Zacks Small-Cap Research

March 14, 2013
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InVivo Therapeutics (NVIV-OTC)

NVIV: HUD and IDE Under Review; Human Study To Hopefully Start Soon…

Current Recommendation	**Outperform**
Prior Recommendation	N/A
Date of Last Change	07/26/2011
Current Price (03/13/13)	$2.25
Target Price	**$5.00**

UPDATE

InVivo may finally be getting close to initiating its first human clinical trial in the second quarter 2013. This is the even that shareholders have been waiting almost two years for. If successful, InVivo may be on the market with its device in 2014.

We are maintaining our 'Outperform' rating and $5.00 price target on shares of InVivo. We remain bullish on the company's long-term prospects with the biopolymer scaffolding device and the injectable hydrogel. Opportunities in spinal cord injury (SCI) and peripheral nerve injury are in the hundred-millions of dollars. In fact, both are blockbuster opportunities given the significant size of the market and the lack of effective treatment options.

SUMMARY DATA

52-Week High	**$2.65**
52-Week Low	**$1.28**
One-Year Return (%)	**-7.08**
Beta	**0.10**
Average Daily Volume (sh)	**191,869**
Shares Outstanding (mil)	**66**
Market Capitalization ($mil)	**$147**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**0**
Insider Ownership (%)	**30**
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 2012 Estimate	**N/A**
P/E using 2013 Estimate	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2012	0 A	0 A	0 A	0 A	0 A
2013	0 E	0 E	0 E	0 E	0 E
2014					9.1 E
2015					30.6 E

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

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2012	$0.05 A	$0.03 A	$0.12 A	-$0.13 E	$0.07 E
2013	-$0.08 E	-$0.10 E	-$0.09 E	-$0.09 E	-$0.32 E
2014					-$0.33 E
2015					-$0.09 E

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WHAT'S NEW

IDE Trail To Start In Q2-2013

In July 2011, InVivo Therapeutic filed an Investigational Device Exemption (IDE) application for its biocompatible polymer scaffolding (BPS) device to treat acute spinal cord injuries. It's been almost two years since the original IDE application, but we believe the goal is in sight, and InVivo should be in position to start the human clinical trial in the second quarter 2012. We remind investors that management at InVivo met with the U.S. FDA in April 2012, and announced shortly after confirmation that the agency will regulate BPS as a Class III medical device. Since that time, management has been engaged in additional back-and-forth discussion with the FDA on the planned human clinical study.

InVivo spent much of 2012 preparing the new 21,000 square foot manufacturing facility in Cambridge, MA. The company moved into the new facility in September 2012. During the fourth quarter 2012, the company began validating the clean room and manufacturing GMP test batches for commercial trials.

A Class III medical device typically will require FDA approval of a Pre-Market Approval application (PMA) before the company can start marketing the product in the U.S. However, in December 2012, InVivo filed a request with the FDA for Humanitarian Use Device (HUD) designation for its biopolymer scaffolding product. This would allow for commercialization under a Humanitarian Device Exemption (HDE) rather than a PMA.

We note devices eligible for HUD designations are developed to treat rare diseases or conditions. In order for a device to be eligible for an HDE, it must be first designated by the FDA as a HUD intended to benefit patients in the treatment or diagnosis of a disease or condition that affects fewer than 4,000 individuals in the U.S. per year. InVivo has requested designation for the use of its biopolymer scaffolding in the treatment of complete functional spinal cord injuries that do not involve penetrating injury or the complete severing of the spinal cord.

According to the National Spinal Cord Injury Statistical Center (NSCISC), an estimated 12,000 individuals will become fully or partially paralyzed each year due to spinal cord injury. NSCISC data show that approximately 22% of these individuals will have complete tetraplegia and 25% will have complete paraplegia. That would bring the proposed population down to 5,640 individuals. If we assume that half of this population does not have a penetrating injury or the complete severing of the spinal cord, investors can see that InVivo is well below the 4,000 maximum eligible population. On a side-note, we fully expect that if approved with the proposed label (ASIA-A complete thoracic injury), InVivo's device will be used, and could even be approved, for a much wider patient population than just medically plausible subset outlined in the HUD request.

HUD requests are typically reviewed in 45 days. According to company filings, InVivo received comments from the FDA's Office of Orphan Products Development (OOPD) on the HUD request and responded to those comments in February 2013. At the very latest, we are expecting the FDA-OOPD to respond back on the application by early April 2013.

Following approval of the HUD application, InVivo will be required to conduct the human clinical study. In February 2013, InVivo filed a supplement to the July 2011 IDE application requesting approval to being this study. The proposed study will seek to enroll five patients with acute thoracic injuries in an open-label design to take place at two level one trauma centers, one in Boston and the other in Philadelphia. The primary outcome of the study will be to assess signs of improvement below the level of the spinal cord injury. InVivo will use standardized American Spinal Injury Association (ASIA) scoring to assess efficacy over a year-long period.

We expect enrollment and treatment to take approximately two to three months, with data beginning to dribble out a month later. Patient follow-up will last twelve months. The cost will be around $1.5 million. We expect InVivo to look to duplicate positive results in patients with cervical injury. If results of the IDE trial are successful, we expect the company to be in position to file the HDE application shortly after. The FDA would then review the HDE application and have 75 days to respond. If all goes well, InVivo would be in position to start marketing its biocompatible polymer scaffolding product for acute spinal cord injury as early as 2014. If the product is approved by the FDA, we suspect that InVivo will need to expand manufacturing capacity, and establish sales, marketing and distribution channels to sell the product. InVivo plans to market and sell the product through a direct sales force in the U.S. on its own. Approval under the HDE pathway will also protect InVivo from competition with a similar device for seven years.

Primate Data Validates Potential

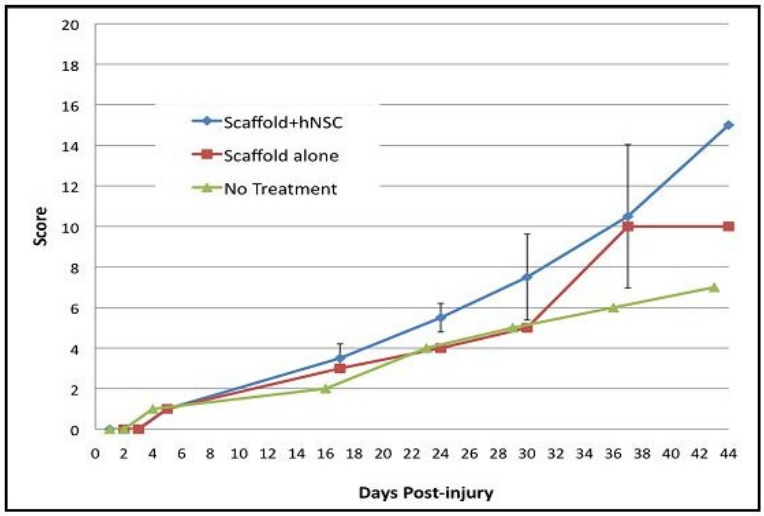
Based on preclinical data from the company's three primate studies, we are optimistic on this program. Previously completed non-human primate data from 2008 has been published in the Journal of Neuroscience Methods, and won the prestigious 2011 Apple Award from the American Spinal Injury Association recognizing excellence in SCI research. This data focused mainly on neuromotor assessment criteria following the model of spinal cord injury. The second primate study from 2010, which involved sixteen primates, also included collecting quantitative electromyographic and kinematic analyses. The company is saying that this data will be published shortly.

…The 2008 Pilot Primate Study…

In April 2008, InVivo conducted the first non-human primate study with an induced spinal cord injury model. The study utilized a lateral hemisection spinal cord injury model in four African Green monkeys, in which the left-half segment of the spinal cord between T9 and T10 was surgically removed. Immediately following tissue removal, our biopolymer devices were inserted into the resulting lesion. The injury model resulted in Brown-Séquard syndrome: paralysis of the animals' left hind limb and loss of sensory function in the animals' right hind limb. The injury model was successful in preserving bowel and bladder function in all animals. Animals were monitored for six weeks post-injury, and behavioral scoring was performed to measure functional recovery by a neuroscientist blinded to the injury model or treatments performed on each subject. The study was conducted at the St. Kitts Biomedical Research Foundation in St. Kitts and Nevis.

Preliminary video data of the primates was reviewed and rated by a blinded reviewer not involved in the conduct of the study based on a twenty point neuromotor observational scale. This scale assesses the degree of neuromotor recovery in the hind-limbs of primates after the lateral hemisection injury model. For example, a score of zero means the primate has no voluntary muscle function after injury, a score of twenty means a completely recovery after injury. Any score greater than eight indicates the subject has regained the ability to bear weight and perform deliberate stepping. The two African Green monkeys that received scaffolds seeded with human neural stem cells (n=2) demonstrated an improved level of functional recovery compared to the control animal (n=1). Results show implantation of the scaffold alone demonstrated improved efficacy in promoting functional recovery compared to the control in both one monkey (Figure-1).

…Neuromotor Performance – 2008 Primate Study…



Source: InVivo Therapeutics, 2012 Form-10K

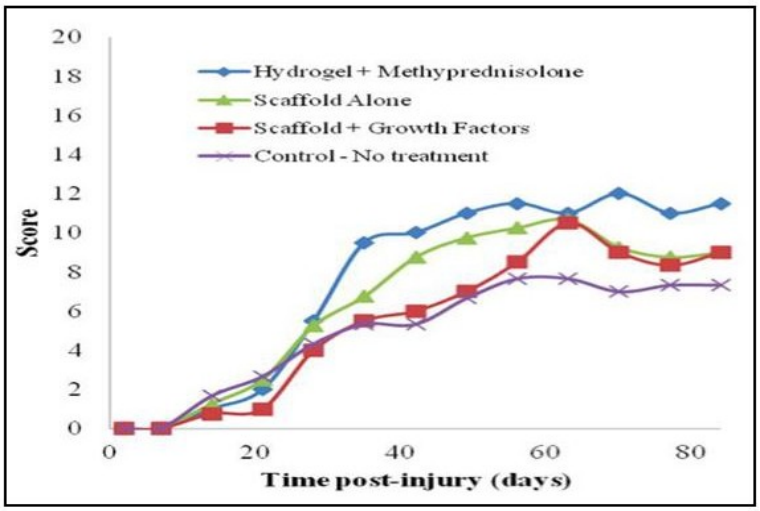
…The 2010 Primate Study…

A second primate study involving 16 primates was also conducted at the St. Kitts Biomedical Research Foundation in St. Kitts and Nevis in 2010. A segmental thoracic hemisection was used in African green monkeys for the evaluation of biomaterial implants in a pre-clinical model of spinal cord injury in the non-human primate. The model's physiological tolerance permitted behavioral analyses for a 12-week period post-injury, extending to termination points for immuno-histochemical analyses.

Implementation of surgically-induced spinal cord injury through T9-T10 thoracic lateral hemisection on 16 African green monkeys with administration of a PLGA-polylysine scaffold (n=4), a PLGA-polylysine scaffold soaked in growth factors (EGF, bFGF, 15µg each) (n=5), a thiol-acrylate poly (ethylene glycol) based hydrogel containing 150µg methylprednisolone sodium succinate (n=4), or no treatment for control (n=4). Implants were administered at the time of lesioning. The objective was to determine the feasibility and reliability of this pre-clinical model of spinal cord injury, the safety and efficacy of the implants in a non-human primate model, as well as the establishment of assessment measures. Analysis of functional neuromotor improvements was performed by statistical evaluation of 3D kinematic and electromyographic ("EMG") recordings, InVivo's 0-20 neuromotor scoring system and histological and immuno-histochemical stains on post-mortem spinal cord thoracic and lumbar cross-sections.

The neuromotor assessment by a blinded trained neuroscientist for each group over the twelve-week period for the left hind limb was charted (Figure-2). All groups show an initial paralysis 2 days post-injury. The treatment groups exhibited an improved recovery compared to untreated injured controls on average. Kinematic and EMG analyses exhibited the same trend. While only sixteen primates were evaluated, the initial results are consistent with data from prior monkey and rodent studies.

…Neuromotor Performance – 2010 Primate Study…



Source: InVivo Therapeutics, 2012 Form-10K

…The 2011 Primate Study…

A third primate study was begun in 2011 at the St. Kitts Biomedical Research Foundation in St. Kitts and Nevis. The study included 24 additional primates utilizing the same study design as the 2010 African green monkey study. Animals were assigned to one of three groups, including a treatment group (n=8) treated with the PLGA-polylysine scaffold, a treatment group (n=8) treated with the thiol-acrylate poly (ethylene glycol) based hydrogel containing 150µg methylprednisolone sodium succinate, and a control group (n=8) that received no treatment.

Results are consistent with data from prior monkey and rodent studies. The results from the 2011 and 2010 studies are being drafted in a manuscript that will be submitted to a peer-reviewed journal. In both the 2010 and 2011 primate studies, treatment with InVivo's BPS resulted in improved functional recovery coupled with the generation of new tissue that was conducive to the growth of axons. According to management, these results show functional recovery observed in the treatment group was attributable to the biopolymer scaffolding alone, and was not due to spontaneous recovery.

Hydrogel Up Next

Meanwhile, InVivo is working with the FDA to submit additional data around the company's drug releasing hydrogel for both spinal cord injury and peripheral nerve pain. Management intends to meet with representatives from the FDA's Office of Combination Products in the coming months to map out a clinical development plan. Ideally, the hydrogel would be regulated as a device by the FDA, allowing InVivo to move into an IDE programs in spinal cord injury and peripheral nerve pain in late 2013 or 2014 and file for approval under the PMA pathway, potentially in 2016 or 2017. Only before that can take place, the pathway needs to be confirmed and additional preclinical data needs to be submitted to the FDA for review.

To help obtain some of this necessary preclinical data, in January 2012, management announced collaboration with the Geisenger Health System (GHS) to conduct a preclinical study using the injectable hydrogel for the treatment of chronic pain caused by peripheral nerve compression. The study was conducted jointly in the Tapinos Lab of Molecular Neuroscience at the Weis Center for Research and the Slotkin Lab of Spinal Cord Injury Research at the Geisenger Clinic's Neurosciences Institute. InVivo paid Geisenger $60,000 upfront and will fund the cost of the study, which is estimate to be $150,000.

The endpoint of the study was the effectiveness of using injectable hydrogels for the controlled release of drugs to alleviate chronic pain resulting from compression-induced peripheral nerve damage looking at both molecular and behavioral impact in rodents. The study is planned to have four arms: 1) injectable scaffold with drug therapy, 2) the injectable scaffold alone, 3) injectable drug therapy alone, and 4) a control group receiving no injection. InVivo completed the study late in 2012 and the data will be submitted for publication in 2013.

The hydrogel is designed to release drugs over at least 10 days in order to synchronize the rate of delivery to match the period in which the inflammatory response A localized injection using the hydrogel to provide time-released anti-inflammatory therapies like methylprednisolone could provide pain relief for up to twelve months with limited systemic side effects. The company is aiming to file an IDE application to the U.S. FDA to start the first-in-human studies before the end of the year.

We see an enormous opportunity for the injectable hydrogel. Methylprednisolone is FDA-approved, and is currently a treatment option for spinal cord injuries and is used to treat peripheral nerve injuries. However, high-dose intravenous administration of the drug can result in harmful systemic side effects, including increased risks of pneumonia, sepsis and mortality. InVivo believes that by precisely controlling the release of methylprednisolone at the site of injury, therapeutically effective doses can be delivered to the point of inflammation while mitigating the risk of harmful systemic side effects. The acute and chronic spinal cord injury market is estimated at $20 to $25 billion in the U.S. alone. For peripheral nerve pain, there are an estimated 3.2 million nerve block injections done in the U.S. each year. It's another estimated $20 billion market opportunity.

In August 2012, InVivo announced that one of the company's neurosurgeons, Amer Khalil, MD, has been selected as the winner of an MDH Research Award, a grant given by MDHonors, to further InVivo's research on spinal cord injury. Dr. Khalil was awarded a grant of $10,000 for his project titled, "Spinal cord repair using biomaterial-based drug-releasing strategies for reducing scarring and promoting regeneration."

Management sees Dr. Khalil's project as an exciting opportunity to expand its technology into a potential product for the treatment of fibrosis. InVivo believes its hydrogel can be used to reduce scarring in both reparative surgical and dermatological applications. We believe minimizing scarring after reparative surgery or scarring following plastic surgery procedures is an enormous market opportunity – potentially millions of treatments per day in the U.S.

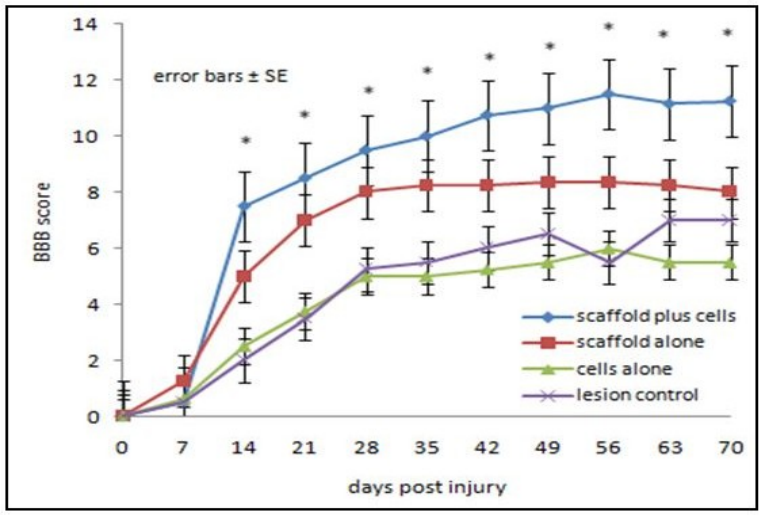
InVivo has also commenced the development of novel injectable hydrogels to be used as dural sealants, dural replacements, and nerve conduits. The FDA regulates biomaterials used as dural replacements and nerve conduits as 510(k) products, and management expects to file 510(k) applications for these indications in 2014.

Polymer Scaffold Seeded With Human Neural Stem Cells

Perhaps the most exciting opportunity for investors in InVivo lies deep in the company's pipeline, and it involved using the biocompatible polymer scaffold device seeded with autologous human neural stem cells (hNSC). This could allow the company to expand the use indication for the BPS device beyond acute injuries into chronic spinal cord injury patients, a market an estimated 15-times the size of the acute market.

According to the U.S. Center for Disease Control and Prevention, an estimated 200,000 Americans are living with spinal cord injury. The concept of using the BPS seeded with hNSC combines the two major concepts of regenerative medicine – scaffold and cells. The scaffold acts as a synthetic extracellular matrix on which cells can be transplanted. Proof-of-concept for the combination of BPS-hNSC stems from the company's preclinical rodent studies in 2002.

…Scaffold Seeded Cell Therapy – Proof-of-Concept…



Source: InVivo Therapeutics, 2012 Form-10K

Sizing Up The Opportunity For InVivo

InVivo exited 2012 with $13.4 million in cash and equivalents. The company has burned approximately $12.3 million from operating and investing activities in 2012. We find the current cash balance to be sufficient to fund operations into the first quarter of 2014 (current management guidance). As of March 6, 2013, the basic share count stood at 66.1 million. We remind investors that there are a total of 15.8 million warrants outstanding as of December 31, 2012. This includes 13.4 million warrants currently exercisable at $1.40 per share and 1.9 million warrants currently exercisable at $1.00 per share. In total, the exercising of these warrants could supply an additional $20.6 million in cash to the company.

We see the opportunity in acute thoracic spinal cord injury, as defined under the HUD application, as a peak $240 million opportunity. This includes treating the maximum 4,000 patients at a price of roughly $60,000 per treatment. We think InVivo could actually charge more for the BPS device. Data from the NSCISC shows that the average cost to care for a spinal cord injury patient in the first year of the injury ranges between $335,00 and $1,025,00. For a 25 year old with complete tetraplegia, the lifetime cost of care is an estimated $4.5 million. For a complete paraplegic, its an estimated $2.5 million. We remind investors that if HUD is granted and the IDE trial succeeds, InVivo could be on the market selling its BPS device into this estimated $250 million opportunity as soon as early 2014.

Now the upside to the story: The hydrogel and the BPS-hNSC. With the hydrogel for SCI, we estimate that nearly all of the 12,000 acute injury patients per year could be eligible for treatment. With a premium price of $75,000 per surgery, InVivo is looking at an estimated $900 million opportunity. In peripheral nerve pain, above we note an estimated 3.2 million procedures per year. With as little as 5% market share and a yearly price of only $10,000, InVivo is looking at another $1.6 billion market. That alone makes InVivo an interesting long-term investment.

But what really gets us excited is the potential for use of the BPS seeded with autologous human neural stem cells. There are an estimated 200,000 chronic spinal cord injury patients in the U.S. If InVivo can treat just 20% of these patients, with an estimated price of around $100,000 per surgery, the market opportunity would be approximately $4.0 billion.

PROJECTED FINANCIALS

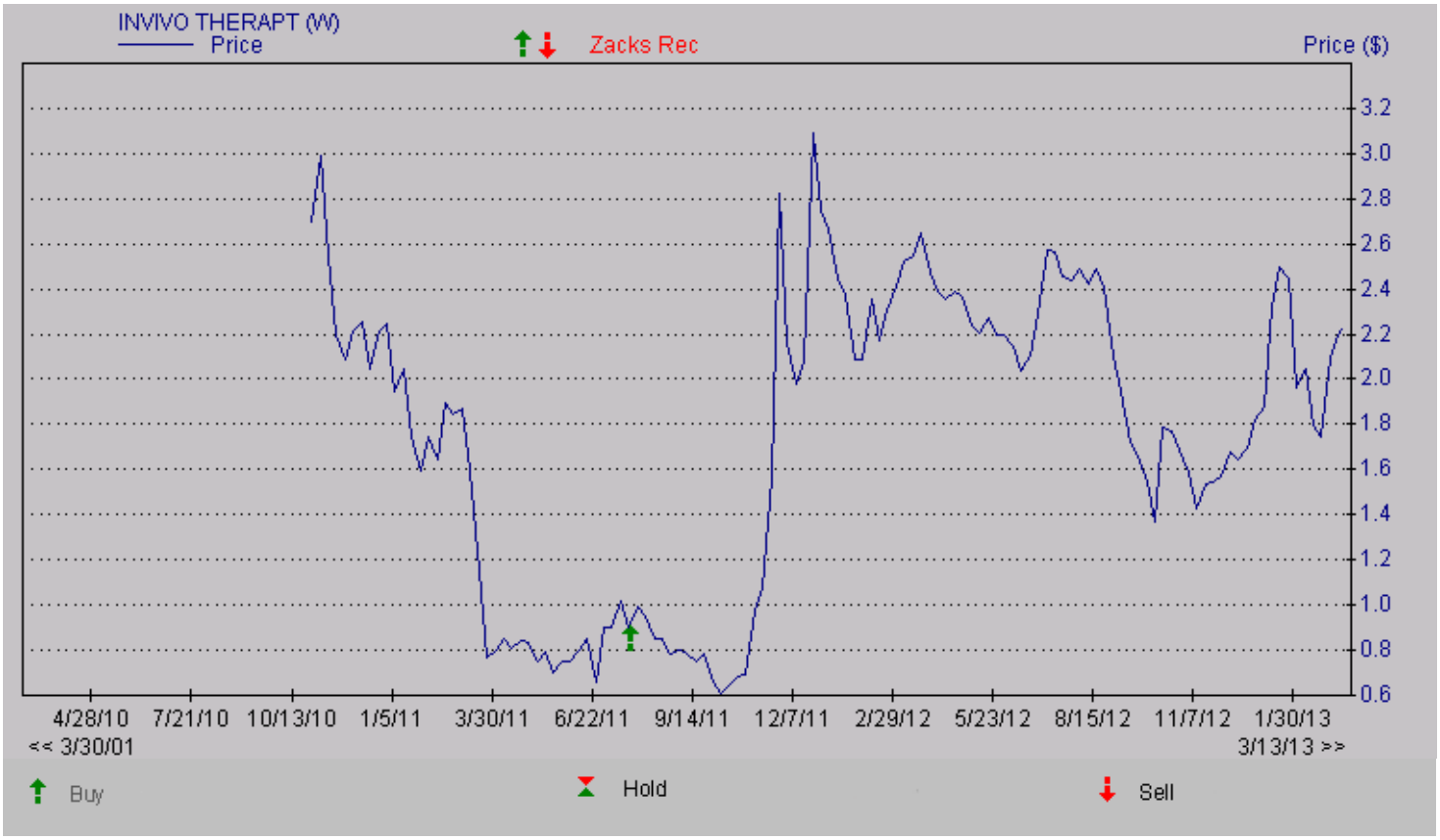
InVivo Therapeutics Holdings Corp.
Income Statement

InVivo Therapeutics	2010 E	2011 A	Q1 A	Q2 A	Q3 A	Q4 A	2012 A	Q1 E	Q2 E	Q3 E	Q4 E	2013 E	2014 E	2015 E
Product Sales	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$9.1	$30.6
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Collaborative & Licensing	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total Revenues	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0.0	$9.1	$30.6
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cost of Goods / Services	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$1.5	$3.4
Product Gross Margin	-	-	-	-	-	-	-	-	-	-	-	-	-	-
R&D	$1.7	$4.1	$0.9	$1.3	$1.4	$2.8	$6.4	$2.5	$3.5	$3.5	$3.5	$13.0	$15.0	$15.0
% R&D	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SG&A	$1.7	$4.6	$1.5	$1.4	$1.5	$2.0	$6.4	$2.0	$2.1	$2.1	$2.3	$8.5	$17.2	$19.3
% SG&A	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Operating Income	($3.4)	($8.7)	($2.5)	($2.8)	($2.8)	($4.7)	($12.8)	($4.5)	($5.6)	($5.6)	($5.8)	($22.0)	($24.6)	($7.1)
Operating Margin	*0.0%*	-	-	-	-	-	-	-	-	-	-	-	-	-
Net Other Income	($4.5)	($26.1)	$5.6	$5.0	$10.9	($4.0)	$17.4	($1.0)	($1.0)	($1.0)	($1.0)	$0.0	$0.0	$0.0
Pre-Tax Income	($7.9)	($34.8)	$3.1	$2.2	$8.0	($8.7)	$4.7	($5.5)	($6.6)	($6.6)	($6.8)	($22.0)	($24.6)	($7.1)
Taxes	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0.0	$0.0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0.0%*	*0.0%*
Net Income	($7.9)	($34.8)	$3.1	$2.2	$8.0	($8.7)	$4.7	($5.5)	($6.6)	($6.6)	($6.8)	($22.0)	($24.6)	($7.1)
Net Margin	*0.0%*	-	-	-	-	-	-	-	-	-	-	-	*-268.8%*	*-23.2%*
Reported EPS	**($0.24)**	**($0.67)**	**$0.05**	**$0.03**	**$0.12**	**($0.13)**	**$0.07**	**($0.08)**	**($0.10)**	**($0.09)**	**($0.09)**	**($0.32)**	**($0.33)**	**($0.09)**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Wt. Ave Shares Outstanding	33.4	51.9	58.0	64.1	65.1	65.7	63.2	66.5	68.0	70.0	72.0	69.1	75.0	80.0

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

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