Phase I Clinical Trial of Human Embryonic Stem Cell-Derived Oligodendrocyte Progenitors in Patients with Neurologically Complete Thoracic Spinal Cord Injury: Results and Next Steps

Jane S Lebkowski Ph.D.
President of R&D

May 22, 2014
Forward-Looking Statements

Statements pertaining to our future financial and/or operating results, future growth in research and technology, timing and results of clinical development, and potential opportunities for Asterias and its subsidiaries, along with other statements about the future expectations, beliefs, goals, plans, or prospects expressed by management constitute forward-looking statements. Any statements that are not historical fact (including, but not limited to statements that contain words such as “will,” “believes,” “plans,” “anticipates,” “expects,” “estimates”) should also be considered to be forward-looking statements. Any or all of the forward-looking statements in this presentation may turn out to be wrong. Forward-looking statements involve risks and uncertainties, including, without limitation, risks inherent in the development and/or commercialization of potential products, uncertainty in the results and timing of clinical trials or regulatory approvals, need and ability to obtain future capital, and maintenance of intellectual property rights. In particular, Asterias is a newly organized company, with limited financial resources and a history of operating losses and negative cash flows, engaged in early-stage clinical development of products using therapeutic approaches that have never before received regulatory approval. The development of these products will be time-consuming and expensive and we may not have sufficient capital to complete the development of our product candidates. We also might not succeed in developing our product candidates due to technological obstacles, and any clinical trials that we may conduct could fail at any stage. We will depend on others to conduct clinical trials of our products, and we may never receive the regulatory approvals needed to sell our products. Even if we receive regulatory approval in any country, our products may never achieve acceptance in the market, for competitive reasons and/or due to government-imposed limitations on the use of our products, and we may never be profitable. Our intellectual property position may be inadequate to protect our technology. In addition, we are a majority-owned subsidiary of BioTime, who will retain control over us and our business after this offering. We cannot guarantee future results, outcomes, levels of activity, performance, developments or achievements, and we cannot assure you that our expectations, intentions, anticipations, beliefs or projections will be achieved. Actual results may differ materially from the results anticipated in these forward-looking statements and as such should be evaluated together with the many uncertainties that affect the business of Asterias and its subsidiaries, particularly those mentioned in the cautionary statements found in Asterias’ most recent Securities and Exchange Commission filings. This presentation speaks as of the date hereof and except as required by law, Asterias disclaims any intent or obligation to update these forward-looking statements.

INVESTING IS SPECULATIVE AND INVOLVES RISK OF LOSS. PLEASE REVIEW CAREFULLY THE INFORMATION PRESENTED HEREEIN BEFORE MAKING A DECISION TO INVEST.

- Trauma to the spinal cord causes hemorrhagic necrosis
- Secondary damage includes cell death, cavity formation, demyelination, and scarring
- Chronic stage: gray matter replaced by either a lesion cavity or collagenous scar
- Typical spared rim of white matter

Kakulas, Paraplegia, 25:212-216, 1987

AST-OPC1: hESC-Derived Oligodendrocyte Progenitor Cells (OPCs)

**AST-OPC1**

- Cryopreserved Allogeneic Cell Population
- Derived from Human Embryonic Stem Cells (hESCs)
- Characterized Composition of Cells:
  - Oligodendrocyte progenitors
  - Neural progenitors
  - Infrequent mature neural cells and
  - Rare other characterized cell types
- Three identified functions
  - Produces neurotrophic factors
  - Induces remyelination
  - Induces vascularization
- “Off the shelf” administration
- First indication: spinal cord injury
- Potential line extensions in other neurodegenerative diseases
AST-OFC1: Functional Activity

**Formation of compact myelin in shi mouse**

*AST-OFC1* wraps host neurons and can form compact myelin sheaths

+ *shiverer mouse*  
+ *shi mouse + AST-OFC1*

**AST-OFC1** promotes increased neurite outgrowth

*AST-OFC1* produces neurotrophic factors (*Midkine, Activin A, BDNF, TGF-b2, HGF*) and promotes neovascularization

- *Control Media*  
- *AST-OFC1 CM*

**Rat spinal cord 9 months post transplantation**

*Rag2"/"γc"/"shi mouse + AST-OFC1*
Models of Spinal Cord Injury Used to Evaluate Safety/Activity of AST-OPC1

- Unilateral Contusion Injury at C5/C6
- Midline Contusion Injury at T10

Transplant AST-OPC1 7 days post-injury at injury site

Evaluate
- Efficacy & Activity
- Histological Effects
- Cell Survival
- Cell Phenotype
- Cell Migration
- Toxicity
AST-OPC1 Improves Locomotor Recovery in Rats with Thoracic or Cervical SCI

Locomotor Improvement in Thoracic SCI

- Increased Running Speed
- Increased Right Forelimb Stride Length
- Increased Right Forelimb Maximal Longitudinal Deviation
- Increased Right Rear Stride Frequency

Locomotor Improvement in Cervical SCI

- Increased Weight Bearing
- Improved HL-FL Coordination
- Improved Hind Paw Clearance
- Improved Trunk Stability
- Decreased Tail Drag

Graphs showing improvements over time with AST-OPC1 treatment compared to control groups.
AST-OPC1 Decreases Parenchymal Cavitation In Injured Rats

Area of Parenchymal Cavitation (mm$^2$)

- AST-OPC1
- HBSS

$p<0.05$
AST-OPC1 Reduces SCI Cavity Formation and Induces Persistent Myelination

Rat Thoracic Spinal Cord Injury Model

9 months vehicle

hNuc EC

Cavity forms in untreated SCI lesion

1 mm

100 µm

50 µm

Myelinated axons do not extend across cavity

9 months post-transplant with AST-OPC1

hNuc EC

AST-OPC1 in SCI Lesion; Significantly Reduced Cavity Formation

1 mm

100 µm

50 µm

Robust AST-OPC1 survival (brown)

Myelinated Fibers (blue)

Brown: antibody to human nuclear antigen labels AST-OPC1; Blue: Eriochrome Cyanine stains myelin
Safety/Efficacy Profile of AST-OPC1 in Nonclinical Studies

28 Animal Studies
>3000 Rodents and Pigs

- Activity/ Efficacy
- Biodistribution
- Dosing/Delivery
- Toxicity
- Tumorigenicity
- Ectopic Tissue
- Immune Rejection

- Survives in the Spinal Cord
- Predominantly Neural Cell Types
- Improves Locomotor Activity
- Reduces Parenchymal Cavitation
- Migrates Up 5cm in Spinal Cord
- No Distribution Outside CNS
- Does Not Increase Mortality
- Does Not Induce Allodynia
- Does Not Induce Systemic Toxicity
- Does Not Produce Teratomas
- Produces Low Frequency (1-2%) Small Ectopic Tissue Observed Restricted to the Injury Site at Same Frequency as Rat Endogenous Ectopic Tissue
- Not Highly Susceptible to Direct Immune Responses
First Clinical Trial of AST-OPC1
Designed to Establish Product Safety

- Open Label Trial
- Subacute, Functionally Complete T3-T11 Lesions
- \(2 \times 10^6\) Cells
- Transplant 7-14 Days Post Injury
- Temporary Immunosuppression
- Primary Endpoint: Safety
  - Neurological
  - Overall
- Secondary Endpoints:
  - INSCSCI Grade and Score
- Exploratory Endpoints
  - UAB-IMR
  - Independence Measurements
  - Bowel and Bladder Function
  - Pain Assessment
AST-OPC1
Phase 1 Thoracic Trial Study Schema

SCHEMA

SUBJECT

Acute complete SCI

Day -14 Day -11 Day -3 Day -2 Day -1

Day 0

Day 1 Day 7 Day 30 Day 60 Day 90 Day 120 Day 180 Day 270 1 Year 5 Years 15 Years

Days 46-60

Immunosuppression taper

Discontinue Immunosuppression

Protocol CP35A007

Protocol CP35A008

GRNOPC1 INJECTION
Begin immunosupression

screening baseline

In person visits Phone f/u

MRI

MRI MRI MRI MRI MRI MRI MRI MRI MRI
Delivery of AST-OPC1: Elective Surgical Delivery

**Delivery**

- $2 \times 10^6$ AST-OPC1
- 50 uL Injection
- 5mm Caudal of Injury Epicenter
- Injection Performed Using Syringe Positioning Device
  - Support Frame
  - Microdrive
  - Syringe and Needle
### AST-OPC1: Patient Demographics

#### Demographic and Baseline Disease Characteristics – All Treated Subjects

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Lowest Intact Neurological Level</th>
<th>Cause of Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>Male</td>
<td>T6</td>
<td>Motor vehicle accident</td>
</tr>
<tr>
<td>23</td>
<td>Male</td>
<td>T8</td>
<td>Restrained driver in rollover motor vehicle collision with ejection</td>
</tr>
<tr>
<td>32</td>
<td>Male</td>
<td>T6</td>
<td>Motorcross</td>
</tr>
<tr>
<td>31</td>
<td>Male</td>
<td>T7</td>
<td>Fell 30 feet down rock embankment</td>
</tr>
<tr>
<td>23</td>
<td>Female</td>
<td>T3</td>
<td>Car accident</td>
</tr>
</tbody>
</table>

**Lead Neurosurgeon: Dr Richard Fessler**

#### Enrolling Sites

- **Shepherd Center**
- **University of Virginia**
- **Northwestern University**

Dr. David Apple  
Dr. Gary Steinberg  
Dr. Richard Fessler
Delivery of AST-OPC1 in Complete Thoracic SCI Is Feasible and Safe

• All Subjects Received AST-OPC1 (2 x 10^6 cells) within 2 weeks of injury
• No SAEs Associated with Delivery of Cells
• 9 Adverse Events Possibly Related to Injection Procedure
  - All Grade 1 or 2 Post-Operative Pain, Transient Fever (1) or Urinary Tract Infection (1)
• All Subjects Completed Tacrolimus Immunosuppression Regimen
• No SAE’s Associated with Immunosuppression
• 16 Grade 1 or 2 Adverse Events Possibly Associated with Immunosuppression
• Nausea, Urinary Tract Infection, Low Magnesium Blood Levels
No Evidence of AST-OPC1 Directed Immune Responses One Year After Administration

- Immune monitoring shows no evidence of antibodies or cellular immune responses to AST-OPC1 through 1 year in all subjects
- Some subjects complete mismatch with AST-OPC1: Closest match was 5 of 10 alleles
AST-OPC1 Well Tolerated

- No SAE’s Associated with AST-OPC1
- No Evidence of Expansive Tumors or Expanded Cysts
- No CSF Leaks, No Enhanced Inflammation, No Infections
- 5 Adverse Events (Grade 1-3) Possibly Associated with AST-OPC1
  - Transient Low Grade Fever (1)
  - Burning Sensation in Trunk and Lower Extremities (4 in one subject)
### 3 SAEs Observed: Not Associated With AST-OPC1, Injection Procedure, or Immunosuppression

<table>
<thead>
<tr>
<th>Subject</th>
<th>SAE</th>
<th>Timeframe</th>
<th>Related to AST-OPC1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1101</td>
<td>Pyelonephritis: Grade 2</td>
<td>Day 215</td>
<td>Not Related</td>
</tr>
<tr>
<td>1204</td>
<td>Urinary tract infection: Grade 3</td>
<td>Day 325</td>
<td>Not Related</td>
</tr>
<tr>
<td>1204</td>
<td>Autonomic Dysreflexia/Dyspnea: Grade 3</td>
<td>Day 720</td>
<td>Not Related</td>
</tr>
</tbody>
</table>
No Major Sensory Neurological Changes Observed

<table>
<thead>
<tr>
<th>Subject</th>
<th>Visit</th>
<th>Neurological Level</th>
<th>Zone of Partial Preservation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Right Side Sensory</td>
<td>Left Side Sensory</td>
</tr>
<tr>
<td>1002</td>
<td>Baseline</td>
<td>T6</td>
<td>T6</td>
</tr>
<tr>
<td></td>
<td>Year 1</td>
<td>T6</td>
<td>T7</td>
</tr>
<tr>
<td></td>
<td>Year 2</td>
<td>T6</td>
<td>T6</td>
</tr>
<tr>
<td></td>
<td>Year 3</td>
<td>T6</td>
<td>T6</td>
</tr>
<tr>
<td>1003</td>
<td>Baseline</td>
<td>T8</td>
<td>T8</td>
</tr>
<tr>
<td></td>
<td>Year 1</td>
<td>T8</td>
<td>T8</td>
</tr>
<tr>
<td></td>
<td>Year 2</td>
<td>T8</td>
<td>T9</td>
</tr>
<tr>
<td>1101</td>
<td>Baseline</td>
<td>T6</td>
<td>T6</td>
</tr>
<tr>
<td></td>
<td>Year 1</td>
<td>T6</td>
<td>T6</td>
</tr>
<tr>
<td></td>
<td>Year 2</td>
<td>T5</td>
<td>T5</td>
</tr>
<tr>
<td>1203</td>
<td>Baseline</td>
<td>T7</td>
<td>T8</td>
</tr>
<tr>
<td></td>
<td>Year 1</td>
<td>T7</td>
<td>T8</td>
</tr>
<tr>
<td></td>
<td>Year 2</td>
<td>T8</td>
<td>T8</td>
</tr>
<tr>
<td>1204</td>
<td>Baseline</td>
<td>T3</td>
<td>T3</td>
</tr>
<tr>
<td></td>
<td>Year 1</td>
<td>T4</td>
<td>T4</td>
</tr>
<tr>
<td></td>
<td>Year 2</td>
<td>T4</td>
<td>T4</td>
</tr>
</tbody>
</table>

* Day 270
MRI Results: Evidence Consistent with Prevention of Lesion Cavity Formation

• No adverse findings on primary MRI safety reads
• In 4 of 5 subjects, graft sites are hyperintense on T2, but signal intensity is < CSF
• Suggests lesion cavity formation may have been prevented by formation of a tissue matrix

Image on right is axial T2 at 3 years post-grafting through center of lesion/graft site – Slice 22 on sagittal image above)
Next Step: Dose Escalation in Cervical Spinal Cord Injury Patients

- Cervical spinal cord injury patients can have severe disability and reduced lifespan.
- Only short distance repair/regeneration of axons at the cervical level required to reinnervate motor neurons for arms & hands
- Multiple outcome measures available
- Only 25% of patients with sensimotor complete cervical spinal cord injuries recover >2 motor levels 1 year post-injury (Steeves et al 2012 Top Spinal Cord Inj Rehabil 18:1-14)
• Safety of Low Dose Established in First Human Clinical Trial
• Extensive Data in Non-clinical Animal Studies Demonstrate:
  . Engraftment Over Periods of At Least 1 Year
  . Extensive Neural Regeneration and Myelination
  . Improved Locomotor Function
  . No Evidence of Tumorigenicity or Toxicity
• Poised to Enter P1/2a Dose Escalation POC Study in Initial Target Registration Indications: Complete Cervical SCI
• Follow-on Opportunities in MS, Stroke, Other Neurodegenerative Diseases
Acknowledgments

Geront/Asterias

- Cathy Priest
- Ed Wirth
- Linda Jones
- Anthony Davies
- Jerrod Denham
- Katy Spink
- Nate Manley
- Kevin Nishimoto
- Naomi Kautz
- AST-OPC1 Team

Pre-Clinical Collaborators

- Hans Keirstead
- Gabriel Nistor

Clinical Investigators

- Richard Fessler
- Steve McKenna
- Gary Steinberg
- David Apple

Steering Committee
- Data Monitoring Committee
- Radiology Committee
- Outcomes Committee