First-in-Human Clinical Trial of Autologous Human B Cells Engineered to Express Human Iduronidase in Subjects with MPS I: Support for Pediatric Studies

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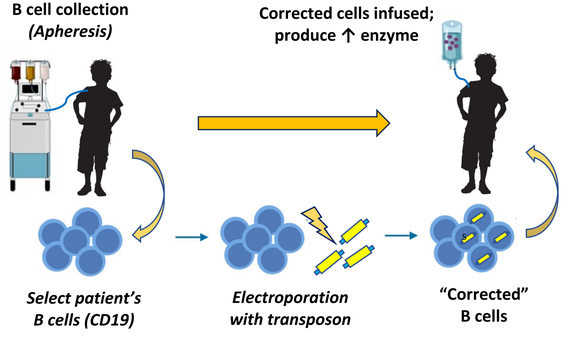
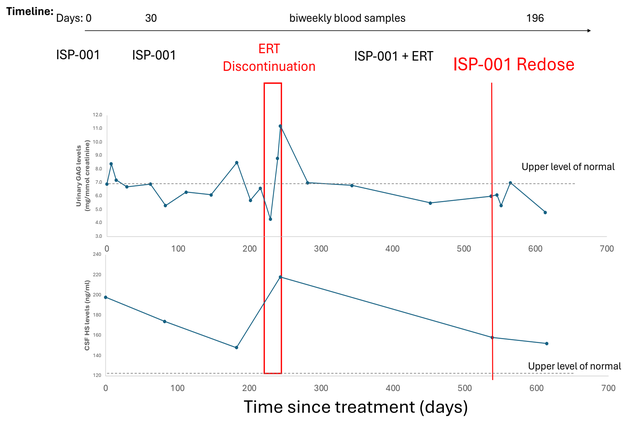
Introduction. We report pharmacodynamic data from the first administration of genetically engineered B cells in two human subjects diagnosed with mucopolysaccharidosis type I (MPS I).
Methods. ISP-001 is generated from a non-mobilized peripheral blood apheresis product, enriched for the CD19+ fraction, expanded in culture and genetically engineered for human IDUA expression using the *Sleeping Beauty* transposon system. ISP-001 was infused intravenously without preconditioning or immunosuppression.
Results. Initial results from Patient 1 were reported previously, demonstrating normalization of urine glycosaminoglycans (GAG) and decreases in cerebrospinal fluid (CSF) heparan sulfate (HS) levels with concomitant improvement in functional outcomes. New data show normalized urine GAG levels in Patient 2 and successful re-dosing of Patient 1, 18 months after the initial dose. Efficacy of ISP-001 is further supported by results from a preclinical GLP pharmacology study. Serum levels of bone resorption biomarker pyridinoline (PYD) were normalized in NSG-MPS I mice after treatment with ISP-001, indicating beneficial effects on skeletal disease manifestations. Additional preclinical studies demonstrated transmigration of luciferase-expressing ISP cells to the brain following peripheral administration, providing support for ISP cell migration to the CNS as the mechanism underlying reduced CSF HS levels observed in Patient 1.
Conclusions. Both patients have demonstrated excellent safety to date and encouraging biochemical activity in combination with ERT. Moreover, we establish that patients can be safely re-dosed – an important consideration, especially in the pediatric population. Beneficial biochemical effects on skeletal dysplasia in mice further supports the potential for effectiveness of ISP-001 in pediatric patients, where skeletal disease manifestations may be addressed. Finally, pharmacodynamic reduction of CSF HS levels in conjunction with evidence of transmigration of ISP cells to the brain in mice raises the prospect of addressing CNS manifestations. These results support the further development of ISP-001 in adult attenuated MPS I patients, with approval to expand the trial to include pediatric attenuated patients to address both dysostosis multiplex and neurological disease. This work was funded in part by the California Institute for Regenerative Medicine.

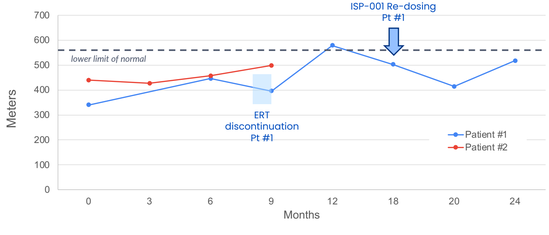
Trial Name: ISP-001: Sleeping Beauty Transposon-Engineered B Cells for MPS I
NCT#: NCT05682144
PIs: Paul Orchard MD, and Paul Harmatz, MD
Patient Population: Adult subjects, diagnosed with MPS I HS or S



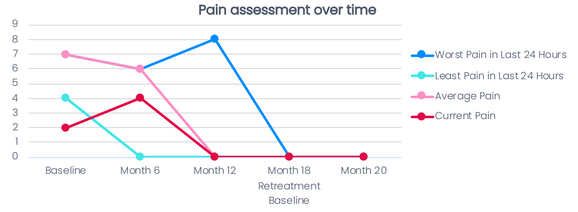
Patient 1: ISP-001 Treatment Results in Reduced Urine GAGs and CSF HS; ISP-001 Can be Re-dosed.

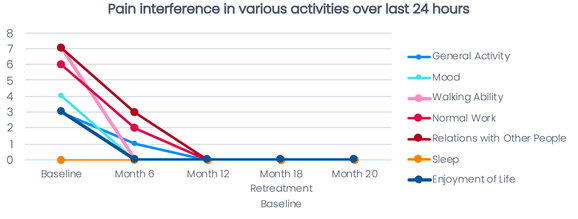


Patient 1: Increased Distance in 6-Minute Walk Test



Patient 1 QOL: Less Pain



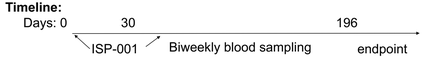


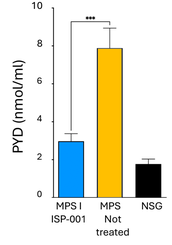
Patient 2: Reduced Urinary GAG Levels

	Days since ERT	Total Urine GAG (mg/mmol creatinine)
Baseline (average)	15	7.8
Day 28	13	7.3
Day 56	14	9.5
Day 70	13	6.1
Day 84	14	7.2
Day 112	13	6.0
Day 126	14	8.4
Day 140	14	8.0
Day 154	14	6.4
Day 168	13	6.2
Day 196	15	6.4

GAG levels in the normal range are boxed in blue.

Preclinical Data: GLP Pharmacology Study of NSG-MPS I Mice Administered ISP-001 cells: Beneficial Effects on Dysostosis Multiplex in Mice

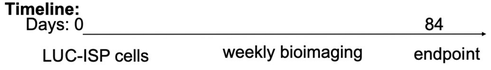


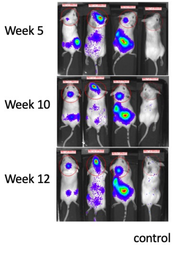


Dysostosis multiplex is a debilitating symptom of MPS I. Elevated pyridinoline (PYD) is a bone marker for Dysostosis multiplex .

Untreated animals showed significantly elevated levels of PYD, while treatment with ISP-001 prevented the increase in serum PYD, suggesting beneficial effects on skeletal manifestations.

Preclinical Data: NSG Mice Administered LUC-Positive ISP Cells: Peripherally Administered ISP Cells Transmigrate and Engraft in the CNS





NSG mice were IV injected with LUC-positive human ISP cells.
Location of cells was monitored via weekly bioimaging (IVIS).

Strong bioluminescence signals were detected in areas of the spleen and pelvis. Additionally, strong signals were detected in the head area of the animals, indicating transmigration of ISP cells to the CNS, followed with long-term engraftment

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