Zacks Small-Cap Research

September 10, 2013
Jason Napodano, CFA
John Tucker, PhD
312-265-9421 / jnapodano@zacks.com

scr.zacks.com
111 North Canal Street, Chicago, IL 60606

# Neurocrine Biosciences, Inc.

**(NBIX-NASDAQ)**

## *NBIX: NBI-98854 Offers Mixed Data From Phase 2b In TD…*

## UPDATE

We are maintaining our Buy rating on the shares of Neurocrine. While we are clearly disappointed in the outcome of the KINECT-1 study, pushing back the launch timelines of the drug by only twelve months has minimal impact on our DCF model. The added costs of KINECT-3 ($8-10 million) are easily supported by the existing cash balance, which stood at $166.5 million as of June 30, 2013. The net effect of pushing timelines back twelve months and increase costs in 2014 to run KINECT-3 is approximately a $4 per share hit to our previous $18 fair-value calculation.

| | |
|---|---|
| **Current Recommendation** | **Buy** |
| Prior Recommendation | Neutral |
| Date of Last Change | 06/16/2010 |
| Current Price (09/10/13) | $11.25 |
| **Target Price** | **$14.00** |

## SUMMARY DATA

| | |
|---|---|
| **52-Week High** | **$16.70** |
| **52-Week Low** | **$6.88** |
| **One-Year Return (%)** | **111.93** |
| **Beta** | **0.52** |
| **Average Daily Volume (sh)** | **744,840** |
| **Shares Outstanding (mil)** | **67** |
| **Market Capitalization ($mil)** | **$1,120** |
| **Short Interest Ratio (days)** | **6.17** |
| **Institutional Ownership (%)** | **78** |
| **Insider Ownership (%)** | **5** |
| **Annual Cash Dividend** | **$0.00** |
| **Dividend Yield (%)** | **0.00** |
| **5-Yr. Historical Growth Rates** | |
| **Sales (%)** | **36.2** |
| **Earnings Per Share (%)** | **N/A** |
| **Dividend (%)** | **N/A** |
| **P/E using TTM EPS** | **13.9** |
| **P/E using 2013 Estimate** | **N/A** |
| **P/E using 2014 Estimate** | **N/A** |

| | |
|---|---|
| **Risk Level** | **Below Avg.** |
| **Type of Stock** | **Small-Growth** |
| **Industry** | **Med-Drugs** |

## ZACKS ESTIMATES

**Revenue**
(in millions of $)

| | Q1 (Mar) | Q2 (Jun) | Q3 (Sep) | Q4 (Dec) | Year (Dec) |
|---|---|---|---|---|---|
| 2012 | 11.3 A | 10.6 A | 9.4 A | 21.9 A | 53.1 A |
| 2013 | 0.7 A | 0.7 A | 0.8 E | 0.8 E | 2.9 E |
| 2014 | | | | | 5.0 E |
| 2015 | | | | | 50.0 E |

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

| | Q1 (Mar) | Q2 (Jun) | Q3 (Sep) | Q4 (Dec) | Year (Dec) |
|---|---|---|---|---|---|
| 2012 | -$0.01 A | -$0.01 A | -$0.05 A | $0.14 A | $0.08 A |
| 2013 | -$0.18 A | -$0.18 A | -$0.18 E | -$0.18 E | -$0.73 E |
| 2014 | | | | | -$0.50 E |
| 2015 | | | | | -$0.02 E |

© Copyright 2013, Zacks Investment Research. All Rights Reserved.

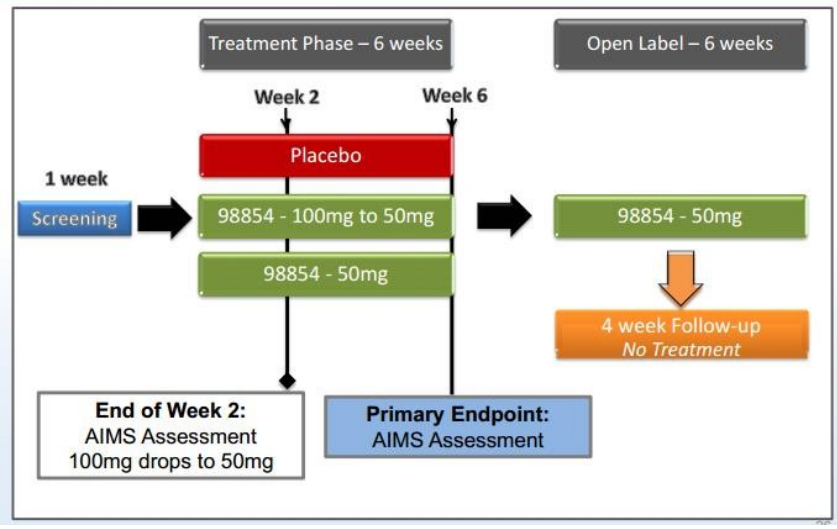
**NBI-98854 Misses On Primary Endpoint, But All Is Not Lost**

On September 9, 2013, Neurocrine Bio (NBIX) reported results from the much anticipated KINECT-1 trial, testing the company's small molecule VMAT2 inhibitor, NBI-98854, for the treatment of tardive dyskinesia. The KINECT-1 study enrolled a total of 109 patients with moderate-to-severe tardive dyskinesia (TD) with underlying schizophrenia or schizoaffective disorder. The trial took place at 33 sites around the U.S. Below we present a snap-shot of the patient profile for the KINECT-1 trial:

| Characteristic | Placebo n=54 | 50 mg n=28 | 100mg n=27 | Total N=109 |
|---|---|---|---|---|
| Mean Age in years (SD) | 54.5 (11) | 56.0 (8.9) | 55.4 (11.3) | 55.1 (10.5) |
| Mean Age years at time of TD Diagnosis (SD) | 46.9 (13) | 48.5 (8.2) | 47.5 (12.8) | 47.5 (11.8) |
| Male % | 63% | 70% | 69% | 66% |
| AIMS Total Score by Site Rater (SD) at Baseline | 15.3 (4.4) | 14.5 (5.8) | 14.4 (4.7) | 14.9 (4.8) |
| AIMS Total Score by Video Rater (SD) at Baseline | 12.1 (5.4) | 12.9 (4.6) | 12.0 (4.9) | 12.3 (5.1) |
| Tobacco use | 65% | 41% | 73% | 61% |
| Antipsychotic use | 100% | 100% | 100% | 100% |

Investors can see this was a fairly well randomized trial, with baseline AIMS scores between the three arms offering adequate control. However, the AIMS (Abnormal Involuntary Movement Scale) assessment score varied greatly between the on-site rater, which consisted of 33 separate individuals at each study site location (baseline: 14.9 (±4.8)) and one centralized rater group based on videotaped analysis (baseline: 12.3 (±5.1)). More on that later!

For the primary endpoint, KINECT-1 assessed AIMS at week 6. However, an initial AIMS assessment was conducted at week 2. Patients were randomized to either placebo (n=54), 50 mg (n=27), or 100 mg (n=26) for the first two weeks. All patients on 100 mg were then moved to 50 mg at the start of week three. Following the six week primary endpoint, all patients were eligible to enroll in a six week open label assessment on 50 mg. Below is a schematic of the trial design and endpoint timelines:



A total of four patients from the intend-to-treat (ITT) population (one on 50 mg and three on 100 mg) were later determined to have never received drug. Thus in addition to the ITT analysis, Neurocrine also analyzed the data on a per protocol (PP) basis, excluding data from these four patients. Data from the trial showed that 50 mg of NBI-98854 did not offer a statistically significant or clinically meaningful separation from the placebo at week six. This was true for both the ITT and PP populations, regardless of whether the AIMS assessment took place at on-site or a centralized video rater. Below is a snap-shot of the primary endpoint:

| | | Week 6 | | |
|---|---|---|---|---|
| | | PBO | 50mg | p-value |
| **AIMS Change from Baseline (on-site assessment)** | | | | |
| | LS Mean AIMS ANCOVA (ITT) | -2.5 | -3.3 | ns |
| | LS Mean AIMS ANCOVA (PP) | -2.4 | -3.0 | ns |
| | Responder Rate (ITT)* | 11% | 24% | ns |
| | Responder Rate (PP)* | 10% | 21% | ns |
| **AIMS Change from Baseline (video assessment)** | | | | |
| | LS Mean AIMS ANCOVA (ITT) | -2.2 | -3.5 | ns |
| | LS Mean AIMS ANCOVA (PP) | -1.9 | -3.3 | ns |
| | Responder Rate (ITT)* | 21% | 29% | ns |
| | Responder Rate (PP)* | 18% | 28% | ns |

** a responder is defined as 50% reduction in AIMS*

However, when Neurocrine looked at the AIMS assessment at the end of week two, the 100 mg dose did achieve nominally statistically significant and clinically meaningful separation from the placebo. We caution investors that this data, although encouraging, is based on only a small number of patients (n=26) over a very short period of time. Below is a snap-shot of that secondary analysis:

| | | Week 2 | | | | |
|---|---|---|---|---|---|---|
| | | PBO | 50mg | p-value | 100mg | p-value |
| **AIMS Change from Baseline (on-site assessment)** | | | | | | |
| | LS Mean AIMS ANCOVA (ITT) | -1.2 | -2.1 | ns | -2.1 | ns |
| | LS Mean AIMS ANCOVA (PP) | -1.3 | -2.4 | ns | -2.5 | ns |
| | Responder Rate (ITT)* | 7% | 7% | ns | 12% | ns |
| | Responder Rate (PP)* | 7% | 8% | ns | 14% | ns |
| **AIMS Change from Baseline (video assessment)** | | | | | | |
| | LS Mean AIMS ANCOVA (ITT) | -2.7 | -3.9 | ns | -4.8 | 0.034 |
| | LS Mean AIMS ANCOVA (PP) | -2.7 | -3.9 | ns | -5.5 | 0.008 |
| | Responder Rate (ITT)* | 23% | 30% | ns | 40% | ns |
| | Responder Rate (PP)* | 23% | 31% | ns | 48% | 0.034 |

** a responder is defined as 50% reduction in AIMS*

Based on previous clinical work, Neurocrine believed that the 100 mg dose would be the maximum tolerated dose. However, it seems as though patients with moderate-to-severe TD, all with either schizophrenia or schizoaffective disorder and taking antipsychotic medication, can tolerate a drug like NBI-98854 far better than healthy volunteers. In fact, management now believes that patients may be able to tolerate well above 100 mg, and the next phase 2 study will test 100 mg and higher. We note that the safety and tolerability of NBI-98854 looks fantastic. For example, the frequency of treatment-emergent adverse events during the initial two-week period was 17%, 18% and 15% in the placebo, 50mg and 100mg groups, respectively. During the six-week treatment period the frequency of treatment-emergent adverse events was 37% for placebo and 26% for NBI-98854. There were no drug related serious adverse events. Below is a snap-shot of the adverse event profile:

| AE | Placebo | 50 mg | 100 mg |
|---|---|---|---|
| Somnolence | 0 | 2 | 1 |
| Dry mouth | 2 | 0 | 0 |
| Bronchitis/URI | 2 | 0 | 0 |

Previously, management noted that the dropout rate was tracking well below expected. We remind investors that the company is currently conducting additional safety analysis of NBI-98854, including hepatic safety and drug-drug interactions. However, the fact that NBI-98854 was so well tolerated (50 mg offered lower averse events than the placebo) begs the question – were patients getting enough drug?

We note that this was a new formulation of the drug used in phase 2b KINECT-1 study versus the previous phase 2a study. Neurocrine moved to a commercial "solid dose tablet" formulation for KINECT-1. The previous phase 2a study employed a "mixed on site" API in solution formulation. This might suggest a pharmacokinetic issue, although management did note on the conference call that they did conduct a bioequivalence "bridging" study between the two formulations.

The data above suggest a meaningful "signal to noise" issue for KINECT-1. Potential hiccups for the trial included the differences between the on-site and centralized readers, and the variability as such, and patients not getting enough drug. Was the signal too low or the noise too high, or both?

Management conducted several secondary assessments of efficacy, including analysis based on a responder rate and Clinical Global Impression – Tardive Dyskinesia (CGI-TD). Treating clinicians determined that 36% of the subjects taking 100 mg of NBI-98854 were "much improved" or "very much improved" at week two compared to only 8% of the placebo subjects (p=0.002) in this pre-specified key secondary efficacy endpoint. This analysis was performed by a group of assessors that was distinct from those performing the AIMS assessment, and was performed without access to the AIMS results. Below is a snap-shot of the CGI-TD data:

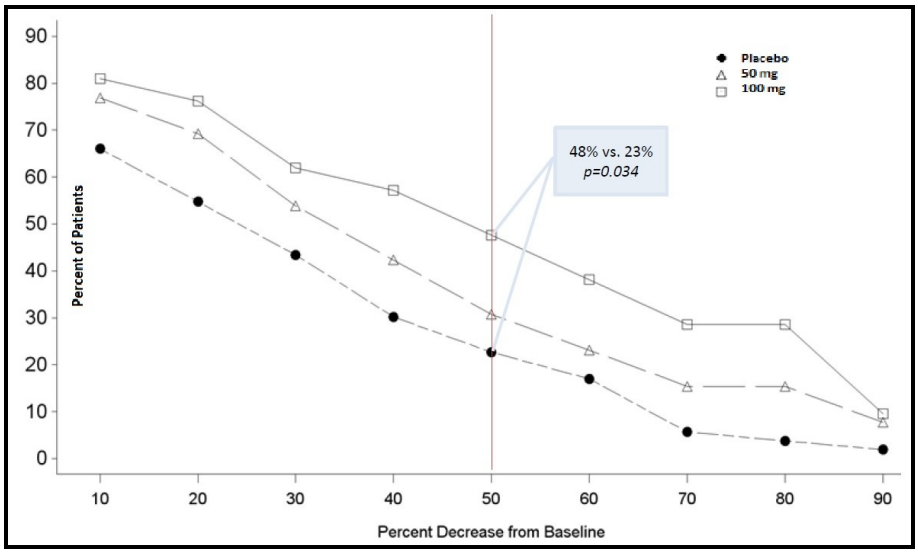
| | | Week 2 | | | | |
|---|---|---|---|---|---|---|
| CGI-TD | | PBO | 50mg | p-value | 100mg | p-value |
| | LS Mean Score | 3.6 | 3.2 | ns | 3.0 | 0.007 |
| | Responder Rate* | 8% | 15% | ns | 36% | 0.002 |

*a responder is defined as "much improved" or "very much improved"*

| | | Week 6 | | |
|---|---|---|---|---|
| CGI-TD | | PBO | 50mg | p-value |
| | LS Mean Score | 3.2 | 3.3 | ns |
| | Responder Rate* | 22% | 23% | ns |

*a responder is defined as "much improved" or "very much improved"*

The data from CGI-TD is consistent with the AIMS assessment showing a statistically significant effect of the 100 mg dose at the end of week 2. It does look like NBI-98854 had a meaningful impact over the short period of time patients were exposed to 100 mg of drug. Management noted on the conference call that better drug exposure led to better outcomes. Below is an assessment of the primary endpoint in graph form. It shows the separation of the 100 mg dose from the 50 mg and placebo



## The Takeaways

While certainly not the result that Neurocrine was looking for, there are a few positive takeaways from the trial. There are also several lingering concerns. The primary concern is that this is the second phase 2 study with NBI-98854 that has failed to achieve the primary endpoint. We wrote an article back in October 2012 discussing the results of the previous phase 2a study and the one "outlier" site that wreaked havoc on the primary endpoint. If management has learned one thing from these studies, it's that they must employ a centralized reader on the AIMS assessment, because getting 33 different and independent readers to agree on baseline characteristics and clinically meaningful signs of improvement is never going to work. And that's cause for concern.

However, at this stage it remains too early in the data analysis process to conclude where the key variability lies – either in the raters assessment of the patient or the patient's response. Clearly if patients are having varied response to the same exposure of drug, NBI-98854 is not nearly as attractive a drug as we previously believed. However, if patient response is generally pretty consistent, and a factor of drug exposure, then success should be possible by just getting the baseline and subsequent ratings standardized. If that's the case, then Neurocrine should be in pretty good shape. The U.S. FDA has clearly been amendable to these types of centralized assessments in the past (see example).

But although the baselines of the two raters varied, 14.9 for the 33 separate raters vs. 12.3 for the centralized video tape analysis, the standard deviations did not vary greatly (±4.8 vs. ±5.1, respectively). If the true issue is that getting 33 separate raters to agree on AIMS assessment is impossible, the data do not back that up. This brings us back to the key issue of signal vs. noise. In our view, KINECT-1 failed because the signal was not strong enough (i.e. dose was not adequate to drive separation in response between 50 mg and placebo), not because the background noise was too great. Nevertheless, management will be squarely focused on centralized ratings in the future.

As for raising the dose to increase the signal, that is precisely what management plans to do in the next phase 2 study. We suspect that KINECT-3 (not the official name, just what we are calling it) will look very similar to KINECT-1, only with doses starting at 100 mg and perhaps even moving to 200 mg. CEO Kevin Gorman noted on the call that the company has a lot of flexibility here based on the tolerability and safety data from KINECT-1. Neurocrine is currently conducting hepatic impairment and drug-drug interaction studies to support the clinical package for the drug. We believe the costs of KINECT-3 are similar to KINECT-1 (around $8 to $10 million), and the delay in meeting with the FDA for an end-of-phase 2 meeting is around 12 months.

We remind investors that KINECT-2 continues on plan, with top-line data expected in the fourth quarter 2013. The KINECT-2 trial is examining a dose-titration regimen of NBI-98854, but only up to 75 mg. Therefore, expectations for KINECT-2 have to be low. Nevertheless, KINECT-2 should give management additional valuable information on the AIMS assessment from an on-site vs. centralized rater standpoint. Additionally, the company has initiated preclinical studies to support the advancement of NBI-98854 into clinical trials for individuals suffering from Tourette's syndrome. Upon successful completion of these preclinical studies, management anticipates entering phase 1 and phase 2 clinical studies in 2014.

## Price Target Drops To $14

We are maintaining our Buy rating on the shares of Neurocrine. While we are clearly disappointed in the outcome of the KINECT-1 study, pushing back the launch timelines of the drug by only twelve months has minimal impact on our DCF model. The added costs of KINECT-3 ($8-10 million) are easily supported by the existing cash balance, which stood at $166.5 million as of June 30, 2013. The net effect of pushing timelines back twelve months and increased costs in 2014 to run KINECT-3 is approximately a $4 per share hit to our previous $18 fair-value calculation.

Besides NBI-98854, Neurocrine obviously still has elagolix pushing forward at AbbVie (ABBV), and early-stage collaborations with Boehringer Ingelheim around the research and development of G-protein coupled receptor (GPCR) small molecules for the treatment of Type-2 diabetes. Phase 2 data on elagolix were just recently published electronically ahead of print in the Journal of Endometriosis and Pelvic Pain Disorders. We believe elagolix is worth $8-10 per share based on the rate at which the two ongoing phase 3 studies at AbbVie enroll and report data, and the timelines for the uterine fibroids phase 3 study.

## PROJECTED FINANCIALS

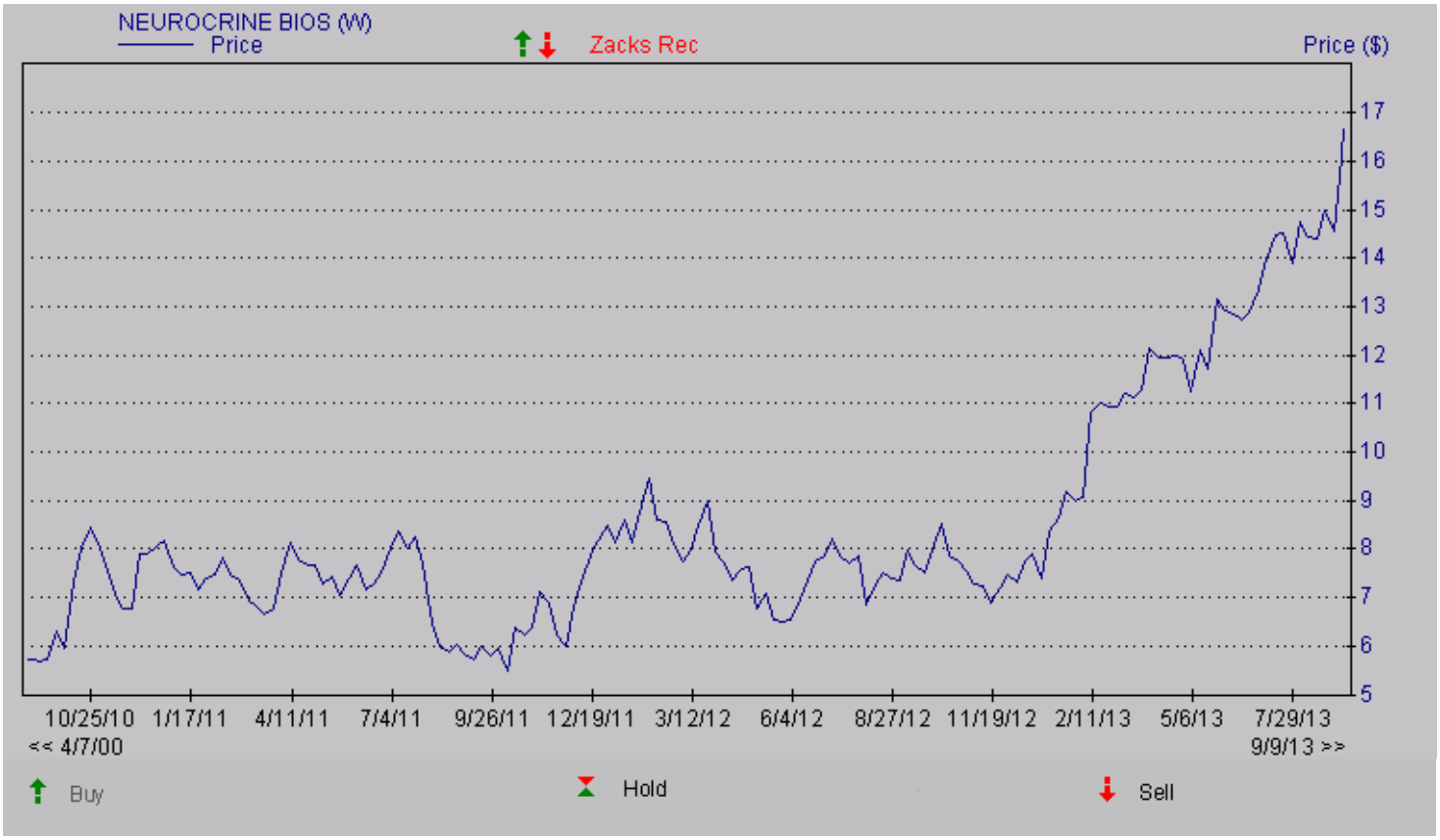
**Neurocrine Biosciences Inc.**
Income Statement

| Neurocrine Bio | 2011 A | 2012 A | Q1 A | Q2 A | Q3 E | Q4 E | 2013 E | 2014 E | 2015 E | 2016 E |
|---|---|---|---|---|---|---|---|---|---|---|
| **R&D / Milestones & Fees** | **$77.4** | **$53.1** | **$0.7** | **$0.7** | **$0.8** | **$0.8** | **$2.9** | **$5.0** | **$50.0** | **$50.0** |
| *YOY Growth* | *131.1%* | *-31.4%* | *-93.5%* | *-93.4%* | *-92.0%* | *-96.6%* | *-94.5%* | *70.6%* | *900.0%* | *0.0%* |
| **elagolix Royalties** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** |
| *YOY Growth* | - | - | - | - | - | - | - | - | - | - |
| **VMAT-2** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** |
| *YOY Growth* | - | - | - | - | - | - | - | - | - | - |
| **Total Revenues** | **$77.4** | **$53.1** | **$0.7** | **$0.7** | **$0.8** | **$0.8** | **$2.9** | **$5.0** | **$50.0** | **$50.0** |
| *YOY Growth* | *131.1%* | *-31.4%* | *-93.5%* | *-93.4%* | *-92.0%* | *-96.6%* | *-94.5%* | *70.6%* | *900.0%* | *0.0%* |
| CoGS / Royalties | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0.0 | $0.0 |
| *Gross Margin* | *100.0%* | *100.0%* | *0.0%* | *0.0%* | *0.0%* | *0.0%* | *100.0%* | *100.0%* | *100.0%* | *100.0%* |
| SG&A | $12.4 | $14.5 | $3.4 | $3.4 | $3.5 | $3.6 | $13.9 | $14.5 | $15.0 | $15.5 |
| *% SG&A* | *16.0%* | *27.3%* | *464.7%* | *485.7%* | *466.7%* | *480.0%* | *474.1%* | *290.0%* | *30.0%* | *31.0%* |
| R&D | $31.0 | $37.2 | $10.3 | $10.5 | $10.5 | $10.5 | $41.8 | $35.0 | $40.0 | $40.0 |
| *% R&D* | *40.0%* | *69.9%* | *1412.7%* | *1500.0%* | *1400.0%* | *1400.0%* | *1427.1%* | *700.0%* | *80.0%* | *80.0%* |
| Operating Income | $34.1 | $1.4 | ($13.0) | ($13.2) | ($13.3) | ($13.4) | ($52.8) | ($44.5) | ($5.0) | ($5.5) |
| *Operating Margin* | *44.0%* | *2.7%* | - | - | - | - | *-1801.2%* | *-890.0%* | *-10.0%* | *-11.0%* |
| Interest / Other Income | $3.6 | $3.6 | $0.9 | $0.9 | $1.0 | $1.0 | $3.8 | $3.5 | $2.5 | $2.5 |
| Pre-Tax Income | $37.6 | $5.0 | ($12.1) | ($12.3) | ($12.3) | ($12.4) | ($49.0) | ($41.0) | ($2.5) | ($3.0) |
| Taxes | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $6.2 | $0.8 | $0.9 |
| *Tax Rate* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *5%* | *15.0%* | *30.0%* | *30.0%* |
| Net Income | $37.6 | $5.0 | ($12.1) | ($12.3) | ($12.3) | ($12.4) | ($49.0) | ($34.9) | ($1.8) | ($2.1) |
| *YOY Growth* | - | - | - | - | - | - | - | - | - | - |
| *Net Margin* | *48.5%* | *9.5%* | - | - | - | - | *-1671.5%* | *-697.0%* | *-3.5%* | *-4.2%* |
| **Reported EPS** | **$0.67** | **$0.08** | **($0.18)** | **($0.18)** | **($0.18)** | **($0.18)** | **($0.73)** | **($0.50)** | **($0.02)** | **($0.03)** |
| *YOY Growth* | - | *-88.5%* | | | | | *-1057.0%* | *-32.1%* | *-95.2%* | *16.0%* |
| Shares Outstanding | 56.3 | 65.6 | 66.6 | 66.9 | 66.8 | 67.0 | 66.8 | 70.0 | 72.5 | 75.0 |

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

© Copyright 2013, Zacks Investment Research. All Rights Reserved.

## HISTORICAL ZACKS RECOMMENDATIONS




## DISCLOSURES

The following disclosures relate to relationships between Zacks Investment Research ("ZIR"), Zacks & Company (ZCO") and Zacks Small-Cap Research ("Zacks SCR") and the issuers covered by the Zacks SCR analysts in the Small-Cap Universe.

ZIR or Zacks SCR Analysts do not hold or trade securities in the issuers which they cover. Each analyst has full discretion on the rating and price target based on their own due diligence. Analysts are paid in part based on the overall profitability of Zacks SCR. Such profitability is derived from a variety of sources and includes payments received from issuers of securities covered by Zacks SCR for non-investment banking services. No part of analyst compensation was, is or will be, directly or indirectly, related to the specific recommendations or views expressed in any report or blog.

ZIR and Zacks SCR do not make a market in any security nor do they act as dealers in securities. Zacks SCR has never received compensation for investment banking services on the small-cap universe. Zacks SCR does not expect received compensation for investment banking services on the small-cap universe. Zacks SCR has received compensation for non-investment banking services on the small-cap universe, and expects to receive additional compensation for non-investment banking services on the small-cap universe, paid by issuers of securities covered by Zacks SCR. Non-investment banking services include investor relations services and software, financial database analysis, advertising services, brokerage services, advisory services, investment research, and investment management.

Additional information is available upon request. Zacks SCR reports are based on data obtained from sources we believe to be reliable, but is not guaranteed as to accuracy and does not purport to be complete. Because of individual objectives, the report should not be construed as advice designed to meet the particular investment needs of any investor. Any opinions expressed by Zacks SCR Analysts are subject to change. Reports are not to be construed as an offer or the solicitation of an offer to buy or sell the securities herein mentioned.

ZCO and Zacks SCR are separate legal entities. ZCO is U.S. broker-dealer registered with the U.S. Securities and Exchange Commission and a member of the Financial Industry Regulatory Authority and the Securities Investor Protection Corp. This report is for your information only and is not an offer to sell, or a solicitation of an offer to buy, the securities or instruments through ZCO.

Zacks SCR uses the following rating system for the securities it covers. Buy/Outperform: The analyst expects that the subject company will outperform the broader U.S. equity market over the next one to two quarters. 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 of Zacks Ratings is as follows on the 1029 companies covered: Buy/Outperform- 14.5%, Hold/Neutral- 78.4%, Sell/Underperform – 6.1%. Data is as of midnight on the business day immediately prior to this publication.

© Copyright 2013, Zacks Investment Research. All Rights Reserved.