A	-$0.11 A	-$0.09 A	-$0.14 E	-$0.59 E
2016					$0.39 E
2017					$0.39 E

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WHAT'S NEW

FDA Panel Votes To Approve Probuphine

On January 12, 2016, The Psychopharmacologic Drugs Advisory Committee (PDAC) of the U.S. Food and Drug Administration (FDA) voted 12-to-5 to recommend approval of Probuphine, the first long-acting, subdermal buprenorphine implant for the maintenance treatment of opioid addiction in stable patients receiving 8 mg or less per day of buprenorphine. The PDUFA date for Probuphine is set for February 27, 2016. There were eight discussion questions asked of the panel, and only one voting question, which we will proceed to highlight below. Briefing materials were also made available prior to the meeting.

As a reminder, the new drug application (NDA) for Probuphine was resubmitted to the FDA in August 2015 by Braeburn Pharmaceuticals, Inc. on behalf of Titan Pharmaceuticals (NASDAQ: TTNP), and was later accepted for six-month priority review in September 2015. The Probuphine NDA resubmission included results from the Phase 3 double-blind, double-dummy study that we have reviewed in previous updates. The study met the pre-specified primary endpoint of non-inferiority in addition to secondary efficacy endpoints.

Quick Recap of Probuphine Regulatory History

As a reminder to investors, Titan reported positive topline results from a confirmatory Phase 3 study with Probuphine in subjects with opioid addiction on June 8, 2015. This was the third positive Phase 3 trial for the company since 2011. Titan had previously completed two Phase 3 safety and efficacy trials on the drug with both showing superiority over placebo implants and non-inferiority to sublingual buprenorphine/naloxone for the treatment of opioid addiction (1stP3, 2ndP3). The company also conducted two open label long-term treatment safety studies and one relative bioavailability study. Titan filed for U.S. approval in October 2012, and along with commercialization partner, Braeburn Pharmaceuticals, was granted priority review by the agency in January 2013. In March 2013, the FDA's Psychopharmacologic Drugs Advisory Committee (PDAC) voted (10 positive votes, 4 negative votes, and 1 abstention) to recommend approval of the product; however, the FDA issued a complete response letter (CRL) in April 2013 stating that approval was not granted, and requested additional data on the use of the product in patients stable on lower doses of sublingual buprenorphine/naloxone than previously tested in the first two Phase 3 clinical trials. Back in 2013, concerns mainly revolved 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). A post-action meeting took place on November 19, 2013, and it was established that the FDA would consider a limited indication, but a trial would be needed. A series of post-meeting communications to discuss the study design also took place.

PDAC Voting Question

Voting Question #8: 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: 12 YES, 5 NO

The voting went pretty much as we anticipated as we were expecting for the panel to recommend approval of Probuphine. The majority of the panel (12 out of 17 members, or about 71%) voted that based on the data presented and discussed at the meeting, the efficacy, safety, and risk-benefit profile of Probuphine supports the approval of the NDA for the proposed indication of maintenance treatment of opioid dependence in patients who are stable on a dose of 8mg or less per day of sublingual buprenorphine. Several panel members that voted in favor of Probuphine approval stated that the trial data demonstrated non-inferiority in light of the FDA's thorough sensitivity analyses. Furthermore, several committee members emphasized that the patient population needs to be clearly defined and outlined in the labeling material if Probuphine is ultimately approved.

The panel members that voted against approval voiced concerns regarding identification of the appropriate patient population, the missing urine data, the implications of rescue medication use, and mitigating risks that were associated with implantation and removal of the Probuphine implant. We think it's important to point out that a few of the panel members that voted 'NO' had some interesting explanations when accounting for their positions regarding the vote. For instance, one panel member voted 'NO' because she wasn't quite sure what she was voting for, and she mentioned that she could very well change her mind in a month. Another panel member voted 'NO' because of how the question was phrased. Regardless, in our opinion, it seems that although there were some

issues brought up, using the FDA's conservative analysis methods for non-inferiority, the panel generally felt that Probuphine should be approved as the benefits clearly outweigh the risks. Most of the panel members agreed 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.

PDAC Discussion Questions

We will briefly touch upon some major points raised during the PDAC meeting. As buprenorphine continues to be misused, abused and diverted, we believe that the FDA understands the potential that an implant could have on the current public health crisis, and has showed some flexibility for this reason. For instance, as per the briefing documents, "historically, the Division has been reluctant to agree to non-inferiority designs for trials of drugs intended to treat opioid dependence because of the lack of consistent information about the expected response rate, related to the heterogeneity of response definitions, study designs, populations, and treatments. However, some flexibility was deemed appropriate because the Division recognized the potential public health benefit of an implantable formulation of buprenorphine in light of a growing problem of misuse, abuse, and accidental exposure of buprenorphine." In our opinion, we believe that this shows us at the FDA is willing to work with Braeburn/Titan, which is good news.

However, the FDA did have some issues with the way the trial data were analyzed and presented, and spent quite a bit of time focused on the missing urine data, and the need for rescue Buprenorphine use during the PDAC meeting. Additionally, the FDA also focused on patient selection criteria, and the ability of the Risk Evaluation and Mitigation Strategy (REMS) to lessen the risks associated with the implant.

Discussion Question #1: Probuphine is a non-titratable product that provides a fixed plasma level of buprenorphine. The original studies raised concerns about the appropriateness of the dose for a broad population. The Applicant has specified a population, namely stable patients on a relatively low dose of sublingual buprenorphine, for whom they believe the dose provided by Probuphine is adequate.

a. Discuss whether there is a population that would benefit from the use of Probuphine and how to define this population.
b. If there is a population that would benefit from Probuphine, discuss whether the study entry criteria adequately define this patient population.
c. ***Discuss whether the population studied reflected this population.***

Braeburn/Titan defined a narrower population than what was initially proposed – stable patients on a relatively low does of sublingual buprenorphine, which accounts for approximately 25% of all patients that are taking sublingual buprenorphine. The panel was split on whether the study entry criteria were appropriate. Some of the panel members believed the study entry guidelines (clinical stability checklist) that were set by the sponsor were adequate. Some of the members believed that by trying to adjust the entry criteria post-hoc would present with issues, and that in the real-world clinical setting, a physician's judgment of the stability of a patient is quite meaningful. Others believed that the entry criteria that were used were not quite adequate. For instance, one panel member noted that a "behaviorally stable" patient population would be the ideal population for treatment, and the entry criteria should be tweaked. She noted that opiate use disorder is rarely seen by itself, and individuals with the disorder often struggle with polysubstance abuse, and thus some patients would not be considered stable on their buprenorphine dose at the beginning of the treatment. The panel suggested that if Probuphine is approved, the FDA should work closely with Braeburn/Titan to make sure the labeling clearly reflects a well-defined patient population that was studied and most benefited from Probuphine use.

Discussion Question #2: In general, occasional dose adjustments for patients on sublingual buprenorphine can be expected over time. The sponsor chose not to include rescue medication as an element of the responder definition because there was an expectation that patients would require little to no rescue medication. However, that was not the case, as rescue medication was used by a number of patients, some throughout the 6-month treatment period.

Discuss whether use of rescue should be considered in defining a responder for a long-acting formulation of buprenorphine such as Probuphine, where the dose cannot be adjusted over time. If rescue should be part of the responder definition, should the use of rescue buprenorphine be differentiated based on the pattern or the frequency of rescue use over the 6-month treatment? Consider the following patterns of use:

a. Use primarily after first initiating Probuphine

b. Use throughout the 6-month period
c. Use only at the end of the 6-month treatment period

The FDA stated that rescue buprenorphine use was not accounted for in the responder definition, as it was believed that patients would not require rescue medication. However, rescue medication use occurred in 15% of patients on sublingual buprenorphine, and 18% of patients on Probuphine or in 16% of all patients (28 of 173 total patients). Since Probuphine is not titratable, sublingual buprenorphine might be required on an as-needed basis.

The panel stated that, in future trials, the amount and extent of rescue buprenorphine medication used should play a part in the assessment of whether or not a patient is a responder or non-responder. It was brought up that usage of rescue medication at the initiation of treatment might not necessarily indicate non-response, whereas continual use of rescue medication over a 6-month treatment period is more likely to indicate non-response. The committee brought up some interesting points regarding the non-interiority margin, and encouraged the FDA to come up with a threshold/margin that would be appropriate in defining a patient as a non-responder. It sounded like some members believe that it is reasonable to expect some level of supplemental buprenorphine use at the start of treatment, but would become more concerning if it the need continues or increases for an extended period of time. Another concern that was raised was that using oral rescue medication in essence takes away the advantages of the implant, as situations such as accidental pediatric exposure and diversion could arise.

Discussion Question #3. ***Customarily in opioid addiction treatment trials, there are many missing urine samples due to relapse and dropout from treatment. Because relapse is the most common reason for dropout, missing urine samples are assumed to be positive. However, in this study, the patients were stably abstinent from illicit drugs, and they were asked to provide only 10 samples over six months. Therefore, it was expected that there would be few missing samples, and that these could be missing for reasons other than relapse. Therefore, the strategy for imputation of missing data did not assume that all missing samples were positive. However, some situations arose in which it might be appropriate to assume that missed samples are indicators of illicit use.***

Discuss how missing or incomplete urine toxicology results should be considered when defining a responder. Consider the following:

a. Patients who were completely lost to follow-up immediately after receiving the Probuphine implant
b. Samples that were not collected due to:
- ***1. Missed scheduled visit***
- ***2. Missed random sample visit***
- ***3. Refused by patient***

c. Samples that were collected on schedule but were not analyzed in a timely fashion (out of stability window for the test)

The FDA explained that 12% of the urine toxicology samples in each arm of the trial were missing due to missed visits. The FDA highlighted four issues with the original missing data strategy: (1) The missing data were only imputed if no samples were provided for a month; (2) Illicit opioid usage was assumed to be equally likely for missing and observed data; (3) Subjects who provided no post-baseline efficacy assessments had a very high chance of being classified as responders, and (4) No attempt was made to account for specimens that could not be analyzed conclusively. It appeared that the FDA believed that the way the missing urine toxicology data was analyzed was using an optimistic imputation strategy.

The panel had mixed views in regards to the missing urine data. One member stated that all missing urine toxicology samples should be considered positive for illicit use, while another member stated that there may be reasons other than illicit drug use that could result in a missed sample, and that full compliance in any trial is extremely difficult to achieve. There were some concerns regarding the patients that were lost to follow-up, and additional models/predictors of missing samples should be further explored.

Discussion Question #4. ***The protocol-specified responder definition did not take rescue use into account, and employed an optimistic imputation strategy for missing urine toxicology results, yielding a responder rate of 96% vs. 88% for Probuphine and sublingual buprenorphine, respectively. As you have seen, there are many different possible responder rates once these factors are taken into account.***

Discuss which of the various approaches to expressing a responder rate you think is most appropriate.

The panel mainly agreed with how the FDA approached the data and conducted several different sensitivity analyses of the responder rate. Many members believe that patients that were lost to follow-up should be included in the intention-to-treat assessment as non-responders, and should not be excluded. More specifically, the three patients that were lost to follow-up should be included as non-responders. One committee member even recommended that the non-inferiority margin should be lowered from 20% to 10% (or possibly even 5%) because of the belief that non-inferiority trials tend to bias in favor of the treatment arm.

Discussion Question #5. Patients managed with buprenorphine may require dose adjustment over time. However, in clinical practice, unlike patients on sublingual buprenorphine, Probuphine-treated patients would not necessarily be seen for regular visits with buprenorphine dose adjustments.

a. Discuss how the need for occasional supplemental doses will translate to clinical practice for patients treated with Probuphine. If patients need to have sublingual buprenorphine on hand in addition to Probuphine, discuss how these prescriptions will impact the product's ability to mitigate misuse, abuse, and accidental pediatric exposure.

b. Some patients on Probuphine required supplemental sublingual buprenorphine only briefly after insertion of the implant, while others required it only at the end of the dosing period when plasma levels could have been falling. In contrast, some patients required ongoing supplemental dosing throughout the 6-month treatment period.

c. Discuss whether the pattern of supplemental sublingual buprenorphine should be taken into consideration when deciding if Probuphine is effective and should be continued for a given patient in clinical practice. Discuss whether there is a pattern of sublingual buprenorphine use that should result in the discontinuation of Probuphine.

The panel agreed that the use of supplemental sublingual buprenorphine would reduce the benefit to mitigate misuse, abuse, and accidental pediatric exposure. The panel believed that although the Probuphine implant is expected to last for 6 months, patients should still be seen by physicians on a regular (for example, monthly) basis for assessment. The implant is not intended to reduce patient visits, and physicians should still be actively involved in monitoring patients, especially in patients that need supplemental dosing. Patients should not be allowed to self-titrate without physician supervision. One committee member stated that if a patient required long-term supplemental sublingual buprenorphine, this would lead her to discontinue Probuphine use in this specific case. It was mentioned that labeling instructions should be precise, and should highlight the necessity for regular physician visits in order to ensure that patients are properly stabilized.

Discussion Questions #6 & #7. The Sponsor has provided information on a training and certification program to ensure that practitioners can safely insert Probuphine. However, the procedure of removing Probuphine after six months of implantation is not readily modeled for the purposes of training because there is development of fibrotic tissue around the implants. Discuss the steps the Sponsor should take to ensure that removals, including complicated removals, are performed appropriately.

The Sponsor has proposed a Risk Evaluation and Mitigation Strategy (REMS) which consists of restricted distribution and a training/certification program for healthcare professionals who will insert and remove the product. Discuss whether the REMS is adequate to address the risks of potential complications associated with the insertion and removal procedures, and abuse, misuse, and accidental overdose.

The FDA did not identify any new safety concerns related to systemic buprenorphine usage. Safety issues that were discussed revolved around implantation and removal of the Probuphine implant. The FDA compared implantation/removal of the Probuphine implant to that of existing data related to implantable contraceptives and stated that removal of the Probuphine implant may require imaging equipment and surgical exploration in certain situations, especially if fibrotic tissue has developed around the implant. The FDA also had some concerns that if the implant protrudes or comes out of the skin, this may present with a risk of abuse, misuse, and accidental overdose.

There were some concerns raised by the committee regarding the usage of pork tenderloin for insertion/removal and training purposes. We do see how performing the procedure on a pork tenderloin differs from an actual implantation/removal of the Probuphine implant into a human arm, especially when it comes to retrieval of the implant as normal fibrosis would not be seen during the training session in the meat simulation model. Some committee members also thought that it might be difficult for certain health care practitioners to perform the procedure, such as psychiatrists that were not adequately trained in procedures. Braeburn offered reassurance that overall, the newly trained practitioners were doing very well with the training program. One committee member suggested the use of webcast training or having an expert/trainer accessible by phone (or facetime) to assist with

real-life procedures if necessary. The committee seemed to support the idea of exploring more options that would result in greater procedural experience in humans. Another committee member suggested having providers conduct the first implantation and removal under supervision.

***Discussion Questions #9:* Comment on any further development or explorations, e.g. higher doses, the Sponsor should undertake.**

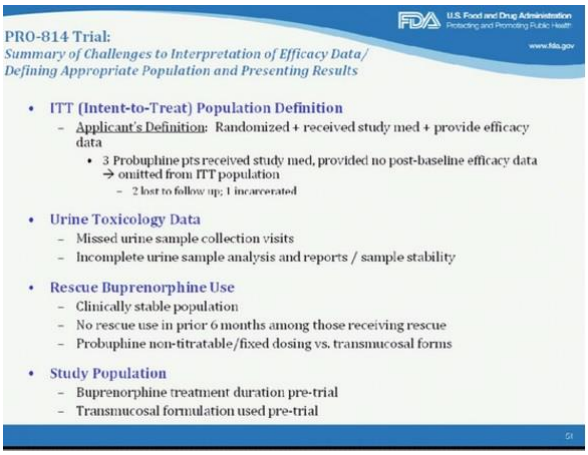
In addressing further development or explorations that Braeburn/Titan should undertake, the panel members had several recommendations including exploration of additional doses (including larger doses), studying Probuphine usage in more diverse patient populations, requiring urine samples or a more frequent basis, induction studies aimed at providing improved guidance regarding supplemental buprenorphine use, continuing assessment of Probuphine use beyond two years, monitoring supplemental buprenorphine use in the post-approval/post-market setting, tracking of safety and efficacy outcomes, and monitoring of patients (for example, in situations where patients may attempt implant retrieval on their own).

Open Public Hearing

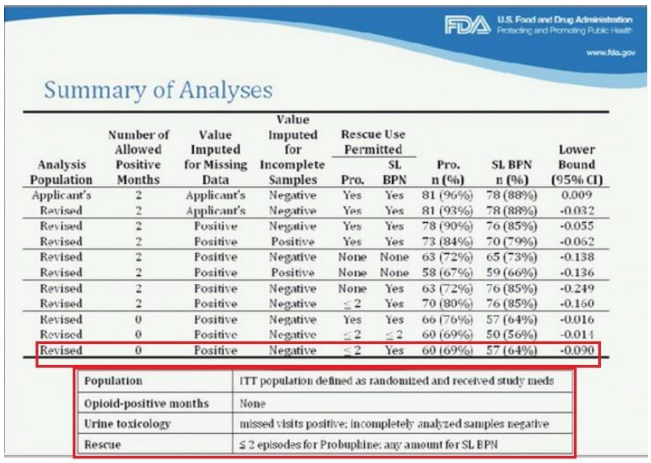
As part of the advisory committee meeting, an open public hearing included first-hand accounts, letters and feedback from patients, physicians, clinical trial investigators, and advocacy organizations. There were 18 speakers during the open public hearing, and 17 of them spoke in favor of Probuphine approval. Only one speaker, a pharmacist from the National Center for Health Research, spoke out against approval, as she believed that there was not enough evidence to support efficacy and that the trial had some flaws. Overall, the hearing demonstrated the public's strong desire for new treatment options like Probuphine to be available for the treatment of opioid addiction in order to combat the current opioid public health crisis.

Our Perspective

We have included slide 51 from the FDA's presentation (by Clinical Reviewer, Dr. Rachel Skeete, of the Division of Anesthesia, Analgesia, and Addiction Products and Statistical Reviewer, James Travis, PhD, of the Division of Biometrics II) below. This slide summarizes the challenges that the FDA saw with the PRO-814 trial data relating to efficacy data, definition of the intent-to-treat population, and presentation of results:



As a reminder, in June 2015, Titan reported that its Phase 3 trial met its pre-specified primary endpoint of non-inferiority. In the trial, patients (n=177) were randomized to treatment with either 4 active implants plus daily placebo tablets or 4 placebo implants plus daily active control tablets (≤8 mg/day sublingual buprenorphine/naloxone) for 6 months. A responder was defined as having at least four out of six months free of illicit opioids based on urine testing and subject self-report. Analyses conducted according to the pre-planned Statistical Analysis Plan indicated response rates of 96.4% for the Probuphine arm and 87.6% for the sublingual buprenorphine/naloxone arm. The two-sided 95% confidence interval (0.009, 0.167) of the treatment difference (Probuphine – sublingual buprenorphine/naloxone) was well within the pre-defined successful margin for non-inferiority. In fact, sequential analysis showed that Probuphine was clinically superior to sublingual buprenorphine/naloxone ($p < 0.05$). The safety and tolerability profiles for both treatment groups were also reported to be comparable.



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Summary of Analyses

Analysis Population	Number of Allowed Positive Months	Value Imputed for Missing Data	Value Imputed for Incomplete Samples	Rescue Use Permitted		Pro. n (%)	SL BPN n (%)	Lower Bound (95% CI)
				Pro.	SL BPN			
Applicant's	2	Applicant's	Negative	Yes	Yes	81 (96%)	78 (88%)	0.009
Revised	2	Applicant's	Negative	Yes	Yes	81 (93%)	78 (88%)	-0.032
Revised	2	Positive	Negative	Yes	Yes	78 (90%)	76 (85%)	-0.055
Revised	2	Positive	Positive	Yes	Yes	73 (84%)	70 (79%)	-0.062
Revised	2	Positive	Negative	None	None	63 (72%)	65 (73%)	-0.138
Revised	2	Positive	Positive	None	None	58 (67%)	59 (66%)	-0.136
Revised	2	Positive	Negative	None	Yes	63 (72%)	76 (85%)	-0.249
Revised	2	Positive	Negative	≤ 2	Yes	70 (80%)	76 (85%)	-0.160
Revised	0	Positive	Negative	Yes	Yes	66 (76%)	57 (64%)	-0.016
Revised	0	Positive	Negative	≤ 2	≤ 2	60 (69%)	50 (56%)	-0.014
Revised	0	Positive	Negative	≤ 2	Yes	60 (69%)	57 (64%)	-0.090

Population	ITT population defined as randomized and received study meds
Opioid-positive months	None
Urine toxicology	missed visits positive; incompletely analyzed samples negative
Rescue	≤ 2 episodes for Probuphine; any amount for SL BPN

Source: Slides 52 & 53 adapted from FDA - Red boxes show recommended presentation of findings.

Our view is that the FDA came up with several different ways to analyze the data to account for the missing samples and need for rescue use, including a preferred analysis of the data (*above in red*). We view the FDA's evaluation of the data and sensitivity analyses to be thorough, and believe that even using the FDA's conservative preferred recommendation of analysis, Probuphine is still within the pre-defined margin for non-inferiority. Although this is the second positive advisory committee for Probuphine, we would like to mention that the FDA is not obligated to follow the recommendations of its panel, but will consider the committee's guidance as it completes its review of the Probuphine NDA.

We continue to believe that Probuphine could be a potentially life-saving treatment option for a particular group of patients that are not responding well to currently available treatment options. We do agree that that the implant has risks associated with it, but a well-defined, stable patient population could greatly benefit from this treatment option if approved. As mentioned before, the FDA recognizes the public health crisis related to opioid abuse and has been willing to be flexible. We believe that the labeling for Probuphine, if approved, needs to be very specific, and there needs to be strict guidelines in place related to prescribing practices. We do believe risk still exists, and that there are some issues with the implant, but like the majority of the PDAC, we believe that the benefits outweigh the risks for a pre-specified group of patients where the treatment could be potentially life-saving. We believe the risks are mainly related to the REMS and use of rescue medication. The patient population at hand is a very difficult one to manage in a clinical trial setting, and we see challenges with trial design and compliance as being unavoidable to some degree. We are not sure if two positive advisory committee votes (2013 & 2016) and positive data from three Phase 3 trials will be enough for approval this time around, so we will just have to wait and see until the agency action date.

We would also like to mention that Probuphine has been gaining quite a bit of media attention since the Psychopharmacologic Drugs Advisory Committee (PDAC) of the U.S. Food and Drug Administration (FDA) voted 12-to-5 to recommend approval of Probuphine. Articles have been popping up in the NY Times, NPR, and USA Today to name a few. President Obama even brought to light the severity of the opioid of the epidemic in the opening remarks of his State of the Union speech. Opioid abuse, addiction and dependence remain major public health and social challenges, especially in the United States. It is estimated that between 26 million and 36 million individuals worldwide abuse opioids (UNODC, World Drug Report 2012) with approximately 2.1 million people in the U.S. suffering from substance use disorders related to prescription opioid pain relievers in 2012, and an estimated 467,000 suffering with heroin addition (National Survey on Drug Use and Health, 2012). Opioid dependence is increasingly being recognized as a global epidemic by various health authorities.

On September 17, 2015, U.S. Health and Human Services Department (HHS) Secretary Sylvia Burwell announced that HHS plans to revise the regulations surrounding the prescribing of buprenorphine to allow for expanded access to medication-assisted treatment (MAT) for the treatment of opioid dependence. Currently, there is a limit to the number of patients that can be treated with buprenorphine products by certified physicians. This cap restricts availability to these important and often life-saving medication-assisted therapies. The HHS revision aims to "provide a balance between expanding the supply of this important treatment, encouraging use of evidence-based MAT, and minimizing the risk of drug diversion." Federal officials are aiming to address the opioid epidemic in an effort to offer greater access to safe and effective treatment options for opioid maintenance. If approved, we see the potential for Probuphine to help address the nation's opioid abuse epidemic, which is consistent with HHS's objectives.

Titan exited the third quarter of 2015 (September 30, 2015) with approximately $9.7 million in cash. We believe that these funds are sufficient to support Titan's planned operations into the fourth quarter of 2016. If Probuphine is approved, Titan will receive a $15.0 million milestone payment from Braeburn. We also believe that potential licenses outside the U.S. could occur in the near future, thus bringing in more non-dilutive cash to the company. All-in-all, we believe Titan is currently in a strong financial position, especially with the possibility of receiving the $15.0 million milestone payment from Braeburn. Titan continues to work with its contract manufacturer and Braeburn in preparation for product launch. We are not sure how long the final labeling and packaging will ultimately take, but if all goes well and Probuphine gets approved this time around, we could see a product launch as early as mid-2016.

We view the recent pullback in the biotechnology sector as a nice opportunity for investors to initiate or add to a position in Titan. We believe that Probuphine approval 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 continues to move forward with the ProNeura in Parkinson's Disease program, and the company announced the addition of an implantable product for hypothyroidism to its pipeline in November 2015 while it continues to evaluate other chronic disease settings for potential ProNeura platform expansion.

We think Titan's stock continues to have some meaningful upside left given the big pull back. We would also like to point out that Titan has also made progress in evaluating additional compounds that can be delivered in the ProNeura implant, and just added an implantable triiodothyronine (T3) product for the treatment of hypothyroidism to its product development pipeline. We are looking forward to learning more about this product and additional pipeline candidates in the future. With both late and early-stage programs utilizing the ProNeura platform under way, we continue to see the shares worth $8.25 right now, with potential upside upon Probuphine approval in 2016. At this point, our model has very little contribution from ProNeura in Parkinson's disease, hypothyroidism or other chronic indications or in value for Probuphine outside the U.S. We believe these situations may also present additional upside to our financial model. However, in the event that Titan receives another complete response letter (CRL) from the FDA, we would re-visit our model and need to make significant changes to our valuation and target price.

PROJECTED FINANCIALS

Titan Pharmaceuticals, Inc. - Income Statement

Titan Pharmaceuticals, Inc.	2014 A	Q1 A	Q2 A	Q3 A	Q4 E	2015 E	2016 E	2017 E
Probuphine Royalty	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$4.1**	**$21.3**
YOY Growth	-	-	-	-	-	-	-	-
Licensing & Grant Revenue	**$3.6**	**$0.9**	**$0.8**	**$0.0**	**$0.0**	**$1.7**	**$15.0**	**$0.0**
Total Revenues	**$3.6**	**$0.9**	**$0.8**	**$0.0**	**$0.0**	**$1.7**	**$19.1**	**$21.3**
YOY Growth	-	-	-	-	-	-	-	-
CoGS	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*
R&D	$4.1	$1.4	$1.1	$1.0	$1.3	$4.8	$5.0	$6.0
SG&A	$3.0	$1.1	$0.8	$0.8	$1.1	$3.7	$4.0	$5.0
Operating Income	($3.5)	($1.6)	($1.1)	($1.8)	($2.4)	($6.9)	$10.1	$10.3
Operating Margin	-	-	-	-	-	-	-	-
Total Other Income	$1.1	($3.3)	($1.2)	($0.0)	($0.5)	($5.0)	($2.0)	($2.0)
Pre-Tax Income	($2.4)	($4.9)	($2.3)	($1.8)	($2.9)	($11.9)	$8.1	$8.3
Taxes & Other	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	($2.4)	($4.9)	($2.3)	($1.8)	($2.9)	($11.9)	$8.1	$8.3
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($0.14)**	**($0.24)**	**($0.11)**	**($0.09)**	**($0.14)**	**($0.59)**	**$0.39**	**$0.39**
YOY Growth	*-219.8%*	*118.8%*	*118.5%*	*-304.4%*	*502.3%*	*321.1%*	*-165.3%*	*-0.4%*
Weight Ave. Shares Out	17.1	20.1	20.1	20.1	20.1	20.1	21.0	21.5

Source: Company Filing // Zacks Investment Research, Inc. Estimates

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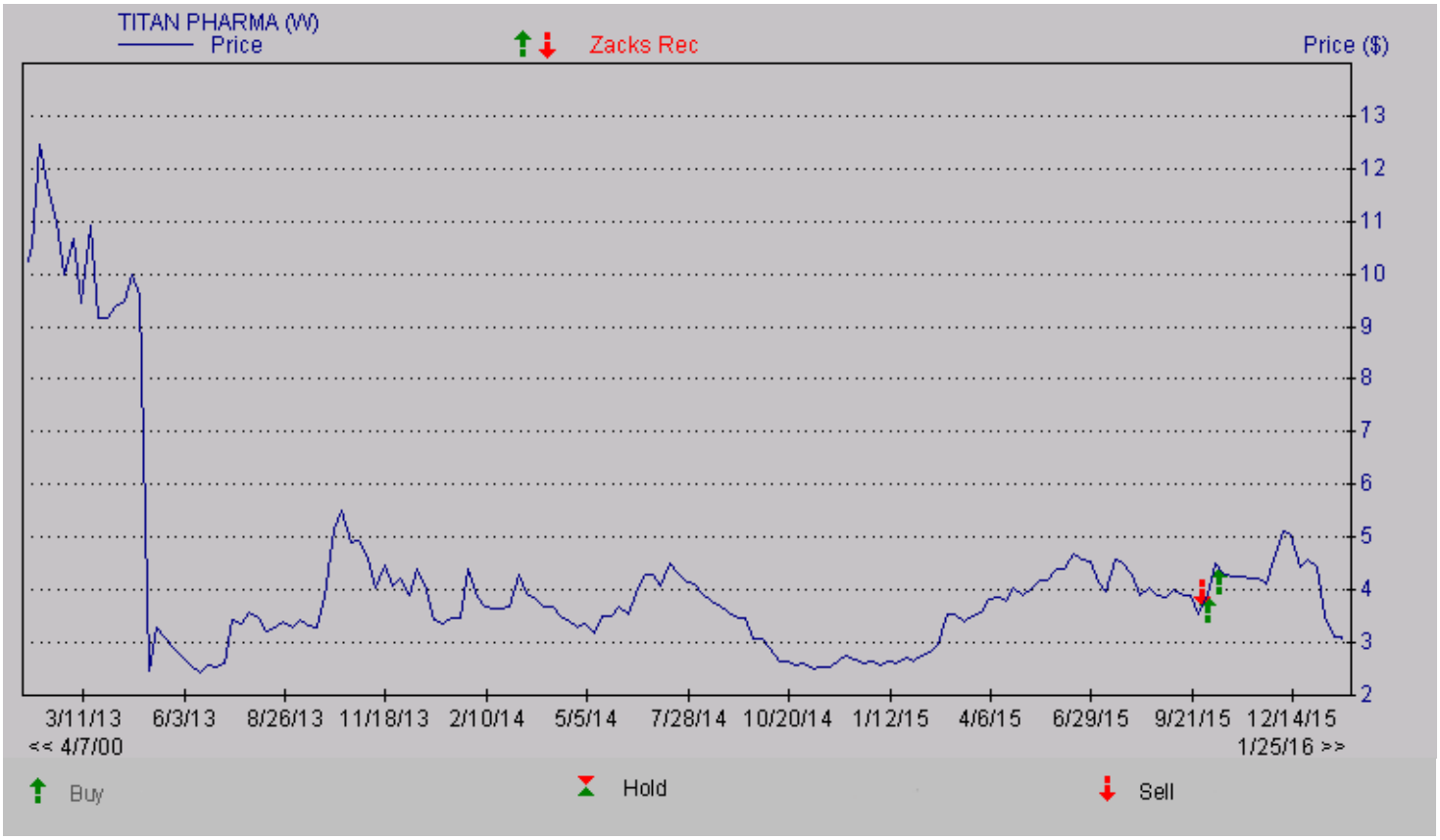

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