Zacks Small-Cap Research

November 19, 2014
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Cynapsus Therapeutics Inc. (CYNAF-OTC)

CYNAF – Positive Phase 2 Data Sets The Stage For Major Revaluation Higher…

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	07/23/2012
Current Price (11/19/14)	$0.77
Target Price	**$2.75**

UPDATE

Little known Toronto, Canada-based Cynapsus Therapeutics is one of our best ideas for investment in the small-cap biotechnology sector.

On November 19, 2014, Cynapsus Therapeutics Inc. (CYNAF) (CTH.V) announced what looks to be a clear demonstration of proof-of-concept via positive top-line results from the CTH-105 Phase 2 clinical trial. The CTH-105 study was the first to test Cynapsus APL-130277, a fast-acting, sublingual, thin filmstrip formulation of apomorphine in Parkinson's patient for the management of "off" motor symptoms. We believe these data set the stage for a significant re-valuation of the shares to meaningfully higher levels. Our target is $2.75 per share, offering 250% upside.

SUMMARY DATA

52-Week High	**$1.26**
52-Week Low	**$0.34**
One-Year Return (%)	**124.49**
Beta	**1.31**
Average Daily Volume (sh)	**138,306**
Shares Outstanding (mil)	**79**
Market Capitalization ($mil)	**$61**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**12**
Insider Ownership (%)	**7**
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 2014 Estimate	**N/A**
P/E using 2015 Estimate	**N/A**

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)
2013	0 A	0 A	0 A	0 A	0 A
2014	0 A	0 A	0 A	0 E	0 E
2015					0 E
2016					0 E

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

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2013	-$0.07 A	-$0.03 A	-$0.03 A	-$0.02 A	-$0.13 A
2014	-$0.03 A	-$0.04 A	-$0.02 A	-$0.02 E	-$0.11 E
2015					-$0.07 E
2016					-$0.06 E

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INVESTMENT THESIS

APL-130277 Shows Clear Proof-of-Concept In Phase 2 Trial

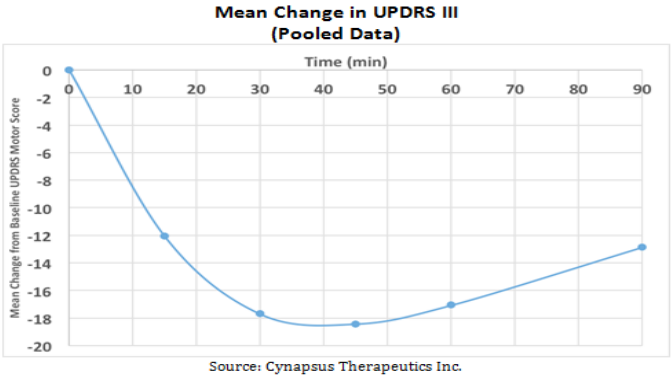
On November 19, 2014, Cynapsus Therapeutics Inc. (CYNAF) (CTH.V) announced what looks to be a clear demonstration of proof-of-concept via positive top-line results from the CTH-105 Phase 2 clinical trial. The CTH-105 study was the first to test Cynapsus APL-130277, a fast-acting, sublingual, thin filmstrip formulation of apomorphine in Parkinson's patient for the management of "off" motor symptoms. We believe these data set the stage for a significant re-valuation of the shares to meaningfully higher levels. Our target is $2.75 per share, offering 250% upside.

…Quick Highlight Of The Data…

The primary objective of CTH-105 (NCT02228590) was to evaluate the efficacy, tolerability and safety of single treatments of APL-130277 in 16 patients with Parkinson's Disease (PD). The primary endpoint was the efficacy based on "time to on" using the percent change in UPDRS. Safety and tolerability, as well as frequency of adverse events, were also primary and secondary outcome measures in the study. In the trial, patients were then given escalating doses of APL-130277 (at a minimum of three hours between doses) until "on" was achieved. UPDRS III score was measured at 15, 30, 45, 60 and 90 minutes. Pooled data from 16 patients was released this morning, with management noting that three additional patients are continuing dosing.

According to management, all five doses of APL-130277 used in the study (10, 15, 20, 25, 30 mg) resulted in patients moving from "off" to "on". We are encouraged by the fact that even the lowest dose showed efficacy, with 3 of the 16 patients (~19%) moving to "on". Out of 16 patients treated with APL-130277, 14 converted from "off" to "on" time. Study investigators hypothesized that the two patients (~13%) that did not convert to "on" probably need more drug, as their baseline UPDRS scores were significantly higher than the mean for the other 14 patients. This is consistent with prescribing label for subcutaneous apomorphine were approximately 20% of PD patients require the highest dose. We suspect that management can dose 35 or 40 mg in the upcoming Phase 3 trial.

Mean baseline UPDRS III scores for the pool group was 41.4. The maximum mean change from baseline was 18.4. This data compares well with published literature for subcutaneous apomorphine. Cynapsus reported that onset to clinically meaningful improvement was seen in as early as 10 minutes and last up to 90 minutes (last measured time point). Mean "time to on" was 22 minutes. Below is a graph showing the mean change in UPDRS III from baseline over the study period for patients converting from "off" to "on" time. We note, even at 90 minutes patients were still "on", suggesting that APL-130277 could act as a bridge between regular oral levodopa dosing.



Source: Cynapsus Therapeutics Inc.

Cynapsus reported that treatment with APL-130277 was safe and well tolerated. Nausea, reported by three subjects at doses of 10, 15 and 20 mg, looked to be the most common side effect. One of these patients also experienced a mild episode of vomiting. There were no reports of nausea at higher doses of 25 and 30 mg. There were no reports of local irritation or hypotension in any subject treated. A total of 60 doses of APL-130277 were administered to the 16 patients who completed dosing in the CTH-105 study. Additional safety data will be presented with all 19 patients complete dosing. We expect to see individual patient data at an upcoming medical meeting or when the results are published by study investigators.

Acorda Acquires Civitas And Validates The Market

We have been saying that the market opportunity for an effective rescue medication to treat off episodes in Parkinson's patients in a potential multi-hundred million-dollar opportunity. In fact, in our most recent Zacks report on Cynapsus Therapeutics, we estimated the peak U.S. sales for APL-130277 were $387 million. And we believe this estimate includes conservative forecasts on both pricing and market penetration (see below). It also does not include forecasts for sales in Europe or Asia.

~1.25 Million U.S. Parkinson's Disease Patients by 2024	Percent of PD Patients	Current Penetration Apokyn®	Estimated Penetration APL-130277	Fold Increase	U.S. PD Patients On APL-130277	Strips Needed Per Day	APL-130277 Strips
- Estimated 35% with "OFF" Issues -							
Mild Disease	35%	2.0%	5.0%	2.5	7,656	1	7,656
Moderate Disease	50%	5.0%	13.5%	2.7	29,531	2	59,063
Severe Disease	15%	7.0%	20.0%	2.9	13,125	3	39,375
						Total APL-130277 Strips Sold (at Peak)	106,094
						Price Per Strip Per Day (at Peak)	$10
						Peak U.S. Sales (Millions)	**$387**

Source: Zacks SCR / Jason Napodano, CFA

On September 24, 2014, Acorda Therapeutics announced it had made an offer to acquire privately-held Civitas Therapeutics for $525 million in cash. The impetus of the acquisition by Acorda was to get CVT-301, a Phase 3 inhaled formulation of levodopa for the treatment of off episodes in Parkinson's patients. With CVT-301, Acorda believes it has an attractive late-stage asset to add to the company's CNS-focused pipeline. The CVT-301 Phase 3 study is expected to begin enrollment in early 2015, with a new drug application (NDA) planned for 2016. Acorda estimates the market opportunity for CVT-301 is in excess of $500 million. Civitas had been previously planning an initial public offering, but the $525 million all-cash offer from Acorda was simply too attractive to pass up.

Civitas' CVT-301 looks only a few months ahead of Cynapsus' APL-130277. Cynapsus just recently completed the CTH-105 study discussed above. The next step is a bridging study, dubbed CTH-200, designed to be a single dose, crossover comparative bioavailability and pharmacokinetic study in healthy volunteers. This study is designed to provide the clinical "bridge" to the FDA's finding of safety and efficacy for the reference-listed drug (Apokyn®) – a necessary step to file an application via the 505(b)(2) pathway. The CTH-200 Bridging Study is expected to begin shortly. Meanwhile, Cynapsus has already schedule an "End of Phase 2" meeting with the U.S. FDA to discuss the Phase 3 program. This meeting is expected to take place in early February 2015. As such, we expect the Phase 3 program for APL-130277 to begin during the second quarter of 2015. Again, based on the recent positive data from CTH-105, we estimated CVT-301 is only a few months ahead of APL-130277.

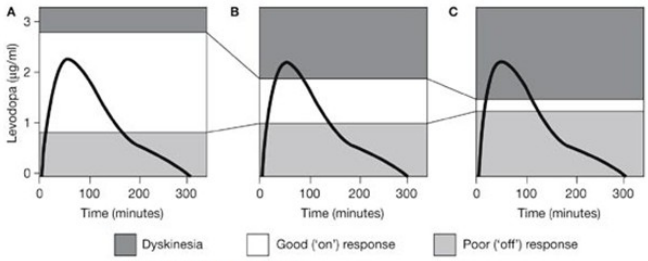
…And We Think Cynapsus Drug Is Clearly The Better Design…

Ever since the announced acquisition of Civitas, investors have been asking, "Why Civitas and not Cynapsus?" and "What does the added competition do to our forecasts?" The answer is simple – We think Acorda bought the wrong drug and that APL-130277 clearly has better attributes than CVT-301.

Specifically, CVT-301 is an inhaled formulation of levodopa. Levodopa is the most common form of dopamine replacement therapy, a backbone regimen and standard of care for the treatment of Parkinson's disease. Parkinson's disease is a slowly progressing neurological disorder characterized by tremor, stiffness and decreased movement. The decreased movement is a direct result of the lack of dopamine in the brain. Levodopa, when taken orally, is converted into dopamine in the substantia nigra by dopa decarboxylase. The administration of levodopa temporarily diminishes the motor symptoms associated with the lack dopamine in the substantia nigra. Carbidopa, a dopa decarboxylase inhibitor, is commonly dosed with levodopa to prevent L-DOPA metabolism before it reaches the blood-brain barrier. In fact, co-formulations of levodopa/carbidopa (Sinemet-CR) are available. Civitas' formulation of levodopa bypasses the gut metabolism through inhalation, a pathway known to for rapid uptake and onset of action.

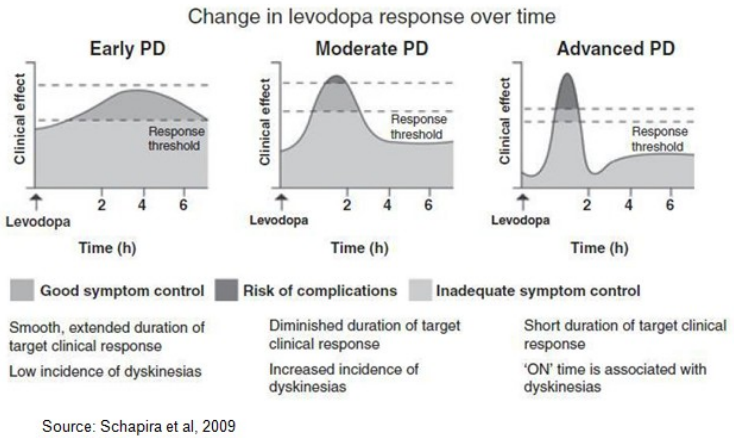
There are, however, major limitations to the use of levodopa as a treatment for Parkinson's disease. Mainly, the patient must have substantial remaining dopaminergic neurons in the substantia nigra to metabolize the drug. However, according to research published in the Journal of Neural Transmission by P. Riederer et al in 1976, pathological studies of Parkinson's disease show at least 70-80% of the dopaminergic neurons are lost before the onset of symptoms. This work was confirmed by K. Yoshikawa et al, 2004. This explains why levodopa is very effective for a period of time, then wanes with disease progression. A newly diagnosed Parkinson's patient has the capacity to process levodopa. As the patient loses this capacity, the therapeutic window for levodopa therapy begins to narrow. Levodopa also has a relatively short half-life of only 60-90 minutes. The drugs effect, even in the mild Parkinson's patient, only lasts for 1.5 to 2.0 hours post dose (Brooks, D, 2008).

Work done by Olanow et al, 2006 shows that a therapeutic window for Parkinson's disease patients rapidly closes (narrows) as patients gain experience with Levodopa use. This is due to a combination of disease progression, loss of dopaminergic neurons in the substantial nigra, and the short half-life of the drug.



Source: Olanow CW et al, 2006

As such, dosing dynamics for levodopa are challenging (Schapira et al, 2009). Too much drug (or too frequent dosing) leads to leads to dyskinesia, a direct result of excess dopamine in the brain. Too little drug leads to increase "off" time (bradykinesia / akinesia), the specific condition that both Civitas and Cynapsus are aiming to treat.



Source: Schapira et al, 2009

We question the concept of treating "off" episodes in Parkinson's patients with more levodopa. Many neurologists and movement disorder doctors will delay the use of levodopa in newly diagnosed Parkinson's patients specifically to avoid the narrowing of the therapeutic window and the risks of complications such as dyskinesia (see this YouTube video from the MJFF talking about Levodopa and Off/On time). We believe CVT-301 complicates the dosing regimen for the Parkinson's patient taking a drug like Sinemet-CR. We suspect substantial acceleration of the narrowing of the therapeutic window and dyskinesia with the drugs use. And as the Parkinson's patient progresses from mild to moderate or severe disease, we suspect that CVT-301 will become a less effective drug. We also strongly question the approvability of an inhaled drug, with chronic use, in an elderly population for a non-pulmonary disease. The pathway to approval for CVT-301 seems arduous.

Apomorphine, the active drug in the only currently approved rescue medication for the treatment of off episodes in the U.S. in Apokyn®, is not a dopamine replacement therapy. Apomorphine is a dopamine agonist, and acts directly at the post-synaptic dopamine receptor, thus bypassing the need for dopamine and dopaminergic neurons in the substantial nigra. Instead, apomorphine can act directly on the gabaergic neurons that are not impacted by Parkinson's disease, and provide an effective treatment option as a rescue medication to patients at all stages of disease progression.

The knock on apomorphine is that because the drug is rapidly metabolized by the liver, it must be administered by a route that bypasses the gut. As such, the currently approved formulation of apomorphine in the U.S. is a subcutaneous injection. Subcutaneous injectable apomorphine, sold in the U.S. as Apokyn®, is a horrible impractical and inefficient drug, flawed by its delivery system and quick peak-to-trough pharmacokinetic profile. Apomorphine is highly lipid soluble and quickly crosses the blood-brain barrier. Onset of action is as little as five minutes, but only lasts for 60-90 minutes. Under QID dosing for levodopa, patients with advanced disease may still experience off episodes.

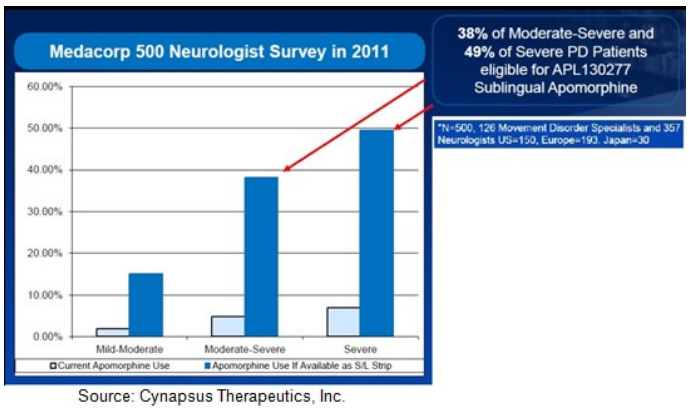
Self-administration of subcutaneous Apokyn is next to impossible for the akinetic (or dyskinetic) Parkinson's patient. For example, the Instructions For Use for Apokyn® is 27 pages long, and consists of steps that logically seem impossible for the frozen or rigid Parkinson's patient to complete. Because self-administration of Apokyn® is nearly impossible, the treatment of off episodes requires direct caregiver support, likely from a skilled nurse. This places undue burden on the healthcare system.



Source: U.S. WorldMeds, LLC 2014

The above inhibiting attributes greatly limit sales of Apokyn in the U.S. Cynapsus' APL-130277 is a sublingual formulation of apomorphine, with each thin film strip found inside an easy to open non-superimposable die cut peelable foil laminate pouch. The product can be self-administered, under the tongue, and is designed to be used anywhere, anytime, with little or no assistance required. The comparable dose strength of Apokyn® sells for $13-15 per injection. We believe Cynapsus APL-130277, with a far more convenient administration and lack of skilled caregiver requirement, will see sizable market shares gains and expansion over the current Apokyn market.

For example, Cynapsus sponsored neurologist surgery (n=500) with data conclusions suggesting a 7.5-fold increase in penetration across the board for mild, moderate, and severe Parkinson's patients. It is for these reasons that we believe APL-130277 has peak U.S. sales far in excess of Apokyn, or Acorda's newly acquired CVT-301.



Source: Cynapsus Therapeutics, Inc.

Conclusion, Valuation & Recommendation

Off time is a significant problem for patients with advanced Parkinson's disease. In the U.S., there are an estimated one million PD patients (4-6 million globally). According to a recent survey by the Michael J. Fox Foundation, more than 90% of PD patients report having "off" episodes each day. Roughly two-thirds have "off" time greater than two hours, with 20% experiencing "off" time of greater than four hours. This is a significant problem for PD patients and an enormous unmet medical need.

Data from the recently completed CTH-105 study clearly validates the proof-of-concept for APL-130277. The drug demonstrated substantial signs of efficacy for all doses (10, 15, 20, 25, and 30 mg). Onset of action was as soon as ten minutes for some patients, with mean "time to on" of 22 minutes – admittedly not as rapid as CVT-301 but still well within the reasonable range for a rescue medication. More importantly, duration of effect was still evident at 90 minutes, exceeding what has been demonstrated with Apokyn or what we suspect will be shown in the CVT-301 Phase 3 trial given the half-life of levodopa has been documented to be less than 90 minutes.

In conclusion, we see API-130277 as an easier-to-use and more effective drug than CVT-301, along with a better mechanism of action and pathway to approval. Data from CTH-105 de-risks the story and Cynapsus has enough cash to fund all necessary clinical trials prior to the U.S. NDA filing (see our quick review of the Q3 financial results). A recent paper published by researchers out of the UK on behalf of EUROPAR and EPDA confirms our belief that this is a potential enormous market. The paper concludes that early-morning "off" episodes are a significantly larger problem than believed even five years ago, with nearly two-thirds of all PD patients suffering across all stages of the disease (Rizos et al, 2012).

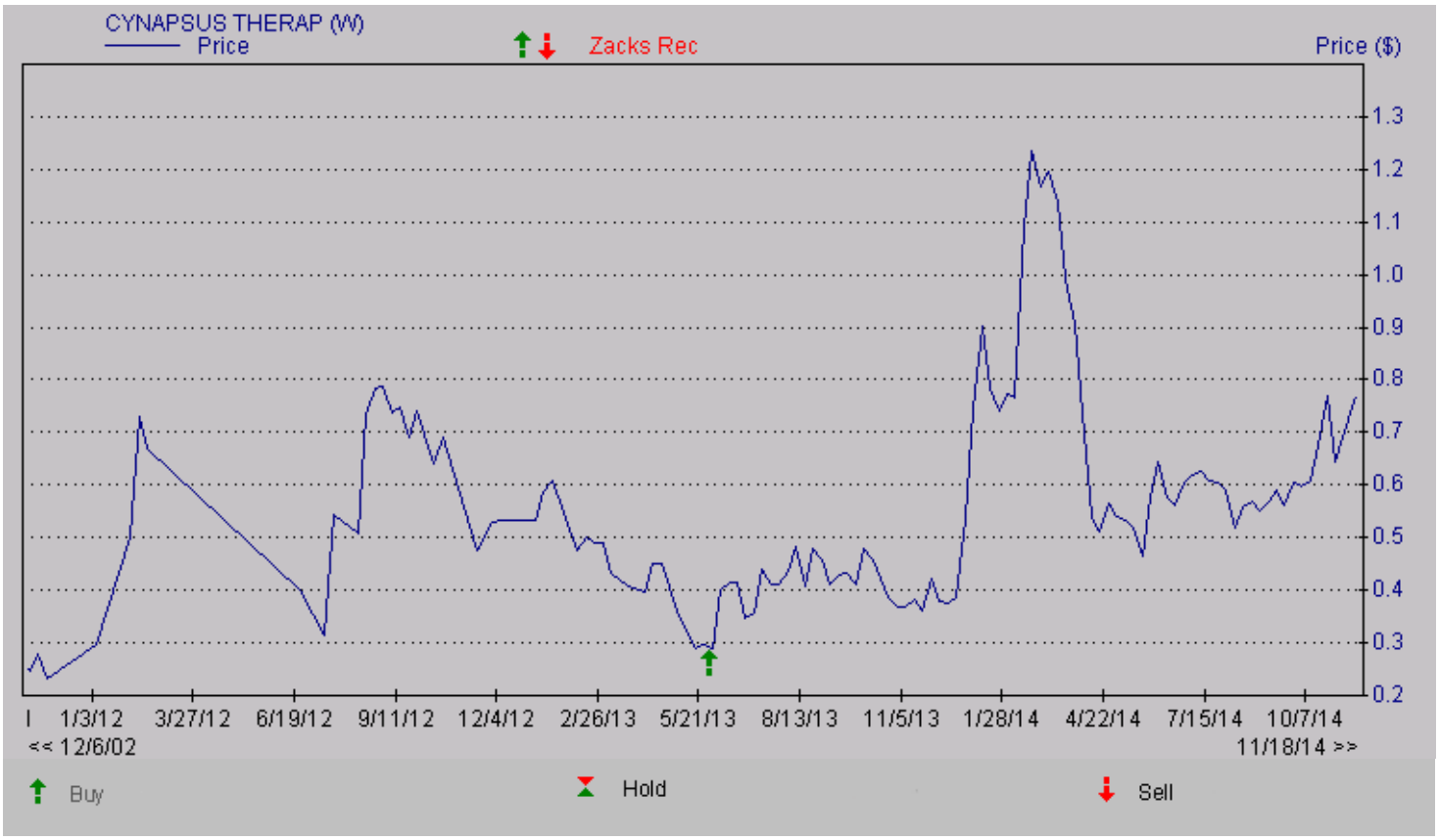
We do not know whether or not Acorda approached Cynapsus with a potential buy-out to acquire APL-130277 prior to its decision to scoop-up Civitas for $525 million. What we do know is that Cynapsus, on a fully-diluted basis, is currently worth only $75 million. If Civitas was worth $525 million, Cynapsus is worth more. As such, we could be looking at a ten-fold increase in valuation for Cynapsus over the next 2 years.

Cynapsus Therapeutics – Income Statement

Cynapsus Therapeutics, Inc.	2012 A	2013 A	Q1 A	Q2 A	Q3 A	Q4 E	2014 E	2015 E	2016 E
APL-130277 WW Sales	$0	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-	-
Royalty Payments	$0	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-	-
Licensing & Collaborative	$0	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-	-
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-	-
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	-	-
Operating, General & Admin	$1.37	$2.64	$0.96	$0.89	$1.01	$0.90	$3.76	$3.00	$3.00
Research & Development	$0.81	$1.63	$0.45	$1.16	$1.25	$1.10	$3.96	$4.00	$5.00
Share-Based Comp	$0.34	$0.52	$0.02	$0.40	$0.21	$0.10	$0.73	$0.55	$0.55
Amortization & Depreciation	$0.06	$0.06	$0.02	$0.02	$0.02	$0.02	$0.06	$0.07	$0.07
Foreign Exchange	($0.01)	$0.04	$0.02	$0.37	($0.64)	$0.01	($0.24)	$0.00	$0.00
Other Expenses	($0.09)	($0.04)	($0.01)	($0.01)	($0.02)	($0.05)	($0.09)	($0.02)	($0.02)
Operating Income	($2.49)	($4.85)	($1.45)	($2.83)	($1.82)	($2.08)	($8.18)	($7.60)	($8.60)
Operating Margin	-	-	-	-	-	-	-	-	-
Grants & Other Income	$0.30	$0.43	$0.24	$0.00	$0.11	$0.15	$0.50	$0.75	$0.75
Interest / Financing Net	($0.88)	$0.01	$0.00	$0.02	$0.01	$0.00	$0.00	$0.00	$0.00
Pre-Tax Income	($3.06)	($4.43)	($1.21)	($2.82)	($1.69)	($1.93)	($7.68)	($6.85)	($7.85)
Income Taxes Paid	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Tax Rate	0%	0%	0%	0%	0%	0%	0%	0%	0%
Net Income	($3.06)	($4.43)	($1.21)	($2.82)	($1.69)	($1.93)	($7.68)	($6.85)	($7.85)
Net Margin	-	-	-	-	-	-	-	-	-
Reported EPS	**($0.22)**	**($0.13)**	**($0.03)**	**($0.04)**	**($0.02)**	**($0.02)**	**($0.11)**	**($0.07)**	**($0.06)**
YOY Growth	*($0.20)*	*($0.43)*	-	-	-	-	*($0.11)*	*($0.42)*	*($0.04)*
Basic Shares Outstanding	13.65	34.67	39.46	72.39	78.97	80.00	67.70	105.00	125.00

Source: Zacks Investment Research, Inc. *Jason Napodano, CFA*

HISTORICAL ZACKS RECOMMENDATIONS



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Hold/Neutral: The analyst expects that the company will perform in line with the broader U.S. equity market over the next one to two quarters.
Sell/Underperform: The analyst expects the company will underperform the broader U.S. Equity market over the next one to two quarters.

The current distribution is as follows: Buy/Outperform- 17.1%, Hold/Neutral- 74.9%, Sell/Underperform – 7.1%. Data is as of midnight on the business day immediately prior to this publication.