Zacks Small-Cap Research

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InVivo Therapeutics (NVIV-NASDAQ)

NVIV: FDA Clears INSPIRE Probable Benefit Study; UC San Diego MC Added as Clinical Site…

Current Recommendation	**Buy**
Prior Recommendation	Neutral
Date of Last Change	01/15/2015
Current Price (02/11/16)	$3.66
Target Price	**$24.00**

UPDATE

In January 2016, InVivo Therapeutics (NASDAQ:NVIV) received approval of its protocol amendment from the FDA, which converted its ongoing pilot study into a pivotal probable benefit study entitled The INSPIRE Study ("*InVivo Study of Probable Benefit of the Neuro-Spinal Scaffold™ for Safety and Neurologic Recovery in Subjects with Complete Thoracic AIS A Spinal Cord Injury*"). The company plans to use this single study as the basis for a Humanitarian Device Exemption (HDE) application with planned submission in late 2017.

InVivo has also highlighted a strategy for the treatment of chronic spinal cord injury (SCI) through its Bioengineered Neural Trails™ Program in order to restore neuronal connectivity and promote neurological recovery in patients with chronic SCI. Although it is in the pre-clinical stage, we believe it is important to offer some insight into chronic SCI program as nearly 300,000 Americans currently live with chronic SCI with limited therapeutic options.

At the current price, we view InVivo shares as meaningfully undervalued, and as providing significant long-term upside potential. We believe the recent pullback in the biotech sector presents investors with an interesting long-term buying opportunity. We are maintaining our price target of $24 per share, and continue to rate the stock a 'Buy'.

SUMMARY DATA

52-Week High	**$17.78**
52-Week Low	**$3.66**
One-Year Return (%)	**-58.60**
Beta	**1.57**
Average Daily Volume (sh)	**270,353**
Shares Outstanding (mil)	**27**
Market Capitalization ($mil)	**$100**
Short Interest Ratio (days)	**9.50**
Institutional Ownership (%)	**19**
Insider Ownership (%)	**2**
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 2015 Estimate	**N/A**
P/E using 2016 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)
2014	0 A	0 A	0 A	0 A	0 A
2015	0 A	0 A	0 A	0 E	0 E
2016					0 E
2017					0 E

Earnings per Share
(EPS is operating earnings)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	-$0.28 A	-$0.17 A	-$0.05 A	-$1.49 A	-$0.83 A
2015	-$0.64 A	-$0.39 A	-$0.09 A	-$0.22 E	-$0.87 E
2016					-$0.90 E
2017					-$0.91 E

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WHAT'S NEW

For the purpose of this research report, we will offer a business update and a review of notable events and milestones for InVivo Therapeutics (NASDAQ:NVIV), a biomaterials and biotechnology company focused on technologies and treatments for acute and chronic spinal cord injury (SCI). InVivo currently has two spinal cord injury programs in place: The Neuro-Spinal Scaffold™ pilot study for acute SCI which was recently converted to the probable benefit INSPIRE Study, and the recently announced pre-clinical Bioengineered Neural Trails™ Program for chronic SCI where neural stem cells are delivered in biomaterials by a novel, minimally invasive delivery system.

BUSINESS UPDATE

InVivo Therapeutics was conducting an early pilot study of the Neuro-Spinal Scaffold™ (NSS) under an approved Investigational Device Exemption (IDE) application for the treatment of complete traumatic acute spinal cord injury (SCI). We remind investors that InVivo received a Humanitarian Use Device (HUD) designation for the NSS in April 2013. The FDA approved pilot study was intended to capture data on the safety and feasibility of using the NSS along with gathering preliminary evidence of clinical effectiveness. The pilot study was initially approved to enroll five patients, but InVivo announced that the FDA approved expansion of the study to permit enrollment to ten patients in October 2015, which we viewed as a positive development to the InVivo story. We believe that expansion of the pilot study set the stage for transition into the pivotal probable benefit study, and to use this single study as the basis for a Humanitarian Device Exemption (HDE) application would dramatically reduce clinical trial timelines and time to potential approval and commercialization.

Thus far, there are 15 clinical sites open, and 5 patients have been enrolled in the study and implanted with the NSS. The University of California, San Diego Medical Center was the most recent site to be added on February 3, 2016. The last patient (Patient #5) was enrolled back in September 2015, and we believe that some investors have moved away from the InVivo story due to slow enrollment. We think it's important for investors to keep in mind that not every spinal cord injury patient at each of the centers will qualify for participation into the trial, but we do believe that approximately 9 more trial sites should be added this year, which should help with trial enrollment. We believe that the majority of these sites will be in the U.S.; however there have been talks of opening up trial sites in both Canada and the United Kingdom.

FDA Approves *INSPIRE* Probable Benefit Study of the Neuro-Spinal Scaffold™

On January 4, 2016, InVivo received approval of a protocol amendment from the FDA, which converted its ongoing pilot study into a pivotal probable benefit study. As a reminder, on December 3, 2015, InVivo announced that it has received conditional approval of the protocol amendment, and the approval was conditional solely upon a minor change to the informed consent form. We were expecting full approval of the amendment within 30 days of the conditional approval announcement, and are happy to report that this occurred within the expected timeframe. We see the approval by the FDA for the conversion of the pilot study into a pivotal probable benefit study as good news and as a major milestone for InVivo. It is important to understand that the original pilot study has been converted into the probable benefit study, and that the probable benefit study will not be a new study. We think that InVivo was able to receive approval for the probable benefit study largely due to the fact that both studies have similar outcome measures, and thus rolling the pilot study into the probable benefit study was much easier for the FDA to accept and approve. The company expects completing enrollment of the pivotal probable benefit study and submitting an application for Humanitarian Device Exemption (HDE) approval in late 2017. If all goes well, we believe this supports obtaining FDA approval to commence commercialization under an HDE.

Going forward, the study will be known as "***The INSPIRE Study: InVivo Study of Probable Benefit of the Neuro-Spinal Scaffold™ for Safety and Neurologic Recovery in Subjects with Complete Thoracic AIS A Spinal Cord Injury***," and is designed to enroll 20 implanted patients, which includes the 5 patients already enrolled from the original pilot study. The primary objective of INSPIRE is to evaluate whether the NSS is safe and demonstrates probable benefit for the treatment of patients with complete T2-T12/L1 SCI. The primary endpoint is defined as the proportion of patients achieving an improvement of at least one American Spinal Injury Association (ASIA) impairment scale (AIS) grade at 6 months post-implantation. What this means is that by the 6-month mark, it is expected that a certain proportion of patients will no longer have a complete spinal cord injury, and will have regained some sensory function, and even perhaps both motor and sensory function. Additional endpoints of the trial are mainly various measures of neurological function, and include: ISNCSCI sensory and motor scores, bladder and bowel function, Spinal Cord Independence Measure (SCIM III), pain, Quality of Life and MRI measures (mainly to see cyst formation, which often happens in patients that are untreated). The INSPIRE study is currently approved

to enroll up to 12 patients, but InVivo expects that the FDA will approve the full 20 patients following the review of 6-month safety data for the first 5 patients. The company plans to submit this data in the second quarter of 2016.

The inclusion criteria for the trial have been widened to include patients with T2 injuries (new range: T2-T12/L1; original range: T3-T12/L1) and ages 16-17 (new range: ages 16-70; original range: ages 18-70). We believe that lowering the age limit makes a lot of sense, as there are many cases of motor vehicle accidents in adolescents as they are learning to drive. Additionally, including more thoracic segment injuries allows for more potential patients to qualify for the study. The FDA has also agreed to increase the total number of allowable U.S. sites to 40. In addition to the U.S. sites, the company plans to initiate the study in Canada as well as the United Kingdom as mentioned above. Full inclusion criteria can be found on ClinicalTrials.gov. Other inclusion criteria include: (1) Recent injury: Must receive NSS within 96 hours from injury, and (2): Non-penetrating contusion injury no less than approximately 4 mm diameter by MRI. We believe that the exclusion criteria is typical for such a trial, and can be reviewed on the website mentioned above. We think that widening the criteria makes sense, and we are hoping it will allow for more patients to qualify for the trial (and also bring on more neurosurgeons/investigators) as the population criteria is now expanded. Overall, we believe that by widening the inclusion criteria and adding more trial sites should help patient enrollment pick up during 2016.

Establishing Objective Performance Criterion (OPC)

As a reminder, obtaining marketing approval for the NSS is very different as compared to other devices as InVivo is pursuing the accelerated regulatory Humanitarian Device Exemption (HDE) pathway. An HDE only requires the demonstration of safety and probable benefit, which in our opinion, is a lower regulatory hurdle. InVivo is able to pursue the HDE pathway, which is an efficient pathway to approval, because the company is focused on an area of significant unmet medical need as there are currently no approved therapeutics for these types of SCI patients in a relatively small population. The FDA accepts that there are no approved devices or drugs to treat this patient population. InVivo needs to demonstrate probable benefit of the NSS device in order to get it approved.

As per the FDA and the FD&C Act Section 520(m), probable benefit under an HDE is defined as, "The device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment." We think the definition of probable benefit is vaguely defined for a reason. It really allows for a proposal to be made to the FDA, and is dependant on what one is trying to treat and what one is trying to treat it with, which is what InVivo has clearly done.

To assess probable benefit, InVivo will establish an Objective Performance Criterion (OPC) to define success in this uncontrolled study, which is primarily based on AIS conversion rates. We think that once the OPC is set, we should have a better understanding of the likely path to commercialization. InVivo is currently in late-stage discussions with the FDA regarding the OPC for the study to support probable benefit, and the company's proposal is largely based on data from longitudinal, natural history databases. In large European and U.S. databases [European Multicenter Study about Spinal Cord Injury (EMSCI) - Zaffira *et al*., 2011; Spinal Cord Injury Model System (U.S. database) – Lee *et al*., 2014; Sygen clinical trial in spinal cord injury – Fawcett *et al*., 2007], the published rates of spontaneous improvement of at least one AIS grade for complete (AIS-A), thoracic SCI patients at six months are less than 16% (*below*). In other words, when looking across the large European/U.S. databases, as well as the newer and older databases, it can be seen that patients with thoracic complete injuries typically do not have favorable outcomes, and less than 16% of those patients can be expected to have any type of improvement in AIS scores by six or twelve months. We think it's important to point out that over the last ten years, this percentages really haven't changed all that much in terms of neurological outcome, which leads us to believe that there really hasn't been much progress in regards to new therapeutic options for these particular patients.

Historical Benchmarks for Complete (AIS A) Thoracic SCI AIS Conversions		
EMSCI [1]	Spinal Cord Injury Model Systems [2]	Sygen [3]
15.6% (6 months)	15.5% (12 months)	12.9% (6 months)

InVivo Therapeutics

[1] Zariffa *et al*., Spinal Cord (2011)
[2] Lee *et al*., J. Spinal Cord Med. (2014)
[3] Fawcett *et al*., Spinal Cord (2007)

We believe an additional study protocol amendment may be required to establish the OPC, which could potentially be based on an additional neurological scale such as ISNCSCI sensory and motor scores, bladder and bowel function, Spinal Cord Independence Measure (SCIM III), pain, Quality of Life, and/or MRI measures.

We do not know what the actual OPC is yet, but we do not believe that InVivo will not have any trouble exceeding the historical benchmark range mentioned above (12.9% to 15.6%). We do think the OPC will end up being some percentage or range above 15%. At this point, we are thinking it could be anywhere between 20% and 35%. As a reference point, a 15% responder rate would mean that only one more patient (a total of 3 out of the 20 total enrolled patients) would need to demonstrate an AIS conversion as 2 out of 5 enrolled patients (or 40%) have already improved from AIS-A at 6 months. As a reminder, Patient #1 improved from AIS-A to AIS-C, and Patient #3 improved from AIS-A to AIS-B after following NSS implantation. In the first 3 subjects enrolled (Patients #1, #2, #3), all demonstrated some degree of neurological improvement. If we assume a 20% responder rate, this would require 4 out of the total 20 patients to convert while a 25% rate would require 5 out of the total 20 patients to convert. If we are even more aggressive and assume a 30% or even 35% responder rate, this would require 6 or 7 patients, respectively, out of the total 20 patients to demonstrate an AIS conversion. Regardless of what the final OPC ends up being, we think that InVivo is on the right track.

We will proceed to provide a review of each enrolled patient below so far in the trial.

Patient #1 (Jordan):

The first patient to enroll in the NSS study was involved in a dirt bike accident on October 13, 2014. The injury was classified as AIS-A and graded as complete (total paralysis) at T11 and below. On October 16, 2014, InVivo announced the NSS was successfully implanted in the patient (the surgery took place approximately 8 hours following the accident).

On January 21, 2015 InVivo announced a positive safety update at 3 months post-injury. At that time the injury was graded as "incomplete" and Jordan was reclassified to AIS-C from AIS-A, with motor, sensory, bowel, and bladder functional improvements compared to baseline.

On May 14, 2015 InVivo announced that between the 3-month and 6-month post-injury assessment Jordan had regained partial function of knee extensors and remained classified as AIS-C with a motor incomplete spinal cord injury.

On October 23, 2015, InVivo announced that between the 6-month and 12-month post-injury assessment, Jordan continued to demonstrate motor improvement with an additional 8 points gained on the AISA impairment scale. He demonstrated further bilateral improvements in the motor function of hip flexors and knee extensors, and also demonstrated first time bilateral contractions of the ankle dorsiflexors and ankle plantar flexors. Jordan remains classified as AIS-C. As per the company, a large natural history database shows that patients with similar T10-T12 level injuries have an average increase of lower extremity motor scores between 6 and 12 months of fewer than 2 points.

Patient #2 (Jesi):

The second patient to enroll in the NSS was struck by a car while riding on the back of a motorcycle on January 18, 2015. Her injury was classified as AIS-A impairment and graded as complete at T6 with total paralysis at T8 and below. On January 22, 2015, InVivo announced that the NSS was successfully implanted, however due to the severity of the patient's injuries the doctors had to wait two days after her accident to perform the surgery.

On March 26, 2015, InVivo announced re-opening of enrollment in the pilot study, signifying success with respect to the safety endpoint at 30 days post-surgery for Jesi.

On May 14, 2015, InVivo announced a positive safety and efficacy update on Jesi at 3 months post-injury. Despite a return of some sensory and motor function, including appreciable improvement in trunk stability, self-care, mobility, and bowel and bladder function at the 3-month post-implant assessment, Jesi remained classified as AIS-A on the impairment scale due to a lack of consistent and profound sensory and motor function at the sacral S4-S5 region.

On July 6, 2015, InVivo announced a 6-month post-implant assessment that showed Jesi had marked improvement in sensory function with partial sensation present 5 dermatome levels lower on the right side compared to the 3-month assessment. This translates to regaining partial sensation from the lower ribs to the hip on the right. In addition, Jesi continues to make meaningful progress in activities of daily living.

Although Jesi remains at AIS A, the company reports that she continued bowel and bladder improvement through month 12.

Patient #3 (Roger):

On June 4, 2015, InVivo announced that the third patient was enrolled in the pilot study. The NSS was implanted three and a half days after the high-level T4 injury occurred at Carolinas Medical Center in Charlotte, NC. Roger, a 55-year-old construction worker, fell out of a deer stand and was left with a damaged spinal cord with no sensation from the middle of his chest down.

On July 6, 2015, InVivo announced that in the time between implantation and the 1-month post-injury assessment, the third patient improved from a complete AIS-A spinal cord injury to an incomplete AIS-B spinal cord injury and that the patient regained sacral sensation with improved bladder function. In addition, there were no reported serious adverse events associated with the NSS.

As per the company presentation at the 2015 Stem Cell Meeting on the Mesa, InVivo fact sheet, and updated January 2016 corporate presentation, we gather that Roger had regained partial sensation from the mid-chest to mid-abdomen at the 3-month and 6-month assessments.

Patient #4

On August 20, 2015, InVivo announced that the fourth patient was enrolled in the pilot study. The NSS was implanted 53 hours after the T3 injury occurred at the UC Davis Medical Center in Sacramento, CA. The patient remains ASI-A at month 3. No other follow-up data has been reported to date.

Patient #5

On September 8, 2015, InVivo announced that the fifth patient was enrolled in the pilot study. The NSS was implanted 69 hours after the T8 injury occurred at Keck Hospital of University of Southern California (USC) in Los Angeles. The patient remains ASI-A at month 3. No other follow-up data has been reported to date.

InVivo will continue to follow all of the patients enrolled in the INSPIRE trial for 10 years. Jordan and Jesi have completed their 12-month assessments. Patient #3 has completed his 6-month exam, and Patients #4 and #5 have completed their 3-month assessments. We believe that the study will continue to enroll patients until it has reached the full 20 individuals. We look forward to hearing updates as they are made available.

Policy Change on Patient Updates

On September 30, 2015, InVivo filed a Form 8-K stating that it would only provide updates on patients enrolled if the results were dramatically positive or negative and as per industry standards (*below*).

Item 7.01. Regulation FD Disclosure.

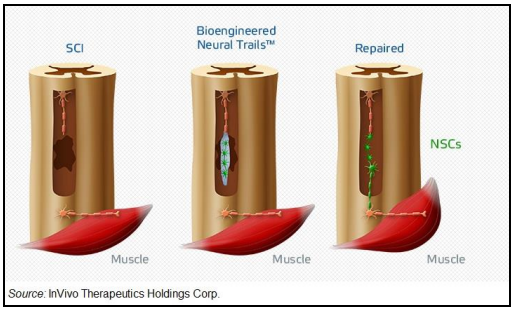
On September 30, 2015, InVivo Therapeutics Holdings Corp. (the "Company") posted an updated investor presentation, including updated patient information, in the "Investor Relations" section of its website at *www.invivotherapeutics.com*. As previously communicated, with the exception of dramatically positive or negative results, the Company expects to communicate any interim information according to industry standards. The Company does not consider a patient's unchanged American Spinal Injury Association Impairment Scale (AIS) classification or a medically insignificant adverse event to be material.

We spoke to management, and the company will continue to announce the enrollment of each patient and any conversions of AIS classification as well as any other dramatically positive or negative events. Some examples of dramatically positive and negative events include improvement in classification on the AIS scale or patient death, respectively. Although we will not be receiving patient updates every 1, 3, 6, and 12 months going forward, we do believe that meaningful updates will be shared with the public, and the company will release information as per industry standards. We think it's important to point out that "the company does not consider a patient's unchanged American Spinal Injury Association Impairment Scale (AIS) classification or a medically insignificant adverse event to be material." In other words, a patient's unchanged status should not necessarily be viewed as a negative situation. We think some investors became overly concerned with the new policy, which led them to move way from the InVivo story. We also believe that Jordan's (Patient #1) dramatic improvement from AIS-A to AIS-C in 30 days may have led some investors to believe that this type of improvement would be seen in all future patients enrolled in the trial. We would like to clarify that this is not a normal or typical response, and to expect every patient to respond this way after NSS implantation would be completely unrealistic. However, we do find Jordan's improvement to be quite amazing. We also think that some investors are concerned with the unchanged AIS status of Patients #4 and #5, but again, we would like to point out that spinal cord injuries are drastically different on a case-to-case basis, and not all patients will have similar response rates with the device. We think that re-aligning the release of

information as per industry standards makes a lot of sense, and that investors should not be too concerned with the policy change. We understand that some investors may have become accustomed to receiving frequent patient updates, and so waiting for news may be difficult. InVivo will communicate interim results at various scientific and medical meetings. We still believe in the InVivo story, and look forward to seeing more information regarding patient updates and enrollment status once available. We think we will have more clarity on the path forward as more sites are activated and additional patients are enrolled in 2016.

Addressing Chronic Spinal Cord Injury: Bioengineered Neural Trails™ Program

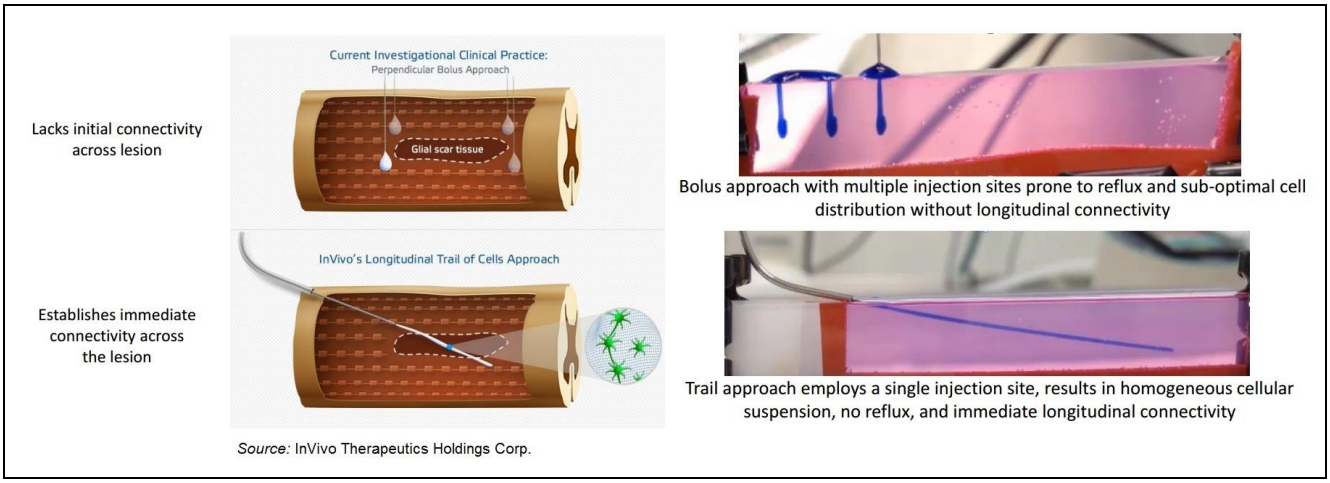
On December 2, 2015, InVivo announced a strategy for the treatment of chronic spinal cord injury (SCI) through its Bioengineered Neural Trails™ Program in order to restore neuronal connectivity and promote neurological recovery in patients with chronic SCI. Although it is in the pre-clinical stage, we believe it is important to offer some insight into chronic SCI program.



Source: InVivo Therapeutics Holdings Corp.

The program was further highlighted on December 3, 2015 during the Key Opinion Leader (KOL) Event and Company Update in New York City at the Palace Hotel. The event included presentations by key opinion leaders (KOLs) Bob Langer, ScD, the David H. Koch Institute Professor at Massachusetts Institute of Technology and co-founder of InVivo; and Nick Theodore, MD, Chief of Spinal Surgery at the Barrow Neurosurgical Institute and the neurosurgeon who performed the first Neuro-Spinal Scaffold™ implantation. Dr. Langer discussed his contributions to the development of the field of biomaterials and InVivo's product candidates that evolved from work performed in his laboratory. Dr. Theodore presented on current state-of-the-art surgical treatment of spinal cord injury patients and a case study of the first patient in InVivo's ongoing Neuro-Spinal Scaffold study. Additionally, management also provided several company updates including introduction of its chronic spinal cord injury Bioengineered Neural Trails™ Program during the event.

Bioengineered Neural Trails™ are injectable combinations of biomaterials and neural stem cells (NSCs) delivered using minimally invasive surgical instrumentation and techniques to create trails across the chronic injury site. Another way to look at the program is to think of it as the NSS device with stem cells. The multimodal approach aims to bridge the spinal cord lesion at the time of implantation with a trail of neural stem cells (NSCs) delivered in a soft, gel-like scaffold that is both injectable and biodegradable.



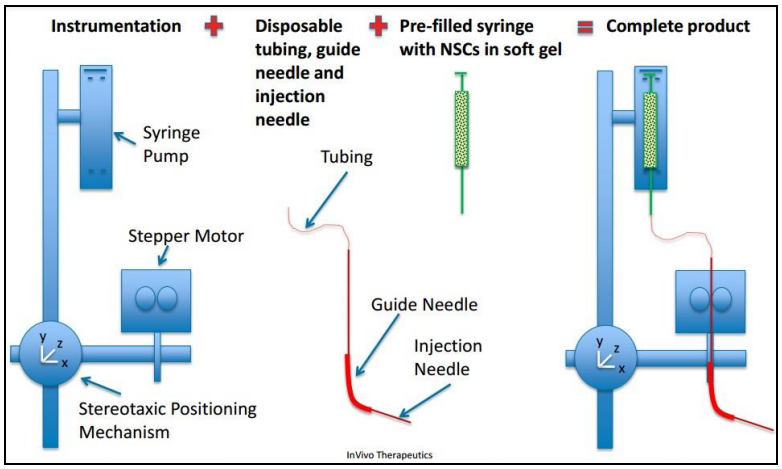
Source: InVivo Therapeutics Holdings Corp.

As per InVivo, the current practice is to inject boluses of stem cells in a perpendicular fashion via a needle, which lacks connectivity across the injury site, and can result in pressure/reflux issues as well as multiple injection sites

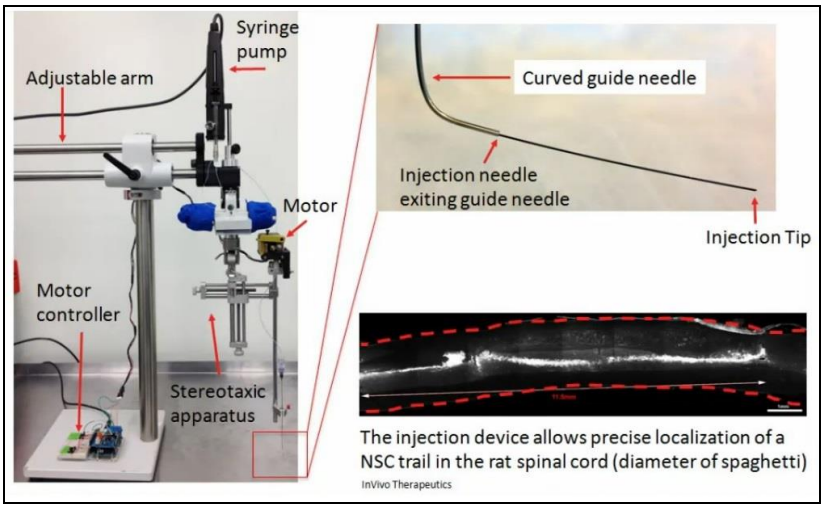
and cell settling. InVivo is proposing to use a guide needle with a shape retaining injection needle in order to create a trail of stem cells across the lesion (*above*). The injected material is a soft, biomatrix containing neural stem cells that differentiate into neurons. InVivo's technique involves advancing the injection needle through a guide needle (with the assistance of fluoroscopy and ultrasound), and once fully extended, it is retracted with a motor. Subsequently, a syringe pump shoots out cells that create the neural trail. As the needles are retracted, a trail of cells is left behind, which InVivo believes will establishes immediate connectivity across the lesion site. As per InVivo, the injectable scaffold is a soft, biomaterial aimed to improve the viability, delivery and differentiation of the NSCs. The biomaterial is formed of a polymer, and serves as a scaffold with attachment sites for receptors on NSCs, which promotes migration of the cells. The biomaterial maintains homogenous cell suspension during shipment, and has the unique property of liquefying as it is injected, to only return back to a gel state in the body.

We believe what sets InVivo apart is that the company is focused on using neural stem cells that create neural connections as opposed to just injecting mesenchymal stem cells that give trophic support to existing cells within the spinal cord or just injecting cells that will turn into myelinating cells/axons. NSCs are able to differentiate into the 3 main cell types of the central nervous system (CNS): astrocytes, oligodendrocytes, and neurons, and these NSCs can help to repair the spinal cord via regeneration by secreting trophic factors, remyelinating bare axons, and/or establishing new neuronal connections.

The image below offers a representation of the patented surgical device and its various components:



A real-life setup of the equipment is shown below, with a visualization of injected NSCs in a rat spinal cord:



In order to support this strategy, InVivo has entered into agreements with the University of California, San Diego and James Guest, M.D., Ph.D., to expand the company's intellectual property portfolio. InVivo entered into an exclusive license agreement with UC San Diego for issued patent US 9,011,410 titled "***Spinal Multisegmental Cell and Drug Delivery System***," and into an assignment agreement with Dr. Guest for issued patent US 7,666,177 titled "***Method and System for Cellular Transplantation in the Spinal Cord***." InVivo also has filed a provisional

application in support of the Bioengineered Neural Trails™ Program titled "***Methods and Systems for Delivery of a Trail of a Therapeutic Substance***." We believe that the patents in addition to the provisional patent application help solidify the IP portfolio for the Bioengineered Neural Trails for InVivo.

Next Steps for Bioengineered Neural Trails™

According to the National Spinal Cord Injury Statistical Center, approximately 276,000 patients currently live with spinal cord injury in the U.S. with limited therapeutic options. Neural stem cell transplantation offers some therapeutic promise, and we believe InVivo aims to tackle a huge unmet clinical need with its Bioengineered Neural Trails™ Program. The goal of the program to improve neurological function in chronically injured patients.
We think it makes a lot of sense for the company to pursue this chronic SCI strategy, and in our opinion, is a natural course of progression to the InVivo story. Although it is too early for us to include sales of this product in our current model, the Bioengineered Neural Trails™ Program presents with enormous potential upside to the InVivo story as the chronic SCI market is approximately 25x that of the acute SCI market.

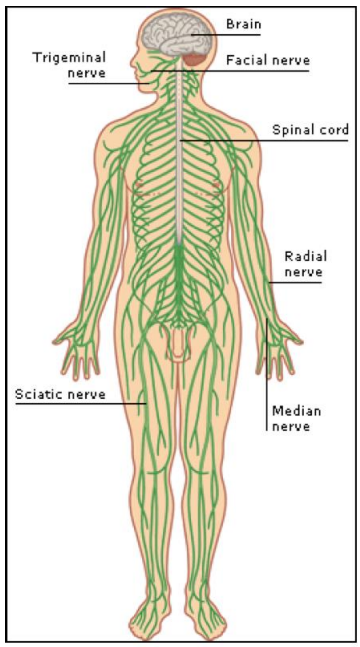
We will proceed to highlight some of the next steps for InViVo as it pertains to the chronic SCI program:

- Optimize all aspects of product profile in preparation for IND: instrumentation, biomaterial, and NSCs
- Strengthen and broaden intellectual property portfolio
- Aim to partner with a stem cell company to accelerate project timelines
- Target pre-IND meeting with the FDA by the end of 2016

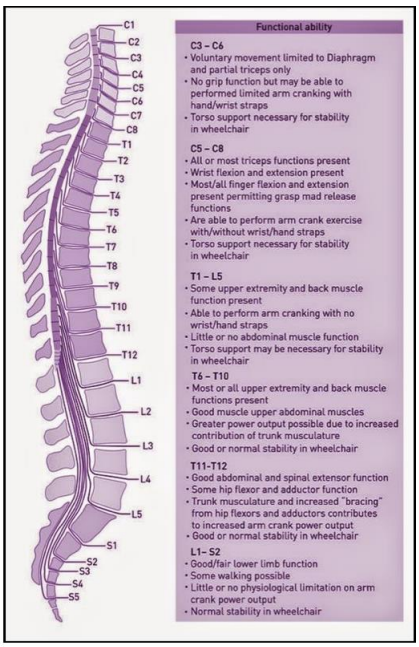
Overall, we think using the NSS device with neural stem cells makes a lot of sense in the setting of chronic SCI patients. We look forward to hearing more about the program, and would like to point out that the company hopes to have a pre-IND meeting with the FDA by the end of 2016.

Review of Spinal Cord Anatomy

In order to understand spinal cord injuries in humans, it is important to understand how the spinal cord functions with the peripheral nerves in the body. The site of a spinal cord injury is not geographically associated with physiological control because there are sensory root ganglion that branch off from the central canal containing peripheral nerve cells that travel down the body to the pelvis, hips, legs, and feet. There are peripheral nerves that travel down the legs and attach to the central cord at regions all along the spine. The figures on the right depict the peripheral nerves and the different groups of vertebrae that control various regions of the body. For example, an injury at the C8 level just below the base of the neck will cause a loss of sensory and motor control to the chest, abdomen, pelvis, legs, and feet. However, the patient may still be able to move their fingers because this is controlled by peripheral nerves and dorsal root ganglia that attach at the C7 region of the spine.



Source: aviva.co.uk



Source: Michael Feger Paralysis Foundation

Injuries below the C8 level will likely leave arm and hand function unharmed. An injury at the L3 vertebra, located just below the belly button, will likely still allow a patient to roll their hips and contract their quadriceps muscles, as these are controlled by nerves that connect at the L1 and L2 region.

Assessment of Spinal Cord Injuries

The American Spinal Injury Association (ASIA) impairment scale (AIS) describes a person's functional impairment as a result of their spinal cord injury. It is based on neurological responses, touch and pinprick sensations tested in each dermatome (area of the skin), and strength of the muscles that control ten key motions on both sides of the

body, including hip flexion (L2), shoulder shrug (C4), elbow flexion (C5), wrist extension (C6), and elbow extension (C7). Traumatic spinal cord injury is classified into five categories on the ASIA Impairment Scale:

A = Complete. No sensory or motor function is preserved in the sacral segments S4-S5.

B = Sensory Incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5 (light touch, pin prick at S4-S5: or deep anal pressure (DAP)), AND no motor function is preserved more than three levels below the motor level on either side of the body.

C = Motor Incomplete. Motor function is preserved below the neurological level, and more than half of key muscle functions below the single neurological level of injury (NLI) have a muscle grade less than 3 (Grades 0-2).

D = Motor Incomplete. Motor function is preserved below the neurological level, and at least half (half or more) of key muscle functions below the NLI have a muscle grade > 3.

E = Normal. If sensation and motor function are graded as normal in all segments, assuming the patient had prior deficits, then the AIS grade is E.

Its important to remember that someone without an initial SCI does not receive an AIS grade, so while AIS-E is considered "normal" sensory and motor control, this does not mean no injury is present. Also, for an individual to receive a grade of C or D, i.e. motor incomplete status, they must have either (1) voluntary anal sphincter contraction or (2) sacral sensory sparing with sparing of motor function more than three levels below the motor level for that side of the body. The standards at this time allows even non-key muscle function more than 3 levels below the motor level to be used in determining motor incomplete status (AIS-B vs. -C). When assessing the extent of motor sparing below the level for distinguishing between AIS-B and -C, the motor level on each side is used; whereas to differentiate between AIS-C and -D (based on proportion of key muscle functions with strength grade 3 or greater) the single neurological level is used.

The key takeaway from the ASIA Impairment Scale is the heavy focus on the sacral region S4-S5 in moving from AIS-A to AIS-B. As noted above, any injured subject with no sensory or motor function in the sacral segment S4-S5, which includes the sphincter muscle and region around and inside the anus, is classified as AIS-A. To move from AIS-A to AIS-B, the subject must demonstrate, at a minimum, sensory function of the S4-S5 region as assessed by light touch, pin-prick, or deep anal pressure. The key-gating factor in moving from AIS-B to AIS-C is motor control.

The Potential For the NSS is Enormous

In 3 months, Jordan (Patient #1) went from complete AIS-A with no motor or sensory function below the belly-button to incomplete AIS-C and the ability to control his bowels/bladder. At 12 months, Jordan continued to gain additional points on the AIS impairment scale with lower limb motor and sensory improvement in addition to regained bowel function and improved bladder function. In 2 months, Jesi (Patient #2) went from being completely paralyzed to being able to move her leg, and at 12 months, has regained partial sensation from the lower ribs to the hip on the right side of her body. In 1 month, Roger (Patient #3) went from complete AIS-A to incomplete AIS-B with regained sacral sensation and improved bladder function, and now at 6 months, has regained partial sensation from the mid-chest to mid-abdomen. We suspect that with additional physical therapy and time, all three patients will continue to progress in the right direction. We are hoping to see similar results in Patients #4 and #5 as well as in future patients that will be enrolled in the INSPIRE study.

	Average Yearly Expenses (in 2014 dollars)		Estimated Lifetime Costs by Age At Injury (discounted at 2%)	
Severity of Injury	First Year	Each Subsequent Year	25 years old	50 years old
High Tetraplegia (C1–C4) AIS ABC	$1,064,716	$184,891	$4,724,181	$2,596,329
Low Tetraplegia (C5–C8) AIS ABC	$769,351	$113,423	$3,451,781	$2,123,154
Paraplegia AIS ABC	$518,904	$68,739	$2,310,104	$1,516,052
Motor Functional at Any Level AIS D	$347,484	$42,206	$1,578,274	$1,113,990

Data Source: Economic Impact of SCI published in the journal *Topics in Spinal Cord Injury Rehabilitation*, Volume 16, Number 4, in 2011.

Source: The National Spinal Cord Injury Statistical Center, Facts and Figures at a Glance. Birmingham, AL: University of Alabama at Birmingham, February 2015.

According to the NSCISC's February 2015 report "Spinal Cord Injury Facts and Figures at a Glance (*above*)," (i) during the first year, average "cost of care" ranges from $347,484 to $1,064,716, depending on the severity of the injury, and (ii) the NPV to maintain a paraplegic injured at age 25 for life is $2,310,104. All of the patients that have been enrolled in the INSPIRE study have been paraplegia AIS-A, and so if we focus on this type of patient

(Paraplegic AIS ABC on the chart below), the average yearly health care and living expense cost is $518,904, with each subsequent year resulting in $68,739 of additional expenses. Because these costs place a tremendous financial burden on families, insurance providers, and government agencies, and because of the HUD designation, we believe a cost for implantation of the NSS of $150,000 is fair (and actually quite conservative) for our financial modeling.

The potential we discuss above refers only to acute SCI under the HDE, which allows the NSS device to address 4,000 patients. We continue to believe the NSS is a potential $750 million product just in acute spinal cord injury. We also believe after HDE approval, neurosurgeons will be able to use the device in a large proportion of non-penetrating spinal cord injuries, regardless of things like AIS-A impairment level and injury location. Additionally, we think it makes a lot of sense for the company to pursue the chronic SCI strategy via the Bioengineered Neural Trails™ Program. Although it is too early for us to include sales of this NSS seeded with NSCs product in our current model, the Bioengineered Neural Trails™ Program presents with enormous potential upside to the InVivo story. If the company can strike an alliance with a stem cell supplier and can move forward with seeding the NSS with neural-spinal stem cells in human patients, then the market opens up from approximately 12,000 acute patients per year to some 300,000 chronic patients, which represents a 25-fold increase. InVivo has also announced that it plans to initiate an acute cervical spinal cord injury study, which could also add potential upside to the story. These are all things that we believe investors should keep in mind for the long-term.

Conclusion

There remains a huge unmet need in spinal cord injury as there are currently no commercially approved therapeutics (devices or drugs) to treat SCI. Currently, surgical intervention with rehabilitation is the standard-of-care in dealing with SCI patients. There is a great need for new therapeutics and regenerative surgical techniques to address the pathophysiology of spinal cord injury, and we continue to believe that InVivo is working very hard to solve this problem.

To summarize what we have seen so far in the pilot study, which has recently been converted to the INSPIRE probable benefit study, of the NSS:

- Patient #1 has gone from AIS-A to AIS-C in one month, which occurs in fewer than 5% of AIS-A patients with a T10-T12 injury, and has lower limb motor and sensory improvement in addition to regained bowel function and improved bladder function.

- Patient #2 remains AIS-A but has seen improvement in trunk stability, self-care, mobility, bowel and bladder function, and has regained partial sensation from the lower ribs to the hip on the right side of her body.

- Patient #3 went from AIS-A to AIS-B in the first month after his accident, which is observed in fewer than 4% of patients with a T4 injury, and has sensory improvement from mid-chest to mid-abdomen.

- There is no follow-up data reported on Patients #4 and #5 to date, but both remain at AIS-A at three (3) months.

- Perhaps most importantly of all, there have been no serious adverse events due to the NSS or the surgical procedure.

Looking at the results thus far, it appears as though a trend is developing in regards to the safety and efficacy of the NSS. Although enrollment has slowed down, it's hard not to be impressed with the level of efficacy seen thus far with the first three patients. As mentioned above, the last patient was enrolled back in September 2015, and we are hoping that by adding more sites in 2016 and widening the entry criteria, will allow for enrollment to pick up.

Despite there being a stream of news that indicates that InVivo remains on the right track, with the FDA approving conversion of its pilot study into a pivotal probable benefit, and the announcement of the new Bioengineered Neural Trails™ Program for chronic SCI, the stock continues to languish. We believe that slow enrollment and lack of patient updates have led some investors to leave the InVivo story.

In August 2015, InVivo's common stock was transferred from the Nasdaq Capital Market to the Nasdaq Global Market, following an announcement that the company has been added to the Russell Global, Russell 3000®, Russell 2000®, and Russell Microcap indexes. We believe that being listed on the Global Market allows for greater visibility for InVivo, but as of yet has not helped support the share price. Additionally, we believe the broad sell-off in the biotechnology and pharmaceutical sectors has impacted the small cap names even more so than the larger cap

companies. We believe the recent pullback presents investors with an interesting long-term buying opportunity. As of September 30, 3015, InVivo had $22.1 million in cash on the books. We believe the current cash should fund activities through September 2016.

If the pivotal probable benefit study is completed in 2017, InVivo could likely apply for approval under HUD in late 2017 and receive approval in 2018. Our detailed model assumes the INSPIRE trial reaches full enrollment on time, and that approval will be contingent upon showing safety and probably benefit in a larger number of patients, and while we think that a trend has certainly been established with the first 3 patients, we would like to see additional safety and recovery data. That being said, the company looks to have gone “3 for 3” with respect to improving function for the first 3 patients in the pilot study. We are interested in reviewing patient updates on Patients #4 and #5 once available, as well as learning more about the additional patients that will be enrolled. As an aside, if patient enrollment does not pick up in the near term, we may need to revisit our valuation and price target. However, currently we continue to rate the stock a “Buy”, and are maintaining our price target of $24. Accordingly, we recommend the stock for long-term investors.

PROJECTED FINANCIALS

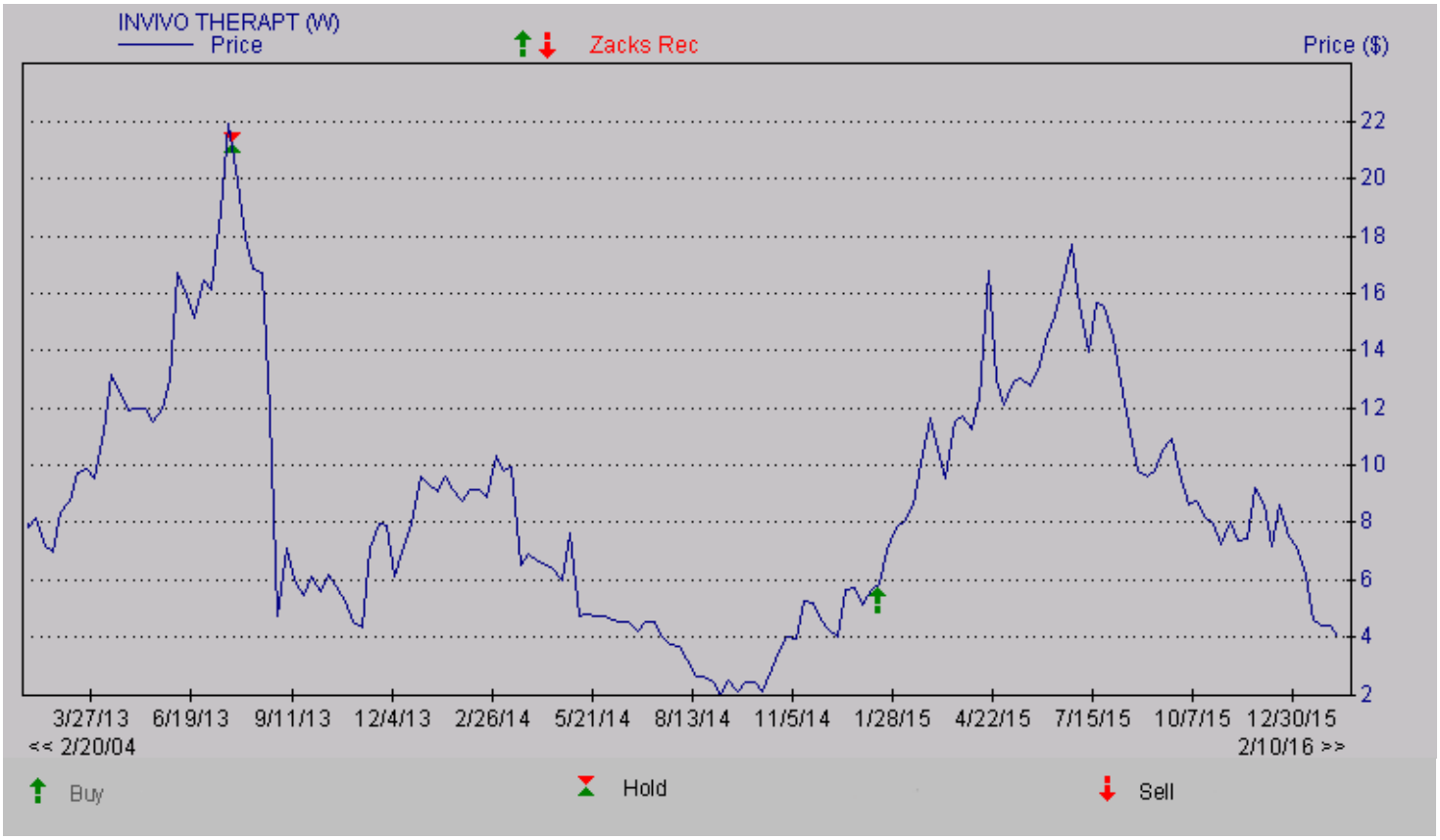
InVivo Therapeutics Holdings Corp. - Income Statement

InVivo Therapeutics	2014 A	Q1 A	Q2 A	Q3 A	Q4 E	2015 E	2016 E	2017 E
Product Sales	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-
Collaborative & Licensing	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-					-	-	-
Cost of Goods / Services	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-					-	-	-
R&D	$10.3	$2.3	$2.5	$2.4	$2.6	$9.9	$12.0	$15.0
SG&A	$7.6	$3.2	$3.2	$3.4	$3.3	$13.2	$14.0	$16.0
Operating Income	($17.8)	($5.5)	($5.8)	($5.9)	($5.9)	($23.0)	($26.0)	($31.0)
Operating Margin	-					-	-	-
Net Other Income	($0.5)	($10.3)	($4.7)	$3.6	$0.0	$0.0	$0.0	$0.0
Pre-Tax Income	($18.3)	($15.8)	($10.4)	($2.3)	($5.9)	($23.0)	($26.0)	($31.0)
Taxes	$0	$0	$0	$0	$0	$0	$0.0	$0.0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0.0%*	*0.0%*
Net Income	($18.3)	($15.8)	($10.4)	($2.3)	($5.9)	($23.0)	($26.0)	($31.0)
Net Margin	-					-	-	-
Reported EPS	**($0.83)**	**($0.64)**	**($0.39)**	**($0.09)**	**($0.22)**	**($0.87)**	**($0.90)**	**($0.91)**
YOY Growth	-					-	-	-
Wt. Ave Shares Outstanding	22.1	24.9	26.5	27.0	27.4	26.4	29.0	34.0

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

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