**Introduction**

- MPS II (Hunter Syndrome) is caused by deficiency of the lysosomal enzyme iduronate 2-sulfatase (ID3) leading to GAG accumulation in multiple tissues and organs.
- The accumulation results in a complex array of progressive, multi-organ, clinical manifestations with ~2/3 of the patients presenting with CNS involvement.
- Approved treatments include enzyme replacement therapy, with gene therapies under investigation.

**Hypothesis**

Sustained therapeutic effect can be achieved by administration of hIDS-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 hIDS
2. In vitro evaluation of engineered cells
3. In vitro evaluation of encapsulated cells
4. In vivo evaluation of the final product

**Results**

**Comparison of hIDS Produced From Engineered Allogeneic Cells to Commercial Idursulfase**

- Equivalent GAG lowering in MPS II fibroblasts by hIDS from cell media vs commercial idursulfase
- Equivalent uptake by MPS II fibroblasts of hIDS from cell media vs commercial idursulfase

**Results (cont’d)**

**Heparan Sulfate (HS) Reduction With Low Dose of SIG-018 Across Tissues in MPS II Mice**

- 4-week treatment with SIG-018 demonstrated reduction of HS across MPS II KO mouse tissues.

**Dose Response PD Study in MPS II Mice**

**Conclusions**

- Iduronate 2-sulfatase produced by the engineered cells has similar biochemical characteristics as recombinant protein.
- Encapsulated engineered cells (SIG-018) produced active human iduronate 2-sulfatase.
- MPS II KO mice treated with SIG-018 showed continuous levels of active hIDS in plasma resulting in sustained reduction of accumulated substrate in multiple tissues.
- Administration of various doses of SIG-018 demonstrated good correlation with substrate reduction.
- Ongoing work is addressing CNS access.
- Data supports transition of SIG-018 into the next phase of preclinical development.

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