Zacks Small-Cap Research

March 28, 2016
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Titan Pharmaceuticals, Inc.

(TTNP-NASDAQ)

Reports 2015 Results; Probuphine Action Date Pushed to May 27; Update on Ropinirole.

Current Recommendation	**Buy**
Prior Recommendation	Hold
Date of Last Change	10/13/2015
Current Price (3/28/16)	$4.79
Target Price	**$8.50**

OUTLOOK

Titan Pharmaceuticals is a development stage company on the cusp of the launch of its lead product candidate, probuphine: an implanted, time-release medicine used for the treatment of opioid addiction. We anticipate approval of probuphine in 2Q:16 and launch of the drug in 3Q:16. Probuphine and the company's other drug candidates use a proprietary drug delivery system called ProNeura. Consisting of ethylene-vinyl acetate and a drug substance, ProNeura is a novel approach to delivery of drugs that benefit from long-duration slow release and controlled substance programs.

In addition to the opioid addiction indication, the company is also pursuing a treatment for Parkinson's Disease (ropinirole) and hypo-thyroidism (T3) which are currently undergoing non-clinical studies prior to an IND meeting with the FDA.

With both late and early-stage programs utilizing the ProNeura platform under way, our DCF model supports an $8.50 price target.

SUMMARY DATA

52-Week High	**$5.29**
52-Week Low	**$2.98**
One-Year Return (%)	**28.4**
Beta	**1.87**
Average Daily Volume (sh)	**280,828**
Shares Outstanding (mil)	**20.1**
Market Capitalization ($mil)	**$89.3**
Short Interest Ratio (days)	**N/A**
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	**12.4**
P/E using 2017 Estimate	**6.8**

Risk Level	**High**
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 E	$15.0 E	$0.3 E	$0.9 E	$16.2 E
2017					$25.0 E
2018					$38.9 E

Earnings per Share

	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	-$0.11 E	$0.62 E	-$0.09 E	-$0.06 E	$0.35 E
2017					$0.65 E
2018					$1.22 E

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WHAT'S NEW

FDA Panel Extends PDUFA Date for Probuphine

Following the Psychopharmacologic Drugs Advisory Committee (PDAC) 12-to-5 vote to recommend approval of Probuphine in January, the FDA extended the action date from February 27, 2016 to May 27, 2016 due to the time needed to review additional data. After the PDAC meeting in January, the FDA requested additional information regarding the Risk Evaluation and Mitigation Strategy (REMS) portion of the NDA. The FDA required more information specifically pertaining to the removal of the subdermal implant, the training required to do so successfully and the distribution of the product. One week prior to the initial Prescription Drug User Fee Act (PDUFA) date, the FDA announced that the REMS changes constituted a major amendment and that they will require additional time to review the submitted materials. We anticipate that the FDA will follow the PDAC recommendation and approve probuphine in late May. Titan is eligible for a $15 million milestone payment from Braeburn upon FDA approval.

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, 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.

Summary of Probuphine Regulatory History

On June 8, 2015, Titan reported positive topline results from a confirmatory Phase 3 study with Probuphine in subjects with opioid addiction. 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 (1st P3, 2nd P3). 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.

FDA Provides Feedback on Ropinirole Development Plan

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, 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 a fourth quarter 2016 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 delivery for the drug.

As background, the 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 GlaxoSmithKline, Dr. Reddy's Laboratories and Sun Pharmaceuticals for the treatment of Parkinson's disease symptoms and restless leg syndrome. The U.S. patent for the ProNeura form of the drug was issued on March 8, 2016 as patent number 9,278,163.

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 dopamine replacement therapy (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 the motor complications and dyskinesias. 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.

New Development Project using ProNeura System for Hypothyroidism

Titan is also working on a new development program that will also use the ProNeura system to administer triiodothyronine (T3), which is a thyroid hormone used to treat patients with hypothyroidism. Currently the drug is approved as an oral formulation under the brand name Cytomel manufactured by King Pharmaceuticals. 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 now performing non-clinical studies to help optimize the formulation of the T3. The company's current timeline calls for a pre-IND meeting by fourth quarter 2016 and a proof-of-concept study by the second half of 2017.

Hypothyroidsim is a deficiency of thyroid hormone triiodothyronine (T3) and thyroxine (T4), which are tyrosine-based hormones secreted by the thyroid gland. Underproduction of these hormones slows the body's metabolism. The condition can result in poor ability to tolerate cold, a feeling of tiredness, constipation, depression, and weight gain. 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. Of the two hormones secreted by the thyroid, T4 only has a slight effect on metabolism and is converted to more potent T3 inside cells through enzymatic action.

2015 Financial Results

Titan Pharmaceuticals reported fiscal year 2015 revenue and earnings results on March 15, 2016. Revenues for the year were $1.67 million consisting entirely of license revenue which represent the amortization of the upfront license fee revenue received from Braeburn in December 2012. Net loss per share was ($0.56) on a share balance of 20.1 million shares.

Research and development expense was $4.68 million for 2015 increasing approximately 15% from the prior year due to higher contract research organization (CRO) expenses, investigator and review board fees, patient expense reimbursements expenses for NDA preparation and contract manufacturing expenses. External R&D costs were $1.5 million for product development expenses.

General and administrative expenses totaled $3.76 million, an increase of 27% over the prior year. Higher expenses were attributed to non-cash stock compensation, employee related costs, legal and professional fees, board fees and travel related expenses, in declining order of importance. Net other expense of $4.52 million was almost entirely attributable to non-cash losses on warrant liabilities. Warrant liabilities increased by $4.51 million for the year due to share price increases during 2015.

Effective September 2015, Titan executed a reverse stock split which effected a 1-for-5.5 consolidation. This action freed up sufficient shares to satisfy a portion of the outstanding warrants and the financial statements reflect an $8.65 million reclassification of warrant liabilities to shareholder's equity.

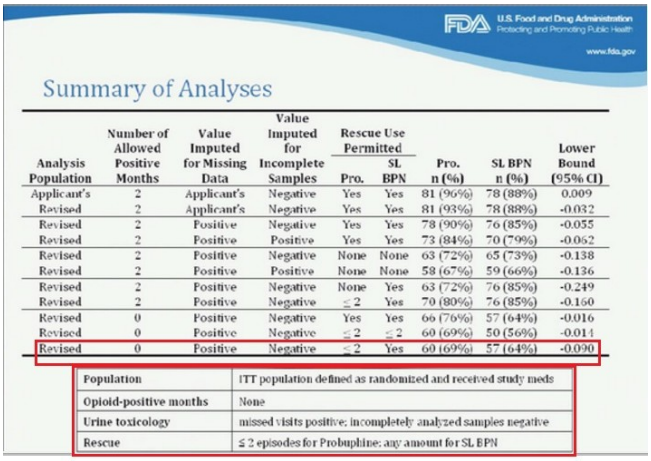
As of 2015 year-end, the company held $7.86 million of cash on the balance sheet, which is expected to be sufficient to fund operations until the close of fiscal year 2016. In 2015, the company used $7.47 million in operating cash and $0.13 million in capital expenditures for a total cash burn of $7.60 million.

For the fourth quarter, Titan generated no revenues, and incurred operating costs of $2.25 million. Including other expense attributable to market value adjustments for the warrant liability, net loss was $2.29 million or ($0.11) per share.

OVERVIEW

Our Perspective

As a reminder, in June 2015, Titan reported that its Phase 3 trial for probuphine 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.



Analysis Population	Number of Allowed Positive Months	Value Imputed for Missing Data	Value Imputed for Incomplete Samples	Rescue Use Permitted Pro.	Rescue Use Permitted SL BPN	Pro. n (%)	SL BPN n (%)	Lower Bound (95% CI)
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, 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 sufficient for approval this time around; however, we anticipate a response by the May 27 action date.

Probuphine has been gaining substantial media attention since the PDAC voted 12-to-5 to recommend approval. Articles 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.

The FDA has become increasingly vocal about the threat that immediate release opioid pain medications are fraught with risks. On March 22, the agency announced required safety label changes for immediate release opioid pain medication. In our opinion, this shift in the regulatory stance is positive for implantable, controlled release products such as Probuphine, as it never enters the hands of the patient and is delivered directly to physicians.

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, however we do not include any of these revenues in our valuation model. All-in-all, we believe Titan is currently in a strong financial position, especially with the likelihood of receiving the $15.0 million milestone payment from Braeburn following a May 27 approval. Titan continues to work with its contract manufacturer and Braeburn in preparation for product launch. We anticipate that final labeling and packaging concurrent with physician training will take from two to three months following approval, after which we foresee a product launch as early as third quarter 2016.

We view the current share price as an 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 mechanism of the ProNeura technology platform. ProNeura is being used in earlier stage projects for Parkinson's Disease and hypothyroidism while the company continues to evaluate other chronic disease settings for potential ProNeura platform expansion.

We believe there is material upside at current share price levels and note that there are several additional opportunities for revenues from international licensing, and the development of PD (ropinirole) and hypothyroidism which we do not include as part of our valuation. With both late and early-stage programs utilizing the ProNeura platform under way, we value the shares at $8.50 using our discounted cash flow model, with potential upside in the short term if probuphine is approved and additional clarity is provided for international development. However, in the event that Titan receives another complete response letter (CRL) from the FDA, we concede that the majority of the value of the shares is attributable to the opioid addiction indication and our target price would be significantly changed.

PROJECTED FINANCIALS

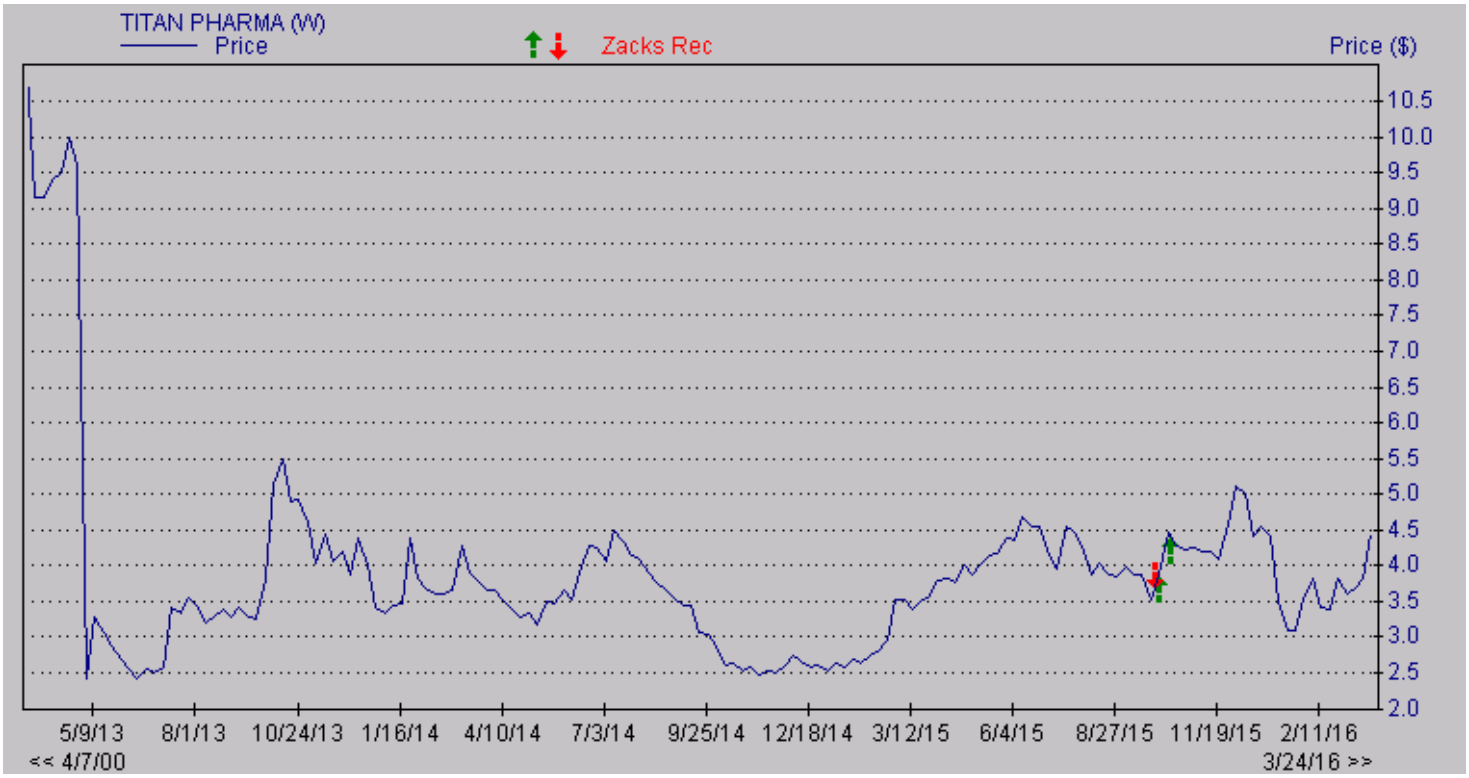
Titan Pharmaceuticals, Inc. - Income Statement

Titan Pharmaceuticals, Inc.	2015 A	Q1 E	Q2 E	Q3 E	Q4 E	2016 E	2017 E	2018 E
Probuphine Royalty	**$0.0**	**$0.0**	**$0.0**	**$0.3**	**$0.9**	**$1.2**	**$17.0**	**$27.9**
YOY Growth	-	-	-	-	-	-	*1372.9%*	*63.6%*
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**	**$0.3**	**$0.9**	**$16.2**	**$25.0**	**$38.9**
YOY Growth	-	*-100.0%*	*1873.7%*	-	-	*866.9%*	*54.9%*	*55.3%*
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	$1.2	$1.2	$1.2	$1.2	$4.8	$6.0	$6.0
SG&A	$3.8	$1.0	$1.0	$1.0	$1.0	$4.0	$5.0	$6.0
Operating Income	($6.8)	($2.2)	$12.8	($1.9)	($1.3)	$7.4	$14.0	$26.9
Operating Margin	-	-	*85.3%*	*-661.1%*	*-153.7%*	*45.5%*	*56.1%*	*69.1%*
Total Other Income	($4.5)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Pre-Tax Income	($11.3)	($2.2)	$12.8	($1.9)	($1.3)	$7.4	$14.0	$26.9
Taxes & Other	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	($11.3)	($2.2)	$12.8	($1.9)	($1.3)	$7.4	$14.0	$26.9
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($0.56)**	**($0.11)**	**$0.62**	**($0.09)**	**($0.06)**	**$0.35**	**$0.65**	**$1.22**
YOY Growth	*299.7%*	*-55.8%*	*-643.8%*	*1.0%*	*-45.0%*	*-162.3%*	*86.3%*	*87.1%*
Weight Ave. Shares Out	20.1	20.4	20.7	21.0	21.2	21.0	21.5	22.0

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

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Sell/Underperform: The analyst expects the company will underperform the broader U.S. Equity market over the next one to two quarters.

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