Zacks Small-Cap Research

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John D. Vandermosten, CFA
312-265-9588 / jvandermosten@zacks.com

scr.zacks.com
10 S. Riverside Plaza, Chicago, IL 60606

Titan Pharmaceuticals, Inc. (TTNP-NASDAQ)

2016 Results; Deep Dive on Development Programs

Based on our DCF model and a 15% discount rate, TTNP is valued at approximately $11.00 per share. We currently do not include any contribution from the ropinirole or triiodothyronine programs or for sales of Probuphine outside the US and Canada. Valuation for pre-clinical programs will be included upon commencement of Phase I trials.

Current Price (3/17/17)	$3.65
Valuation	**$11.00**

OUTLOOK

Titan Pharmaceuticals launched its first product, Probuphine, in June 2016 through its partner Braeburn Pharmaceuticals. The company is currently in the process of obtaining approval in Europe and identifying a partner who will commercialize Probuphine outside the US and Canada.

Currently, two other candidates are in the development pipeline which use Titan's proprietary ProNeura drug delivery system. Consisting of ethylene-vinyl acetate and a drug substance, ProNeura is a novel approach to drug delivery that benefit from long-duration slow release and controlled substance programs.

Titan's development products include a treatment for Parkinson's Disease (ropinirole) and hypothyroidism (T3) which are currently being prepared to present in IND filings with the FDA.

SUMMARY DATA

52-Week High	**$8.74**
52-Week Low	**$3.55**
One-Year Return (%)	**-3.06**
Beta	**1.59**
Average Daily Volume (sh)	**88,919**
Shares Outstanding (mil)	**21.2**
Market Capitalization ($mil)	**$77.4**
Short Interest Ratio (days)	**12.25**
Institutional Ownership (%)	**0.3**
Insider Ownership (%)	**22.5**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.0**
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 2016 Estimate	**15.2**
P/E using 2017 Estimate	**7.3**
Zacks Rank	**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)
2015	$0.9 A	$0.8 A	$0.0 A	$0.0 A	$1.7 A
2016	$0.0 A	$15.0 A	$0.0 A	$0.0 A	$15.1 A
2017					$23.5 E
2018					$41.4 E

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	-$0.24 A	-$0.11 A	-$0.09 A	-$0.11 A	-$0.56 A
2016	-$0.09 A	$0.55 A	-$0.12 A	-$0.11 A	$0.24*A
2017					$0.50 E
2018					$1.25 E

*Quarterly totals do not sum to annual due to mix of diluted and undiluted shares

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WHAT'S NEW

Titan Reports Full Year 2016 Financial and Operational Results

Titan Pharmaceuticals, Inc. (NASDAQ: TTNP) reported full-year 2016 results on March 16, 2017 and later participated in an earnings call following the market close. Total revenues, which consisted of a milestone payment and Probuphine royalties were $15.1 million compared to our estimates of $16.1 million. The difference was due to fourth quarter royalty revenues of $35,000 vs. our estimates of $1.1 million. R&D expenses of $6.1 million rose 31% over the prior year due to development expenses related to new ProNeura products. G&A of $4.6 million rose 22%, with the higher total attributable to higher non-cash based stock compensation. Net income of $5.1 million or $0.24 per share in 2016, compares to a loss of $11.3 million or ($0.56) per share.

Free cash flow for 2016 was $6.1 million, generated by the $15 million in milestone payments by Braeburn in the second quarter paid upon FDA approval of Probuphine. Cash levels increased over the year as a result of the positive cash flows, from $7.9 million at the end of 2015 to $14.0 million at year end 2016.

Fourth quarter revenues of $35,000 fell below our estimate due to a number of preparatory efforts that were required prior to activating the 60-person salesforce to market the product. Substantial investments in training providers and qualifying them to implant the Probuphine rods were necessary. Some of these efforts included the use of a specialty pharmacy system approved by the DEA in order to distribute Probuphine and approvals from a variety of payors, some of whom require waiting periods before placing a pharmaceutical product on their formularies. Titan's partner Braeburn was able to build this infrastructure over the last part of 2017 in order to support a commercial launch in January 2017.

4Q:16 R&D of $2.1 million surpassed our $1.5 million estimate and G&A of $1.2 million matched our forecasts. Net loss for the quarter was $2.3 million vs. our estimate of $1.6 million or ($0.11) per share. Cash burn in the fourth quarter was ($2.5) million resulting in a cash balance of $14.0 million.

Revenues were lower than expected due to the substantial upfront work required to develop the distribution systems, reimbursement and training required to commercialize Probuphine. As a result we lower our forward estimates for Probuphine revenues to reflect the slower pace, which reduces our price target. Overall, expenses were slightly higher than our estimates, predominantly due to greater external research and development expenses for product development programs. Future upward revisions will depend heavily on the success of Braeburn's commercial launch and Titan's achievements of milestones for development projects.

Recent Achievements

- Probuphine
  - Full commercial launch in 1Q:17
  - Issued J-code (J0570) by CMS aiding in identification and reimbursement of the drug
  - Over 2,500 health care providers received training on implantation and extraction in 2016
  - 70 payors including private insurers, CMS and the VA authorized use
  - EMA confirmed eligibility for review and approval under the centralized procedure
  - Anticipate 4Q:17 filing of a Marketing Authorization Application in EU
  - Several companies conducting due diligence regarding EU and global commercialization
- Titan granted Small Manufacturing Entity (SME) status in Europe, which provides financial incentives
- Ropinirole
  - IND submitted
  - Phase I PK studies expected mid-2017
- Triiodothyronine
  - Shortage of GMP-qualified T3 supply delayed the final formulation optimization studies until 1H:17
  - Pre-IND review with the FDA anticipated 3Q:17

EU/Other Ex-North America Probuphine Commercialization

Titan is in the process of developing its application for approval with the EMA and potentially other territories. Last December, the company's Chief Development Officer, Katherine Beebe, Ph.D., met with EMA, U.K. and German regulatory authorities to determine necessary items to obtain approval through the centralized authority. Based on the interaction with the representatives, Titan was directed to submit Probuphine using the centralized procedure, which upon approval will allow the implant to be marketed in all member countries. Titan was also granted SME status in Europe which provides monetary benefits during the application and commercialization process. The company is also in discussions with partners who will be responsible for commercializing Probuphine in the EU and in Australia, and several of them are currently conducting their due diligence on the drug.

The market in Europe is somewhat different than in the United States and in many cases methadone is used more frequently than buprenorphine for addiction treatment as the standard of care. We see total annual prescriptions at about one-third of the volume in Europe as in the US. Pricing will also be lower outside the United States. We estimated the differential based on the prices of seven[1] drugs in the US and Europe and determined that a 45% adjustment is appropriate.[2] Based on these assumptions we anticipate the peak revenue potential ex-US to be about 15% of the $2 billion in U.S. sales. We will also use any additional details provided by management and a potential partner to adjust these levels and will add an appropriate valuation when and if an announcement is made.

ProNeura Development Programs

Now that Probuphine has been approved by the FDA and partner Braeburn Pharmaceuticals (NASDAQ: BBRX) has begun to commercialize the product, management and investor focus will begin to shift toward development programs. Currently, Titan is advancing two new devices; both of which employ the ProNeura implant technology. First is the ropinirole implant which is intended as adjunctive therapy in conjunction with levodopa. Titan is currently submitting additional information related to its IND on its behalf and Phase I work should being mid-year 2017. The second development project is the triiodothyronine (T3) implant, which is frequently used as adjunctive therapy in conjunction with thyroxine (T4) for hypothyroidism and we expect phased trials to begin in 2018. The superior steady release characteristics of ProNeura are particularly beneficial for the administration of both drugs and may address several of the shortcomings evident in current forms of administration. This report will discuss the background of ProNeura, the clinical setting for Parkinson's Disease (PD) and hypothyroidism and how Titan's products can potentially improve the treatment of these diseases.

ProNeura

In 1987, inventors at MIT filed for a patent that employed the use of multiwall polymeric microcapsules to provide controlled delivery of substances such as drugs, insecticides, fertilizers, indicators and others. In 1995, Titan obtained an exclusive worldwide license from MIT for the use of this patent and others relating to a long-term implantable delivery system and began its efforts to develop what eventually became ProNeura. The original patents have since expired, but new intellectual property rights have been asserted through follow-on patent filings by Titan.

Titan Pharmaceuticals is the exclusive licensee for two patents relating to a long term drug delivery system from MIT. Titan licensed the patent from MIT in 1996, and applied it towards its first commercial product, in what eventually became Probuphine, in 2000. The original patent (US 4861627 A), Preparation of Multiwall Polymeric Microcapsules, was assigned to Massachusetts Institute of Technology with a filing date of May 1987. Titan made improvements and modifications to the original process and filed for another patent entitled Implantable Polymeric Device for Sustained Release of Buprenorphine (US 7736665 B2). This patent described a process which provides a hydrophobic, biocompatible non-erodible polymeric device which releases its drug continuously with generally linear release kinetics for extended periods of time. The drug used in the ProNeura device is released through pores that open to the surface of the ethylene vinyl acetate copolymer matrix.

In different embodiments, the non-erodible polymer implant can deliver drug for varied lengths from three to 24 months and can release from 0.001 to 100 ng of drug per liter of plasma. Devices may be produced using an extrusion process. Ground EVA is blended with a drug substance, melted, and extruded into rod-shaped structures. Rods are cut into individual implantable devices of the desired length, packaged, and sterilized prior to use. One or more of these devices can be implanted in the medial bicipital groove of the inner arm (the hollow between the biceps and triceps muscles).

[1] Crestor, Lantus, Advair, Solvadi, Humira, Herceptin, Gleevec
[2] https://www.bloomberg.com/graphics/2015-drug-prices/

The 505(b)(2) process for the approval of Probuphine began with a pilot study in June 2004. In October 2006, the company initiated a randomized, double-blind, placebo-controlled, multi-center Phase III clinical study of Probuphine in the treatment of opioid dependence. In October 2012, an NDA was prepared and submitted to the FDA for Probuphine, and shortly after Titan came to a license agreement with Braeburn for commercialization in the US and Canada. The first PDUFA date for Probuphine was in April 2013, however, a CRL was issued and it wasn't until May 2016 that Probuphine was finally approved by the regulatory agency following additional clinical work. In total, five studies were conducted for safety and efficacy to generate the necessary data for FDA approval.

During the Probuphine approval process, Titan gained substantial experience and knowledge regarding the ProNeura implant that we believe will substantially reduce the time and risk of developing follow-on products. Much of the safety work for the implants have already satisfied the FDA's concerns with the Probuphine trials. One of the key concerns for the FDA was related to the training and certification component required for the implantation and extraction procedure. Both Titan and Braeburn have developed effective, efficient and approved protocols for training and certifying providers to work with implants. Vendor relationships are also much stronger and more developed than they had been in the past allowing for rapid turnaround and adjustment of product to satisfy evolving needs. Since neither ropinirole nor T3 are controlled substances, we believe the end products will not face as much resistance as implantable buprenorphine did. As a reminder, Probuphine was required to be distributed via the Risk Evaluation and Mitigation Strategy (REMS) program due to buprenorphine's classification as a controlled substance and due to the training and certification component. Future implants may not be subject to this restriction and additional hurdle.

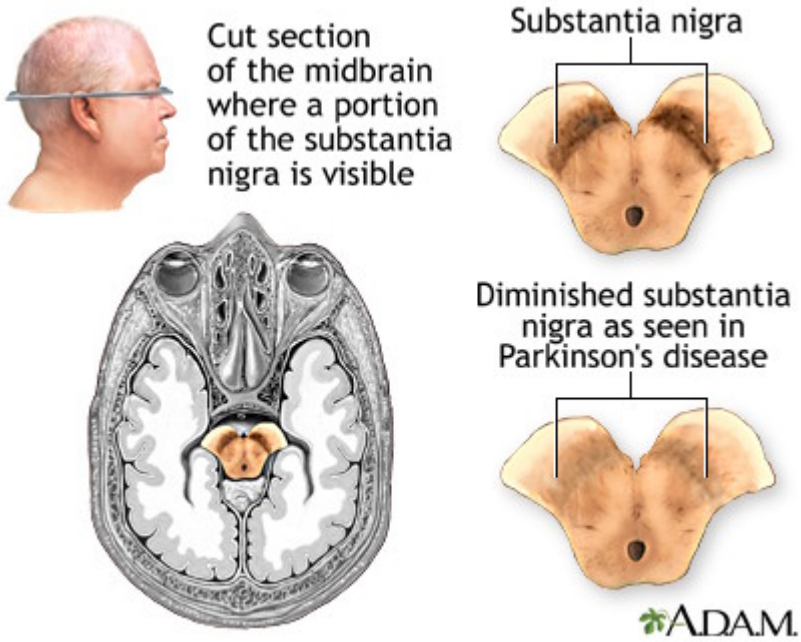
Competing Implant Products

There are other implants that are in the market and perhaps the best known is **Norplant**, which was first approved in Finland in 1983 and developed by the Population Council. The current incarnation of the Norplant, called **Jadelle**, consists of two silicone rods that are implanted in the skin of the upper arm. Currently, the implant is not available in the United States. **Nexplanon** (etonogestrel implant) is another implantable birth control product that is manufactured by Merck and consists of one implant inserted on the inner side on the non-dominant upper arm. The implant itself is an ethylene vinyl acetate (EVA) copolymer implant, 4 cm in length and 2 mm in diameter. Other implants include **Supprelin** (histrelin acetate) which contains a gonadotropin releasing hormone for the treatment of children with central precocious puberty and is marketed by Endo Pharmaceuticals. The implant is a non-biodegradable, diffusion-controlled, hydrogel polymer reservoir containing histrelin acetate, and is designed to deliver the drug over 12 months. Intarcia, a private pharmaceutical development company headquartered in Boston, is also working on an implant to address type 2 diabetes. The implant, called **ITCA 650**, is constructed of titanium and contains a mini pump dispensing exenatide that can treat a patient for up to a full year.

Parkinson's Disease

Parkinson's Disease (PD) is a chronic neurodegenerative disease characterized by progressive movement disorder and a loss of neurons that synthesize and release dopamine. The disorder takes years to develop as the brain slowly reduces production of dopamine, a critical neurotransmitter that helps the body regulate its movements and emotions. While the disease itself is not fatal, complications from PD can cause death. Symptoms include rigidity, resting tremors, akinesia, bradykinesis, loss of facial expression and altered gait and posture. The neurons responsible for the production of dopamine that helps control movements are largely centered in the substantia nigra. When this structure fails to generate dopaminergic neurons, it results in PD. Dopamine is the messenger between the substantia nigra and other parts of the brain to control movement and functions as a neurotransmitter to send signals to other nerve cells.

Exhibit I – Substantia Nigra[3]



Diagnosis

Diagnosis of PD is difficult due to the lack of standard diagnostic tests, and reliance on clinical data, rather than laboratory tests, to make the determination. Generally, after an initial assessment by an internist or family physician the patient will be referred to a neurologist. The neurologist, with a specialty in movement disorders, will provide an additional exam to identify several factors. These include observations regarding:

- Facial expression
- Tremor in limbs, when at rest or extended
- Stiffness in arms, legs or neck
- Ability to rise from a chair
- Gait
- Balance

There are other diseases that may have similar symptoms as PD, including stroke and hydrocephalus, therefore the neurologists' skill is necessary to make a proper diagnosis. A favorable response to the drug levodopa is supportive of a PD diagnosis as it restores dopamine to the brain.

There are a few types of PD, including tremor dominant and postural instability gait dominant (PIDG) which comprise 75% and 25% of the PD population respectively.

PD has several distinct stages as it progresses. The duration of the transition from stage to stage varies widely and can be from just a few years to twenty years. We provide a brief summary of each of the five stages below.

First Stage: Symptoms are mild and do not interfere with a person's lifestyle. Tremors may occur, but they are mild and may only occur on one side of the body. Posture and facial expressions may show a slight change.

Second Stage: Symptoms become worse, with tremors increasing and spreading to both sides of the body (bilateral). Walking becomes more difficult and posture is affected (balance). A person's activities may begin to be affected by the disease.

[3] Animated Dissection of Anatomy for Medicine (ADAM)

Third Stage: At this point, balance becomes difficult and movements slow. Falls may occur and daily activities become more difficult.

Fourth Stage: Symptoms become severe and limit activities. At this point, the PD sufferer requires active care and cannot live alone. Walking by oneself may be difficult or impossible.

Fifth Stage: This is the final stage and the individual is frequently confined to the bed or wheelchair. Nursing care is required at all times and the patient may suffer hallucinations and delusions. There are also other non-motor symptoms such as mood disorders and cognitive changes which occur.

Treatment

Treatment of PD attempts to improve the presence of dopaminergic neurotransmitters with dopamine replacement therapy (DRT) recognized as first line treatment. Dopamine cannot cross the blood-brain barrier, so it is not administered directly as a medicine. Therefore, the alternative levodopa is prescribed, which is able to enter the brain and is converted there into dopamine. This conversion process is brought about by the enzyme aromatic amino acid decarboxylase, which is also present in tissues outside the brain. Due to levodopa's rapid conversion to dopamine when administered to a patient, and to avoid the resulting side effects of nausea and vomiting, carbidopa is added to the drug regimen. Carbidopa, a DOPA decarboxylase (DDC) inhibitor, is responsible for the peripheral conversion of levodopa to dopamine.

The benefits of levodopa frequently wear off after five to ten years and when its effects begins to decline, dose or frequency may be increased and other dopamine agonists such as ropinirole may be used as is combination treatment with levodopa.

Dopamine agonists are also used in PD therapy, and in contrast to levodopa, this class of drug does not need to be modified by brain enzymes to activate dopamine receptors. In many cases dopamine agonists such as pramipexole, rotigotine or ropinirole are used in conjunction with levodopa/carbidopa and in other cases it is used as monotherapy.[4] Ropinirole has a half-life of approximately five to six hours, which requires that it be taken several times throughout the day. Even with frequent dosing, blood plasma levels fluctuate widely and studies have suggested that this volatility can accelerate the progression of PD symptoms. Titan has shown in animal models and hopes to show in clinical trials that steady, non-fluctuating levels of ropinirole can reduce the amount of time patients experience dyskinesias or "off" times and increase the "on" time therapeutic window.

Ropinirole Implant

Titan filed for a continuation patent in March 2016 entitled Implantable Polymeric Device for Sustained Release of Dopamine Agonist in support of its implantable device for subcutaneous administration of a dopamine agonist. Similar to Probuphine, the device also employs a biocompatible, non-erodible polymeric device. In this case the device contains a dopamine agonist that is released steadily over the life of the implant.

There is evidence that the use of dopamine agonists can reduce motor fluctuations (such as dyskinesias and dystonias) and delay the development of complications if administered continuously.[5,6] Research further hypothesizes that fluctuating levels of the drug systemically from daily oral administration are at fault for complications. In contrast, an even release of drug, which more closely approximates the normal physiology of the brain, could extend the duration that the patient operates in the "on" time therapeutic window. Several studies performed in the US and the UK administered levodopa continuously and intravenously to PD patients with severe dyskinesia and dystonia, after which the symptoms disappeared. Animal model testing for ropinirole has also shown an ability to extend functional time and we anticipate that future clinical trials will bear this out.

Titan has conducted a non-clinical study in an MPTP[7] Parkinsonian primate model and demonstrated that a sustained non-fluctuating plasma level of ropinirole could be delivered safely for several months following implantation and could control PD symptoms without triggering dyskenesias in severely lesioned primates. Based on the studies conducted, there is ample evidence to support moving forward to develop an implantable dopamine agonist therapy and potentially solve some of the side effects related to oral dosing.

[4] http://pdcenter.neurology.ucsf.edu/patients-guide/parkinson%E2%80%99s-disease-medications
[5] Olanow CW, Agid Y, Mizuno Y, et al. Levodopa in the treatment of Parkinson's disease: current controversies. Mov disord. 2004;19:997–1005.
[6] Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinsons disease (201): Treatment Guidelines. Neurology. 2001;56:88.
[7] MPTP is a prodrug to the neurotoxin MPP+, which causes permanent symptoms of Parkinson's disease by destroying dopaminergic neurons in the substantia nigra of the brain. It has been used to study disease models in various animal studies.

Number Afflicted

According to the Parkinson's Disease Foundation, as many as one million Americans have PD and about 60,000 new cases are diagnosed each year. The Foundation sees as many as 10 million people worldwide suffering from the disease. The European Parkinson's Disease Association cites slightly lower figures of 6.3 million suffering from PD worldwide and 1.2 million in Europe. The Michael J Fox Foundation estimates about one million people in the US and 5 million worldwide have PD. China and India also have large populations of PD sufferers which are estimated to both be larger than that in the US. The average age of onset for PD is 60 with risk increasing as one ages. Therefore, growth in the PD population is expected to be faster than that of the population overall given population dynamics.

We estimate that 80% of the PD population in the US will be candidates for implantable ropinirole and that Titan or its partner will be able to achieve 1% penetration into this market in 2020, the first full year of launch. Eventually, we estimate that ropinirole implant will be able to achieve a terminal market share of 10% by 2025.

Pricing

Titan's business strategy is to find generic compounds that treat diseases that will benefit from the unique characteristics of the ProNeura implant. Our assumptions call for a similar price point as that announced by Braeburn for Probuphine. Based on Braeburn's list for Probuphine at just under $5,000 per implant and $10,000 per year, we assume that the revenue per procedure is $7,000 per year, after discounts are taken. We apply a discount to ropinirole implant to reflect less complex distribution requirements since it is not a controlled substance and assume a $6,000 annual treatment cost. With implants required every 3 months, this equates to $1,500 per procedure. In Europe and the rest of the world, our pricing estimate is reduced to $500 per treatment.

Ropinirole Development Plan

Titan has completed the manufacture and release of ropinirole implants for good laboratory practice (GLP) toxicity studies. The company has also completed pharmacokinetic and dose ranging studies in non-human primates, some of the required local toxicity studies, and a 13-week chronic toxicity study in non-human primates. These studies are part of the IND package that the company submitted to the FDA in January 2017.

As background, Titan presented a plan to the FDA in December 2015 regarding the development of a ropinirole hydrochloride (HCL) implant for Parkinson's Disease. On March 7, 2016 the FDA responded to Titan's initial development plan for submission of an investigational new drug (IND) application with sufficient feedback for the company to begin the required non-clinical studies in support of an IND application. As with the process for Probuphine, Titan is pursuing 505(b)(2) registration for the product, which relies on existing clinical data to support an improved method of drug delivery.

After the IND was submitted in January for ropinirole implant and shortly after they received a verbal request from the agency for final release test data on the ropinirole implant and applicator and the identity of the principal investigator. This information will take a few weeks to gather and is expected to be submitted in March 2017. Due to the request for additional information the Phase I pharmacokinetic study is now expected to begin in mid-2017.

The ropinirole implant is designed for the long-term, continuous delivery of ropinirole HCL for the treatment of signs and symptoms of Parkinson's disease (PD), including stiffness, tremors, muscle spasms and poor muscle control. Ropinirole is a dopamine agonist provided in an oral format and currently sold as a generic by Glaxo Smith Kline, Dr. Reddy's Laboratories and Sun Pharma for the treatment of Parkinson's disease symptoms and restless leg syndrome.

According to the Parkinson's Disease Foundation, almost one million Americans and ten million people worldwide suffer from the disease, a number that is expected to grow dramatically in coming years. Current treatment for PD is with an oral dose of DRT. However, given the uneven distribution of the dopamine agonist to the brain via oral administration, DRT is often associated with the pulsatile stimulation of dopamine receptors which can eventually result in motor complications and dyskinesias. Titan expects to show that the subdermal ProNeura drug delivery system is able to provide a continuous, non-fluctuating dose of ropinirole that may prevent or delay the onset of these symptoms. Current treatments that offer continuous delivery of medication providing non-pulsatile stimulation of dopamine receptors in the brain appear to be more effective in controlling motor complications, but are surgically invasive and with potential risk of serious adverse effects. Therefore, we see positive market acceptance if there is continued evidence of additional benefit from the ProNeura technology and the implant receives FDA approval.

Hypothyroidism

Hypothyroidism, also known as underactive thyroid, is a condition in which the thyroid gland is unable to produce sufficient thyroid hormone to maintain the body's normal functions. Without enough thyroid hormone, the body's processes will slow and low body temperature, fatigue, and xerosis as well as psychological issues may result. The condition can result in poor ability to tolerate cold, a feeling of tiredness, constipation, depression and weight gain. In some cases, the neck may swell in what is called goiter. Thyroid hormones maintain the rate at which the body uses fats and carbohydrates, help control the body's temperature, influence heart rate, and help regulate the production of proteins. Hypothyroidism has a number of causes but the most common historically has been iodine deficiency. With improvement of iodine availability, hypothyroidism is only now commonly found in developing areas. Other causes include autoimmune disease (Hashimoto's thyroiditis), congenital hypothyroidism, thyroiditis, damage to the pituitary gland and other causes.

In a normal thyroid, serum thyrotropin is secreted by the pituitary gland which in turn stimulates the thyroid to secrete the prohormone thyroxine (T_4). As T_4 travels through the bloodstream, it slowly breaks down into triiodothyronine (T_3) through the process of deiodination, which stimulates metabolism. The transformation from T_4 to T_3 is performed by enzymatic action with deiodinase, mostly in the liver, gut, skeletal muscle, brain and the thyroid itself. Two transport proteins produced by the liver, transthyretin and albumin, carry the hormones to the tissues where they become free T_3 and T_4 to exert their metabolic effect.

In some cases, hypothyroidism is caused by inflammation of the thyroid gland which causes the body's own defense mechanisms to attack and destroy the thyroid gland. This is called Hashimoto's thyroiditis. Radiation treatment, such as that given in cancer treatments, may also damage the thyroid, reducing or eliminating its ability to produce thyroid hormones. If the body fails to produce sufficient T_4 or if T_4 fails to convert to T_3, then symptoms of the disease may become apparent. Below we list many of the most common symptoms suffered.

Exhibit II – Hypothyroid Symptoms

Heavy/Irregular Menstrual Periods	Unexplained Weight Gain	Fatigue	Thinning Hair
Pain/Stiffness/Swelling of Joints	Hoarseness	Constipation	Slower Heart Rate
Elevated Blood Cholesterol	Muscle Weakness	Dry Skin	Depressed Mood
Increased Sensitivity to Cold	Muscle Aches & Pains	Puffy Face	Impaired Memory

Diagnosis

A serum thyrotropin or thyroid stimulating hormone (TSH)[8] test is most commonly performed to screen for hypothyroidism. It measures the quantity of TSH in the blood. TSH is produced by the pituitary gland, which regulates the amount of thyroxine (T_4) and triiodothyronine (T_3) released by the thyroid. The TSH test measures the level of TSH, which is correlated with the pituitary gland's demand for T_4 and T_3. High levels of TSH indicate that there isn't enough T_4 in the blood and that hypothyroidism may be present.

A second test examines the amount of free T_4 in the blood. Most T_4 is bound to a protein called thyroxine-binding globulin, which prevents it from entering cells. Free T4 is not affected by protein levels and is the active form of thyroxine. The free T_4 test is thought to be a more accurate reflection of thyroid hormone function and, in most cases, its use has replaced that of the total T_4 test. The test seeks to determine the 1 to 2% of T_4 that is unattached.

Treatment

The most common treatment for hypothyroidism is the synthetic thyroid hormone levothyroxine (T_4), such as Synthroid or Levothroid. As T_4 moves systematically it breaks down into T_3, the active hormone. Synthetic T_4 is usually administered orally and is recommended to be taken 30 minutes before eating. In some cases, Cytomel will be added to the regimen to augment the therapy if breakdown of T_4 is insufficient. From 10% to 15% of patients do not improve with T_4 monotherapy and it is appropriate to augment this with Cytomel (liothyronine), which is synthetic T_3 and is also taken orally with food. T_3 is now approved as an oral formulation under the brand name Cytomel manufactured by King Pharmaceuticals. T_3 is not recommended for monotherapy, due in large part to the variation

[8] TSH is also known as thyrotropin or thyrotropic hormone

in T_3 levels in the blood from oral administration. However, ProNeura may be able to overcome the fluctuations in oral T_3 given its linear release kinetics for extended periods and may be appropriate for use in monotherapy.

Number Afflicted

In Western countries approximately 0.3 to 0.4% of the population have overt hypothyroidism. Subclinical hypothyroidism afflicts from 4.3 to 8.5% of the population.[9] The disease is much more common in women than in men, approximately 4 to 5 times[10] depending on the definition of the disease. Our model anticipates a population of 14 million hypothyroid sufferers in the United States. Approximately 16% of this number will require T_3, either as combination therapy in conjunction with T_4 (14%) or as T_3 monotherapy (2%). Penetration of Titan's T_3 implant is anticipated to start out slowly at 0.4% in the first year of commercialization and rise over 6% over the next several years. In the EU, we see the market as being about twice the size of the US market and assume that the addressable population remains steady at 16%. Penetration into the EU addressable market is expected to begin at 0.3% and rise to 2.2% over the next several years.

Pricing

We apply a similar approach for our pricing estimates for T_3 as we do for Ropinirole, given that liothyronine is a well understood generic with sufficient supply and is not a controlled substance. Titan has the ability to develop an implant that can release a drug substance for anywhere from three months to twelve months or more. Due to the shorter trial time required to perform trials for a three month therapy, we anticipate four procedures per year for implantable T_3. Again, using Braeburn's list for Probuphine of about $5,000 per implant and $10,000 per year, we assume that the revenue per procedure is $7,000 per year, after discounts are taken. We apply a discount to the T_3 implant to reflect less complex distribution requirements since it is not a controlled substance and assume $6,000 for a year of treatment. With implants required every 3 months, this equates to $1,500 per procedure. Our estimates for pricing outside the United States call for a 2/3rds price reduction to $500 for four treatments in a year.

Triiodothyronine Implant

While some hypothyroidism can be largely addressed by administration of T_4, some sufferers are unable to successfully convert T_4 into T_3. In these cases, T_4 therapy is ineffective and the benefits of a T_3 implant become clear. It is difficult to maintain steady levels of T_3 due to its short half-life, and a peak just a few hours after ingestion. After about six or eight hours, blood serum levels begin to decline and as a result there are wide and rapid fluctuations of the hormone in the bloodstream. In many cases patients who are on T_3 therapy take from three to five divided doses throughout the day. The need for a steady release of T_3 calls for a method of administration that will allow for a slow, even release of the drug over time. ProNeura is able to meet this need and if its efficacy is proven in clinical trials, we believe it is a vastly superior method of administration as compared to oral dosing.

Hypothyroidism Development Plan

The company submitted briefing material to the FDA in December in preparation for a pre-IND meeting and the FDA responded with comments on the company's development plans. Titan is currently testing the current formulation of triiodothyronine in animal models generating data for a pre-IND meeting with the FDA, which they anticipate will take place in 3Q:17. If the pre-IND meeting is successful, we anticipate a PK study by late 2017 or early 2018. Due to a shortage of GMP-qualified T3, studies had been delayed until the first half of 2017. As with Probuphine and ropinirole program, this project will also use the ProNeura system to administer the active drug.

Conclusion

With $14 million of cash on the balance sheet, Titan appears to have sufficient capital resources to fund its current ropinirole and T3 programs. Additionally, we anticipate that growing royalty revenues from Titan's partner will generate sufficient cash flow to avoid any capital raise in the foreseeable future. Based on our conversations with management, we believe a capital raise will only be required if the company plans to accelerate development programs or new products. We do not anticipate any such activity over the next year or two.

Our valuation analysis applies a probability of approval for compounds in development and at each stage of clinical trials. Prior to Phase I testing, however, we do not apply any probability of approval. Upon commencement of trials

[9] Garber, JR; Cobin, RH; Gharib, H; Hennessey, JV; Klein, I; Mechanick, JI; Pessah-Pollack, R; Singer, PA; et al. (December 2012). "Clinical Practice Guidelines for Hypothyroidism in Adults"
[10] Ibid

for ropinirole and T3 implant, we will begin to include a valuation for each based on our estimates for eventual commercialization. Currently there are two new products and ex-US sales of Probuphine that we anticipate adding to our DCF model, and upon confirmation of these programs we will include a valuation component for each.

While we were hoping to see a faster ramp-up in sales, we do understand that the process for training, formulary inclusion and distributing a controlled substance take some time to develop properly and to obtain the necessary approvals. Now that the sales force is fully built out and the commercial launch has commenced, we anticipate an accelerated pace of sales growth in 2017. We reduce our share price target to $11 to reflect lower than expected Probuphine royalty revenues but note the potential from a contribution from Probuphine sales outside North America as well as from ropinirole and T_3 when we reach the appropriate milestones.

PROJECTED FINANCIALS

Titan Pharmaceuticals, Inc. - Income Statement

Titan Pharmaceuticals, Inc.	2015 A	Q1 A	Q2 A	Q3 A	Q4 A	2016 A	2017 E	2018 E
Probuphine Royalty	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.1**	**$15.5**	**$30.4**
YOY Growth	-	-	-	-	-	-	*23743.4%*	*96.1%*
Licensing & Grant Revenue	**$1.7**	**$0.0**	**$15.0**	**$0.0**	**$0.0**	**$15.0**	**$8.0**	**$11.0**
Total Revenues	**$1.7**	**$0.0**	**$15.0**	**$0.0**	**$0.0**	**$15.1**	**$23.5**	**$41.4**
YOY Growth	-	*-100.0%*	*1874.2%*	-	-	*801.6%*	*56.0%*	*76.2%*
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	$4.7	$0.7	$1.7	$1.6	$2.1	$6.1	$6.5	$7.0
G&A	$3.8	$1.1	$1.2	$1.1	$1.2	$4.6	$6.0	$6.5
Operating Income	($6.8)	($1.8)	$12.0	($2.6)	($3.3)	$4.3	$11.0	$27.9
Operating Margin	-	-	*80.3%*	*-10061.5%*	*-9297.1%*	*28.8%*	*46.8%*	*67.4%*
Total Other Income	($4.5)	($0.0)	($0.1)	($0.0)	$0.9	$0.8	$0.0	$0.0
Pre-Tax Income	($11.3)	($1.8)	$11.9	($2.6)	($2.3)	$5.1	$11.0	$27.9
Taxes & Other	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	($11.3)	($1.8)	$11.9	($2.6)	($2.3)	$5.1	$11.0	$27.9
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($0.56)**	**($0.09)**	**$0.55**	**($0.12)**	**($0.11)**	**$0.24**	**$0.50**	**$1.25**
YOY Growth	*299.7%*	*-62.9%*	*-579.5%*	*37.2%*	*-5.7%*	*-142.5%*	*107.0%*	*151.4%*
Weight Ave. Shares Out	20.1	20.4	21.9	21.2	21.6	21.5	22.2	22.4

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

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HISTORICAL STOCK PRICE



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