Monitoring the Safety of Stem Cell Based Therapeutics in Clinical Trials

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Disclosure

- Received salary & ownership interest from Geron Corporation as an employee.
Multiple Considerations in Designing a Clinical Protocol to Test a Stem Cell Therapy

• What is the Clinical Indication?
• What is the Source of Stem Cells: Allogeneic or Autologous?
• Are There Risks of Infection?
• What is the Delivery Route?
• How Long Do the Cells Need to Survive to Be Effective?
• Will Immunosuppression Be Required?
• What is the Anticipated Mechanism of Action?
• What Are the Potential Benefits?
• Are There Toxicological Concerns?
• Are There Tumorigenicity Concerns?
Example of GRNOPC1

- Cryopreserved Allogeneic Cell Population
- Derived from Human Embryonic Stem Cells
- Characterized Composition of Cells
- Contain Oligodendrocyte Progenitor Cells
- Produces Neurotrophic Factors
- Induces Myelination of Denuded Axons

Intended Application
- “Off-the-Shelf” Product
- Spinal Cord Injury
- Other CNS Disorders
Spinal Cord Injury: Pathology of the Lesion Provides Rationale for Oligodendrocyte Progenitor Transplantation

9 months vehicle

hNuc EC

1mm

9 months post-GRNOPC1

hNuc EC

1mm
GRNOPC1 Phase 1 Multi-Center Trial

- Open Label Trial
- Subacute, Functionally Complete T3-T10 Lesions
- $2 \times 10^6$ Cells
- Transplant 7-14 Days Post Injury
Infectious Disease Risk Due to Adventitious Agents in Stem Cell Product

Are There Adventitious Agents Administered Due to the Source of the Cells or the Reagents Used to Prepare the Stem Cell Product?
H1 hESC Line and GRNOPC1 Were Qualified for the Production of Human Biologics

No Evidence Of:
- Mycoplasma
- HIV 1 & 2
- HTLV I/II
- CMV
- HBV or HCV
- HHV-6
- EBV
- Parvovirus B-19
- Mouse Adventitious Agents
- Porcine Adventitious Agents
- Rabbit Adventitious Agents
- Eco-, Xeno- or Amphotropic Retroviruses
- Adventitious Agents Detected In Vitro & In Vivo PTC Assays

Qualified According to FDA Guidance
- No Evidence of Adventitious Agents of Human or Animal Origin
- Normal Karyotype By G-Banding
GRNOPC1 Phase 1 Multi-Center Trial: Adventitious Agent Monitoring

Precautionary Activities in Clinical Trial

- Patients Monitored Routinely for Infectious Disease
- Vials of Product Retained in Case of Suspected Infectious Disease Transmission
- Peripheral Blood Samples Collected Stored Periodically to Monitor Suspected Changes in Pathological Agent Status
Safety of Delivery

Some Risk Due to Administration of Cells

Highly Depends on the Route of Administration and Cell Dose Administered

- Infection
- Surgical Risk

- Minimize Invasiveness of Delivery
- Minimize Damage Done By the Delivery
- Design Specific Subject Monitoring Standards in Peri-Transplant Period
GRNOPC1 Phase 1 Multi-Center Trial: Safety of Delivery

- Intraleisional Injection 7-14 Days Post Injury
- Guided By Prior MRI and Intra-Operative Ultrasound
- Syringe Positioning Device
- Training of Surgeons on Cadavers
- DVT Prophylaxis
- Detailed Subject Monitoring
Stem Cell Product Survival In Vivo

- Ideally Track Cells In Vivo in Subjects
- Track Cells Using Biopsy Material
- Track Products Produced By Cells
  - Look for Evidence of Rejection

Challenge for Most Trials
Imaging Technology Improving
But Not Sufficient Yet for Many Applications
GRNOPC1 Phase 1 Multi-Center Trial: Cell Survival Monitoring

Monitoring Cells in Spinal Cord

- Current Tracking Technologies Not Applicable for Long-Term Monitoring
- Biopsy Material Not Available
- Periodic MRIs
- Sample CSF and Blood for Cell Specific Products
- Monitor Immune Responses
Immunogenicity

- Are the Cells Rejected?
- Consequences for Follow-up Treatments?
- Sensitization?

Careful Selection of Patient Inclusion/Exclusion Criteria to Mitigate Negative Impact on Potential Downstream Clinical Options
Toxicological Effects of Stem Cells Based Products

- Abnormal Local Tissue Responses
  - Metabolic Changes
  - Structural Changes
  - Neurological Changes
  - Induction of Pain Responses

- Careful Selection of Inclusion Exclusion Criteria to Minimize Harm
- Theoretical and Observed Potential Toxicities in Preclinical Studies Need to Be Assessed in Human Trials
GRNOPC1 Phase 1 Multi-Center Trial: Toxicology Assessments

- Subacute, Functionally Complete ASIA A T3-T10 Lesions
- Temporary Immunosuppression with Tacrolimus
- Primary Endpoint: Safety
  - Neurological
  - Overall
- Secondary Endpoints: Safety/Efficacy
  - ASIA Grade and Score
  - UAB-IMR
  - Independence Measurements
  - Bowel and Bladder Function
  - Pain Assessments
Tumorigenicity of Stem Cell Based Products

- Do the Cells form Masses?
- Do the Cells for Ectopic Tissue?
- Are the Cells Proliferative In Vivo?
- Do the Cells Produce Adverse Clinical Consequences Associated with Ectopic Tissue Formation?

- Monitor for Expansile Tissue Masses
- Monitor Clinical Symptoms for Evidence of Expansile Tissue
- Long-term Follow-up
Monitor Clinical Adverse Reactions

- Neurological Deterioration
- Overall Clinical Deterioration
- Increased Evidence of Pain
- Frequent MRIs
- 15 Year Follow-up
MRI Monitoring Scheme for GRNOPC1 Clinical Trial

**SCHEMA**

**SUBJECT**

Acute complete SCI

Day -14 Day -11 Day -3 Day -2 Day -1 Day 1 Day 7 Day 30 Day 90 Day 60 Day 120 Day 180 Day 270 1 Year 5 Years 15 Years

Days 46-60

Immunosuppression taper

Discontinue Immunosuppression

In person visits Phone f/u

Day 0

GRNOPC1 INJECTION Begin immunosuppression

Screening baseline

Protocol CP35A007

Protocol CP35A008

MRI Monitoring Scheme for GRNOPC1 Clinical Trial
Risk Mitigation Strategy

- Initial Staggered Enrollment
- Build in Frequent Monitoring to Detect Potential Adverse SUSARs
  - Real Time Event Review by Data Monitoring Committees
    - Plan For Follow-up of SUSARS
  - Assess Treatment Options in the Event of a SUSAR
    - Defined Trial Suspension Rules
Summary

• Careful Design and Execution of Clinical Trials Are Required to Monitor the Safety of Stem Cell Based Therapeutic Products

• Specific Risks to be Examined Include Those Associated with the Survival, Rejection, Integration, Proliferation and Ectopic Tissue Formation By the Cells.

• Risk Mitigation Strategies Must Be Developed to Minimize the Impact of SUSARS