SIG-005: Novel Encapsulated Non-Viral Cell-Based Therapy for MPS I

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Introduction

- Mucopolysaccharidosis I (MPS I) is a rare genetic disease with incidence of ~1/100,000 live births
- Deficiency of lysosomal enzyme α-L-iduronidase (IDUA) leads to the accumulation of GAGs within cells
- Standard therapy includes enzyme replacement therapy (ERT) for Hurler-Scheie and Scheie and bone marrow transplantation (BMT) for Hurler
- Key challenges include suboptimal long-term efficacy and treatment burden

Hypothesis

Better outcomes could be achieved with sustained, long-lasting hIDUA levels via administration of hIDUA-secreting allogeneic human cells shielded within spheres designed to avoid immune rejection and pericapsular fibrotic overgrowth (PFO) in the patient.

Methods

1. Engineer cells to express hIDUA
2. In vitro evaluation of engineered cells
3. In vitro evaluation of encapsulated cells
4. In vivo evaluation of the final product

Results

- hIDUA produced by engineered cells has comparable biochemical characteristics as the commercial enzyme
- Fibroblasts obtained from MPS I patients can uptake hIDUA produced by engineered cells as demonstrated with reduction of heparan sulfate in the fibroblasts

Results (cont’d)

In Vivo SIG-005 Activity in NSG Mice 3 Months After Administration

Conclusions

- SIG-005 produces active hIDUA with biochemical properties comparable to commercial enzyme
- Single administration of SIG-005 in MPS I mice led to:
  - Significant reduction of heparan sulfate across tissues
  - Long-term study resulted in:
    - Reduced thickness of bone diameter due to reduced GAG levels on surface of the bones
    - Reduction of substrate in tissues with clear improvement in hard-to-target tissues such as kidney and lung
- hIDUA activity was maintained in vitro and in NSG mice for at least 3 months after single administration of SIG-005
- SIG-005 program is on track to move into the next stage of non-clinical development, in preparation for the clinic

Phenotypic Correction in Bone of MPS I Mice 5 Months After SIG-005

Liver

Plasma

Lung

Kidney

Heart

Spleen

Reduction of Substrate in Tissues of MPS I Mice 5 Months After SIG-005

Heart

Kidney

Liver

Lung

Zeiss 20x; Alizarin red S; Black arrow indicates substrate (Unrcst: 0.7-1; Tx. 0.3-1); * Osteonulc; ** Bronchode

Error bars indicate SEM for plasma, SD for other tissues; HS heparan sulfate; each time point, n=10; each dose level, n=10; sham, n=30; untreated ×3 vs sham: **** p<0.0001; *** p<0.001; ** p<0.01; * p<0.05; NS p>0.05

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