Translation of Biomaterial-based Therapies for the Treatment of Acute and Chronic Spinal Cord Injury: The *Neuro-Spinal Scaffold™* and Bioengineered Neural Trails

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Before we begin, we would like to remind everyone that during our presentation, we will be making forward-looking statements about our business, plans, and objectives. These statements are based on how we see things today. These statements can be identified by words such as believes, estimates, expects, or similar references to the future, and include statements we may make regarding our product development strategy, business prospects, and clinical and operational milestones. We wish to caution you that actual events or results may differ materially from those expressed in forward-looking statements made by us or on our behalf. For more information on the many factors that can result in actual performance differing from our forward-looking statements, please see our filings made with the SEC, including our 2015 Annual Report on Form 10-K filed on March 4, 2016 and our Quarterly Reports on Form 10-Q filed on May 6, 2016 and August 4, 2016.
Progress Made to Advance Therapies that Aim to Improve the Lives of Individuals with SCI

- **New executive leadership**
- Company focused solely on SCI
- Initiates pilot clinical study for acute SCI
- First individual implanted with *Neuro-Spinal Scaffold*
- *Neuro-Spinal Scaffold™* receives 2015 Becker’s Healthcare Spine Device Award
- Announced Bioengineered Neural Trails program (pre-clinical) for chronic SCI
- Converted pilot clinical study to INSPIRE Pivotal Probable Benefit Study
- Implanted 10th individual with *Neuro-Spinal Scaffold*
- Expanded clinical study into Canada
- Designed & developed new stem cell injection device
Agenda

• *Neuro-Spinal Scaffold™*: Our approach to acute SCI
  – Technology & mechanism of action
  – Translation to the clinic
  – Clinical results to date and future clinical development plans

• *Bioengineered Neural Trails™*: Our approach to chronic SCI
  – Rationale
  – Pre-clinical development and results to date
  – Future plans
Progression of Acute SCI to Post-Traumatic Cavity in Contusion Injuries

Hemorrhage & Spinal Cord Swelling
Reduced Blood Flow & Ischemic Necrosis
Cavity Development & White Matter Reduction

Chronic injury and mature cavity formation

Acute SCI:
*Neuro-Spinal Scaffold™*

Chronic SCI:
*Bioengineered Neural Trails™*

Histology from rat contusion model of SCI
InVivo Therapeutics
Neuro-Spinal Scaffold™ for Acute SCI
Designed to Promote Healing in Spinal Cord Injury
Novel Clinical Approach for Acute SCI: The *Neuro-Spinal Scaffold™*
First *Neuro-Spinal Scaffold™* Implantation in Human Contusion Injury
**Neuro-Spinal Scaffold™ Mechanism of Action**

- Provides structural support to surrounding viable tissue
- Promotes the formation of neuro-permissive remodeled tissue that supports neural regeneration
- Serves as a locus for 3-dimensional appositional healing
- Preserves macroscopic spinal cord architecture and decreases cyst volume
- Increases spared white matter and promotes remyelination of denuded axons
The Neuro-Spinal Scaffold™ Preserves Macroscopic Spinal Cord Architecture

Rat Acute Spinal Cord Contusion Injury (at 12 weeks)

Control

Neuro-Spinal Scaffold

Cyst Reduction

White Matter Sparing

Remodeled Tissue

*Cyst Reduction

*Cyst Volume (mm^3)

Control

Neuro-Spinal Scaffold

*P<0.05

White Matter Width (mm)

Control

Neuro-Spinal Scaffold

*Remodeled Tissue

Control

Neuro-Spinal Scaffold

*P<0.05

Poster D8-06; National Neurotrauma Society 2015 Symposium; Santa Fe, NM.
The *Neuro Spinal Scaffold™* Increases Remodeled Tissue Supporting Neural Regeneration

Rat Acute Spinal Cord Contusion Injury (at 12 weeks)

**Control**

Minimal neuro-permissive matrix

**Neuro-Spinal Scaffold**

Remodeled tissue with extensive neuro-permissive matrix

Neuro-permissive matrix supports neural regeneration

Company images
Neural Regeneration and Remyelination with Schwann Cells after *Neuro-Spinal Scaffold™* Implantation

**Contusion Injury**
Central epicenter (a) and white matter (b)

**Epicenter**
Schwann Cells aid neural regeneration

**White Matter**
Schwann Cells restore signal transduction

Inset: Schwann cells ensheathing axons

Rat Acute Spinal Cord Contusion Injury (at 12 weeks)

Oligodendrocytes    Schwann Cells
The INSPIRE Study
A Pivotal Trial for Regulatory Approval

**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**

- Designed as 20-patient pivotal study to be used for HDE application
  - Endpoint: improvement in ASIA Impairment Scale (AIS) grade by 6 months

- Objective Performance Criterion (study success definition) – at least 25% of patients improve AIS grade by 6 months

- Additional Endpoints: sensory and motor scores, bladder and bowel function, Spinal Cord Independence Measure, pain, quality of life

- 23 clinical sites (US and Canada)
  - Plan also to include United Kingdom clinical sites

NOTE: FDA has recommended inclusion of a control arm in the study as part of a Study Design Consideration (SDC). As is typical of the regulatory process, InVivo has previously addressed a number of SDCs regarding the study. InVivo is engaged in a discussion with the FDA regarding this SDC and will provide an update if substantial changes are made to the study protocol. InVivo continues to believe that the current study design is sufficient to demonstrate safety and probable benefit in support of an HDE application for marketing approval.
Objective Performance Criterion: 25% AIS Grade Conversion by 6 months

- Historical benchmarks for AIS conversion rates
  - European Multicenter Study about Spinal Cord Injury (EMSCI)\(^1\); \(n = 256\)
  - Spinal Cord Injury Model System (US)\(^2\); \(n = 265\)
  - Sygen clinical trial in spinal cord injury\(^3\); \(n = 139\)

Complete (AIS A) Thoracic SCI AIS Conversions

- EMSCI (6 months): 15.6%
- Model Systems (12 months): 15.5%
- Sygen (6 months): 12.9%
- INSPIRE (6 months): 62.5% = 5/8 patients in follow-up*

* Patients 7 has less than six months of follow-up

OPC = study success

NOTE: Approval is not guaranteed if the OPC is met and HDE approval may still be obtained if OPC is not met.

1 Zariffa et al., Spinal Cord (2011)
2 Lee et al., J. Spinal Cord Med. (2014)
3 Fawcett et al., Spinal Cord (2007)
### Promising Neurologic Outcomes and Favorable Safety Profile in The INSPIRE Study

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Neurologic Level of Injury</th>
<th>Time to Implant</th>
<th>Neurologic Outcome to Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>Adult</td>
<td>T11</td>
<td>9 hrs.</td>
<td>Converted to AIS C at 1 month</td>
</tr>
<tr>
<td>M</td>
<td>Adult</td>
<td>T4</td>
<td>83 hrs.</td>
<td>Converted to AIS B at 1 month</td>
</tr>
<tr>
<td>F</td>
<td>Pediatric</td>
<td>T8</td>
<td>69 hrs.</td>
<td>Converted to AIS B at 6 months</td>
</tr>
<tr>
<td>M</td>
<td>Pediatric</td>
<td>T10</td>
<td>9 hrs.</td>
<td>Converted to AIS B at 2 months</td>
</tr>
<tr>
<td>M</td>
<td>Adult</td>
<td>T4</td>
<td>40 hrs.</td>
<td>Converted to AIS B at 3 months</td>
</tr>
<tr>
<td>F</td>
<td>Adult</td>
<td>T7</td>
<td>46 hrs.</td>
<td>Remains AIS A at 12 months</td>
</tr>
<tr>
<td>M</td>
<td>Adult</td>
<td>T3</td>
<td>53 hrs.</td>
<td>Remains AIS A at 6 months</td>
</tr>
<tr>
<td>M</td>
<td>Adult</td>
<td>T3</td>
<td>21 hrs.</td>
<td>Remains AIS A at 3 months</td>
</tr>
</tbody>
</table>

Note: Two subjects passed away with the cause of death deemed unrelated to *Neuro-Spinal Scaffold™* or implantation

- No obvious correlations between AIS conversions and injury level or time to implant
- No Serious Adverse Events related to *Neuro-Spinal Scaffold™* or implantation procedure
Neuro-Spinal Scaffold™
A Robust Clinical Development Portfolio

• Acute Complete (AIS A) Thoracic SCI via HDE
  – Target full enrollment in H1-2017 and completion of INSPIRE in H2-2017
  – Target Regulatory submission in late 2017 or early 2018

• Acute Complete (AIS A) Cervical SCI via HDE
  – Projected pilot study approval and initiation in Canada in H1-2017
  – Planned expansion into European countries
  – FDA has requested data from INSPIRE before U.S. study approval\(^1\)
  – Pursuing U.S. and Ex-U.S. pathways in parallel

• Acute Incomplete (AIS B, AIS C) SCI
  – Expand to larger acute SCI population (thoracic and cervical injuries)

\(^1\) On September 30, 2016, FDA notified InVivo that its proposed cervical study was disapproved pending submission of results from the INSPIRE study. Previously, the FDA had communicated that data from the first five patients in INSPIRE would be required before considering approval. InVivo will initiate discussions with FDA regarding the disapproval and believes that data generated to date in INSPIRE support moving into cervical SCI.
InVivo’s Chronic SCI Product: Bioengineered Neural Trails™

Neural Stem Cells Incorporated into an Injectable Scaffold for Minimally-Invasive Delivery
Neural Stem Cells Can Differentiate into the Major Three Cell Types of the Central Nervous System

Neural Stem Cells (NSCs)

- Neural Precursors
  - Neurons (wires)
    - Excitatory Neurons
    - Inhibitory Neurons
  - Glial Precursors
    - Oligodendrocytes (insulation)
    - Astrocytes (structural & trophic support)

(Capillary)

Neurons

Oligodendrocyte
Disruption of Motor Control within the Spinal Cord Following Injury

Motor Output

No Motor Output
Trails of Transplanted Cells May Provide a Preferred Delivery Approach to Bridge the Injury

Conventional Bolus Injections Above/Below Injury Site

Multi-modal therapy includes:
1. Neural stem cells
2. Biomaterial matrix
3. Novel Injection device/method

Bioengineered Neural Trials™

“Neuronal Relay” Across/Around Injury Site
The Gap Neuron Hypothesis

Healthy Host Grey Matter Neuron Below the Injury

NSC-derived gap neuron

Stump of Injured Host Axon

Host stump  NSC  Host grey

Drawing courtesy of Dr. James Guest
Bioengineered Neural Trails™ Provide Many Advantages Over Conventional Bolus Injections

**Bolus approach**
- Reflux at multiple injection sites
- Sub-optimal cell distribution
- No longitudinal connectivity

**Trail approach**
- No reflux at single injection site
- Homogeneous cellular suspension
- Immediate longitudinal connectivity

Collagen matrix to simulate spinal cord
Evolution of the TrailMaker™

First Generation

Second Generation
Development of a Novel Device to Inject Therapeutic Trails within the Spinal Cord

The TrailMaker™ Injection Device

Positioning Arm

Cart

Injection needle

Control Panel

Guide needle

Pre-filled syringe with NSCs in biomaterial carrier
Feasibility of Proprietary Device Demonstrated in Pilot Porcine Study

In collaboration with Dr. James Guest
Bioengineered Neural Trails™: InVivo’s Novel Neural Stem Cell Product for Chronic SCI

Porcine Model (1 week after injection)    Rat Model (1 month after injection)

3D MRI of Bioengineered Neural Trail

Histology demonstrating interconnected human cells (STEM121) and neural precursors (rat only) (DCX)
Next Steps for Bioengineered Neural Trails Program

• Continue to evaluate surgical feasibility of delivering cell trails within the spinal cord – improve upon device if needed
• Identify neural stem cell source
• Understand biology of stem cells once injected and evaluate for transplant – host integration
• Perform efficacy and GLP safety/toxicology studies that support clinical translation
Conclusions

InVivo is:

• taking a biomaterials/regenerative medicine approach to SCI
• pioneering new surgical approaches to SCI
• building institutional expertise in the translation of SCI therapeutics