Safety and Initial Activity of Autologous Human B Cells Genetically Engineered to Express Human Iduronidase Using the Sleeping Beauty Transposon System: Results from a First-in-Human Clinical Trial in Subjects with MPS I

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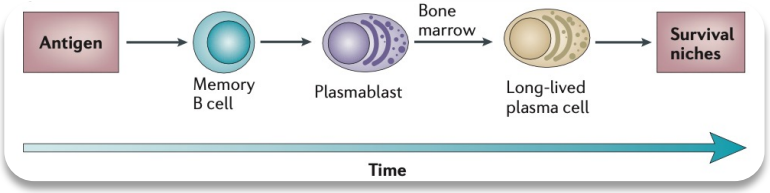
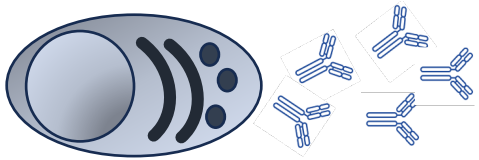
WORLDSymposium February 7, 2025

The B cell (specifically, plasma cell) is a natural protein-producing biofactory that can engraft in the bone marrow for decades

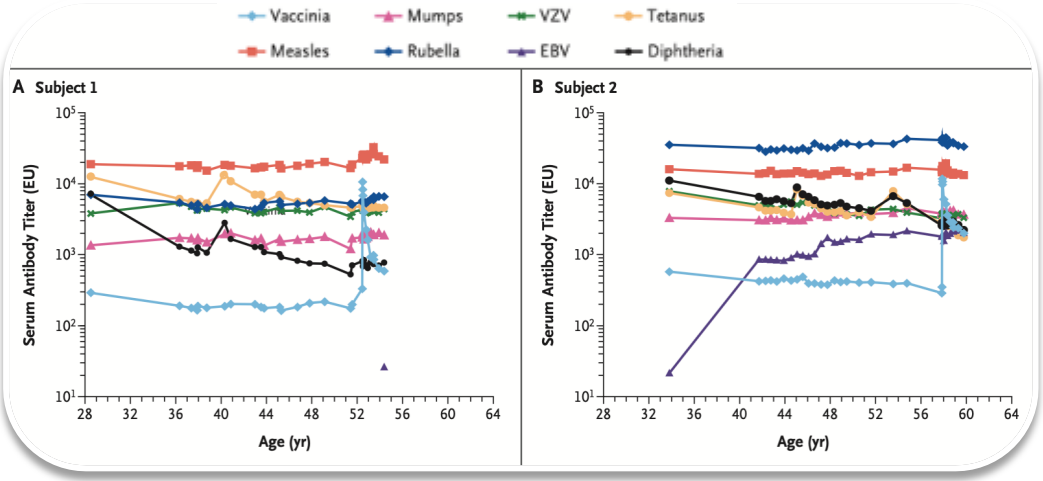
Generation of long-lived plasma cells (LLPCs) from plasmablasts that home to survival niches (bone marrow or inflamed tissue)



Antibody production: 1000s of antibodies/cell/sec



LLPCs can produce antibody responses for 20+ years



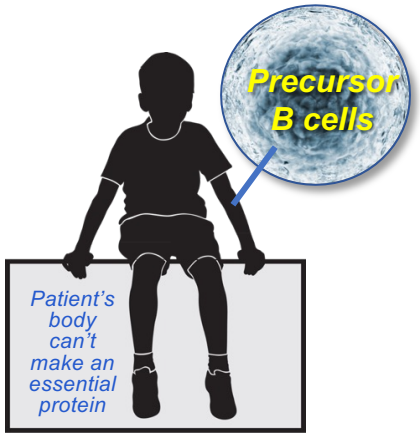
Longitudinal analysis of serum antibody titers demonstrates antigen-specific antibody responses remain stable for greater than 20 years

Harnessing the plasma cell's natural capabilities for antibody production and long-term engraftment enable a new paradigm for administration of protein therapeutics

Radbruch *et al.*, 2006 *Nat Rev*
Khodadi *et al.*, 2017 *Front Immuno*
Amanna *et al.*, 2007 *NEJM*

Platform: Immune System Programming (ISP) Technology

1.
Collect and isolate B cells (precursor to plasma cells) **from patient**

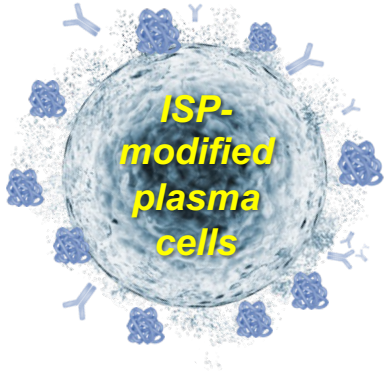


2.
Program B cells to produce therapeutic proteins using a non-viral system

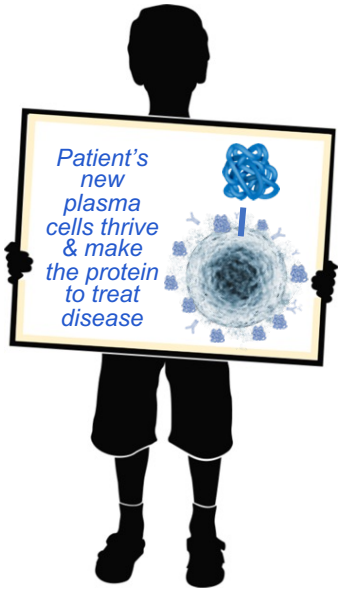
A non-viral integrating gene delivery system

3.
Expand B cells ex vivo using proprietary methods

4.
Differentiate B cells toward plasma cells using exclusive technology licensed from Caltech and differentiation protocols developed



5.
Infuse cells back into the patient, where they engraft as long-lived plasma cells in the bone marrow



ISP-001: Phase I Clinical Trial – Protocol
First genetically modified B cell therapy

Title: A Phase I Open Label Study to Evaluate the Safety and Tolerability of ISP-001 in Adult Patients With Mucopolysaccharidosis Type I Hurler-Scheie and Scheie

Clinicaltrials.gov: NCT05682144

Test Sites: University of Minnesota and University of California, San Francisco

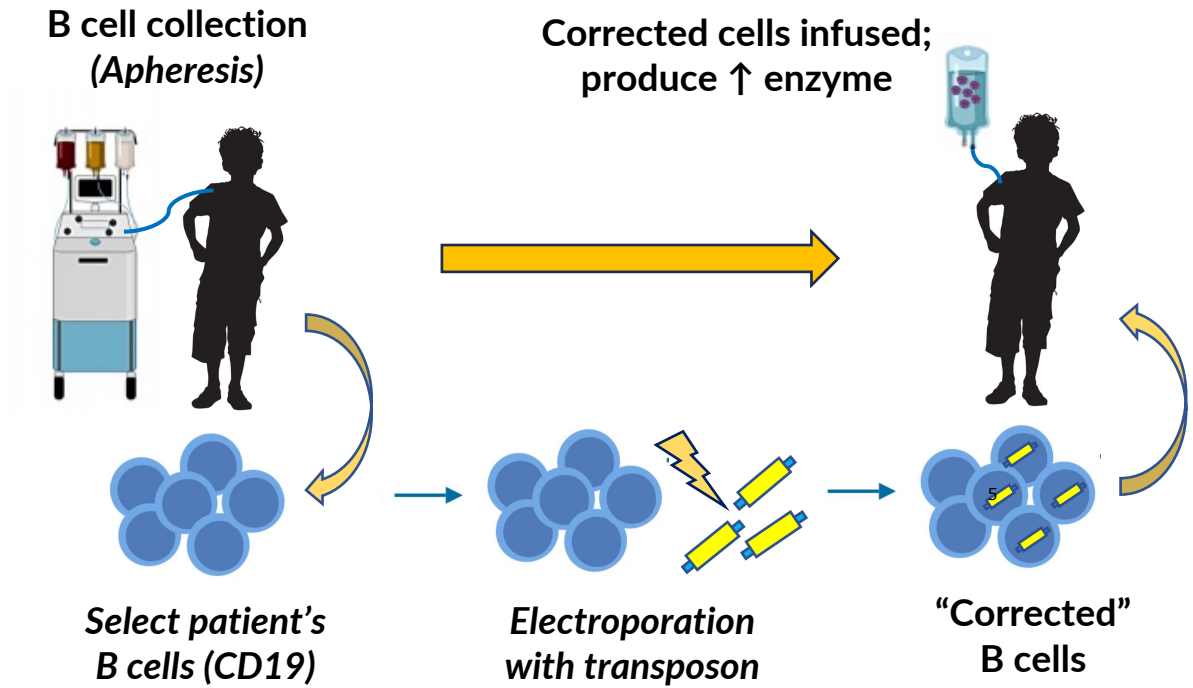
Clinical PIs: Paul Orchard, M.D. and Paul Harmatz, M.D.

Recruitment Goal: Two subjects

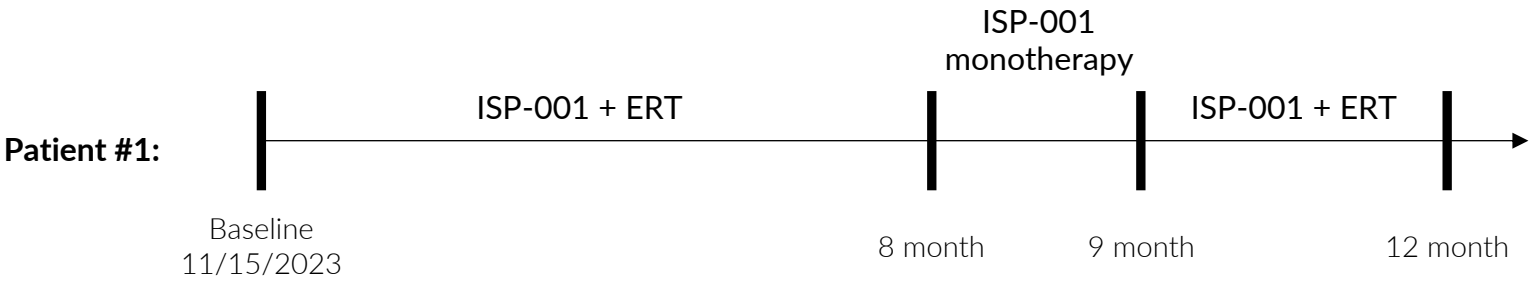
Inclusion Criteria: Diagnosis of MPS I HS or S; Age ≥ 18 years; Creatinine clearance >60ml/min/1.73m2; Ejection fraction ≥ 40%; Agree to travel requirements.

Exclusion Criteria: Known familial inherited cancer syndrome; History of B cell related cancer; Evidence of active graft-vs-host disease; previous hematopoietic stem cell transplant; Requirement for systemic immune suppression; Requirement for continuous supplemental oxygen; Any medical condition likely to interfere with assessment of safety or efficacy of the study treatment.

Treatment with IDUA-engineered B cells
No preconditioning, no immune suppression



Timeline



Patient #2: Successfully screened; Apheresis performed

Urine GAGs decreased to normal levels in combination with ERT

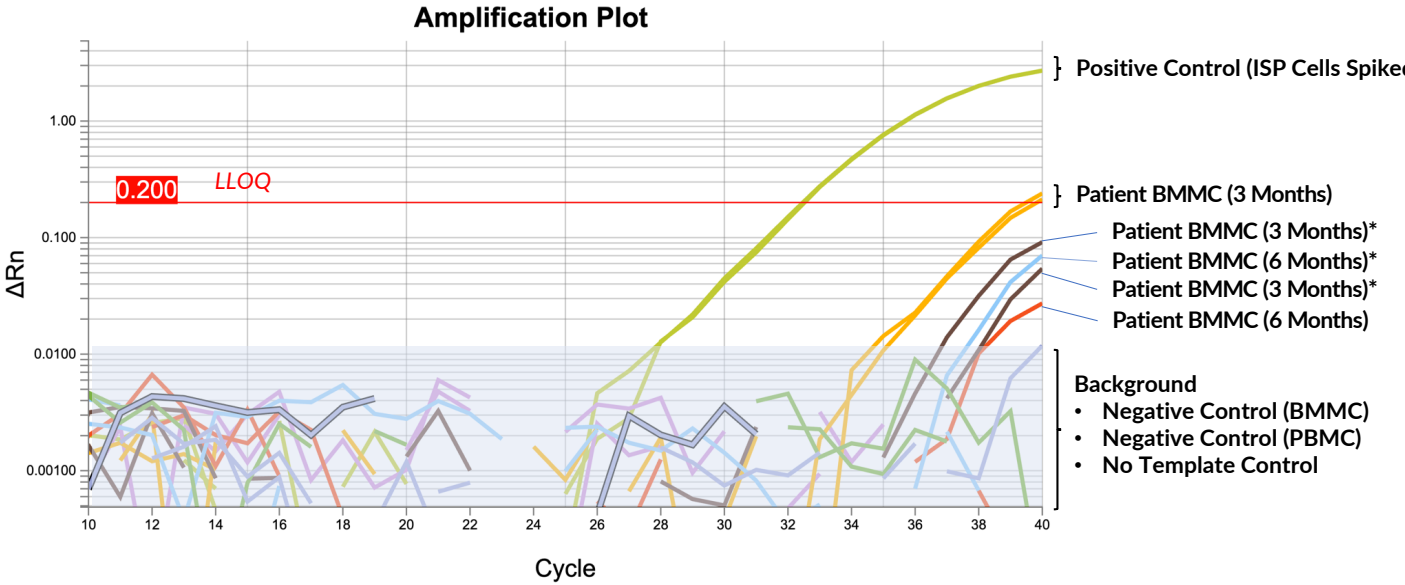
Visit	Date	Days since ERT	Total Urine GAG (mg/mmol creatinine)
Reference range (normal)			<6.5
Baseline (Pre-dose)	15-Nov-23	7	6.9
D7	21-Nov-23	14	8.4
D14	28-Nov-23	4	7.2
D28	13-Dec-23	5	6.7
D63	15-Jan-24	8	6.9
D84 (3-month)	5-Feb-24	7	5.3
D112	5-Mar-24	6	6.3
D147	9-Apr-24	8	6.1
D168 (6-month)	15-May-24	8	8.5
D196	3-Jun-24	6	5.7
D210	17-Jun-24	7	6.6
D224	1-Jul-24	8	4.3
D238	11-Jul-24	18	8.8
D252 (9-month)	15-Jul-24	22	11.2
D280	22-Aug-24	10	7
D336 (12-month)	23-Oct-24	6	6.8

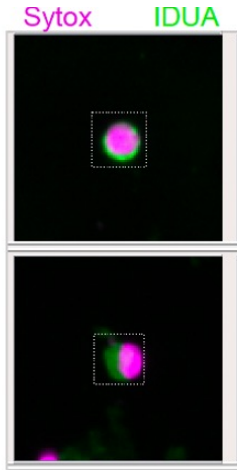
ERT discontinuation

- At eight months, total urine GAGs with ERT combination are the lowest to date and have normalized
- For comparison, from laronidase package insert: "No patient in the group receiving laronidase reached the normal range for urinary GAG levels during this 6-month study"
- However—at this low dose—during the ERT discontinuation, urine GAGs increased

Normal range

ISP-001 cells were detected in bone marrow by qPCR at both three and six months





**DNA was from an RNA/DNA co-extraction, vs pure DNA extraction otherwise*
BMMC = bone marrow mononuclear cells

Sytox: Nuclear staining
IDUA: Strongly positive in cytoplasm
Images from 3-month timepoint

At six months, the regulatory endpoint of Heparan Sulfate (HS) in the spinal fluid approached normal following cell infusion

Post-ERT discontinuation

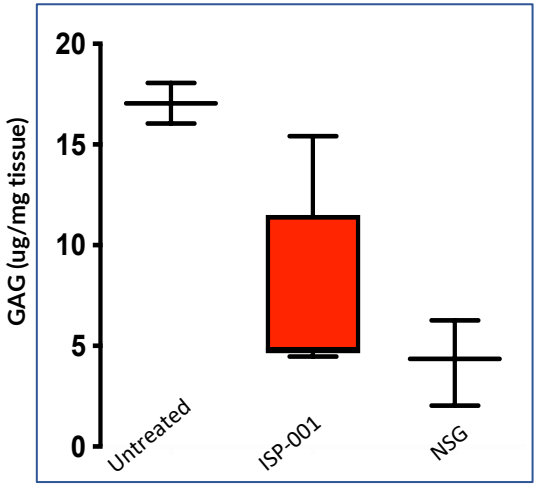
	Baseline	3-month	6-month	6 mo % reduction from Baseline	9-month	Normal
Total HS (ng/mL)	198	174	148	25.3%	218	<120
NRE: IOSO (ng/mL)	12	11	10	16.7%	20	ND
NRE: IOS6 (ng/mL)	74	59	69	6.8%	95	ND

- The enhanced clearing of GAGs in the CSF below the laronidase-alone level is consistent with B cells or additional enzyme crossing the BBB.
- However—at this low dose—during the ERT discontinuation, CSF HS increased.

HS = heparan sulfate, CSF = cerebrospinal fluid
NRE = Non-reducing end; these are markers specific to iduronidase activity, and hence are MPS I-specific
ULN = Upper limit of normal

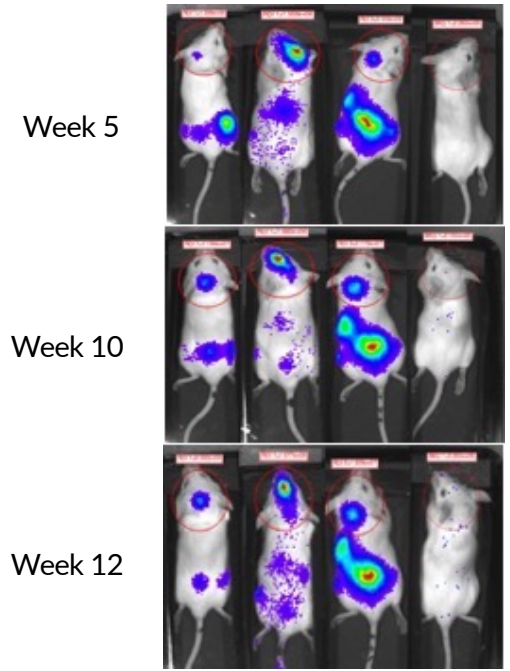
Reduction in CSF GAGs in the first patient is consistent with mouse studies showing brain GAG reduction and cell trafficking from IV injections

GAG reduction in the brain of MPS I mice at three months from IDUA expressing ISP-001 cells



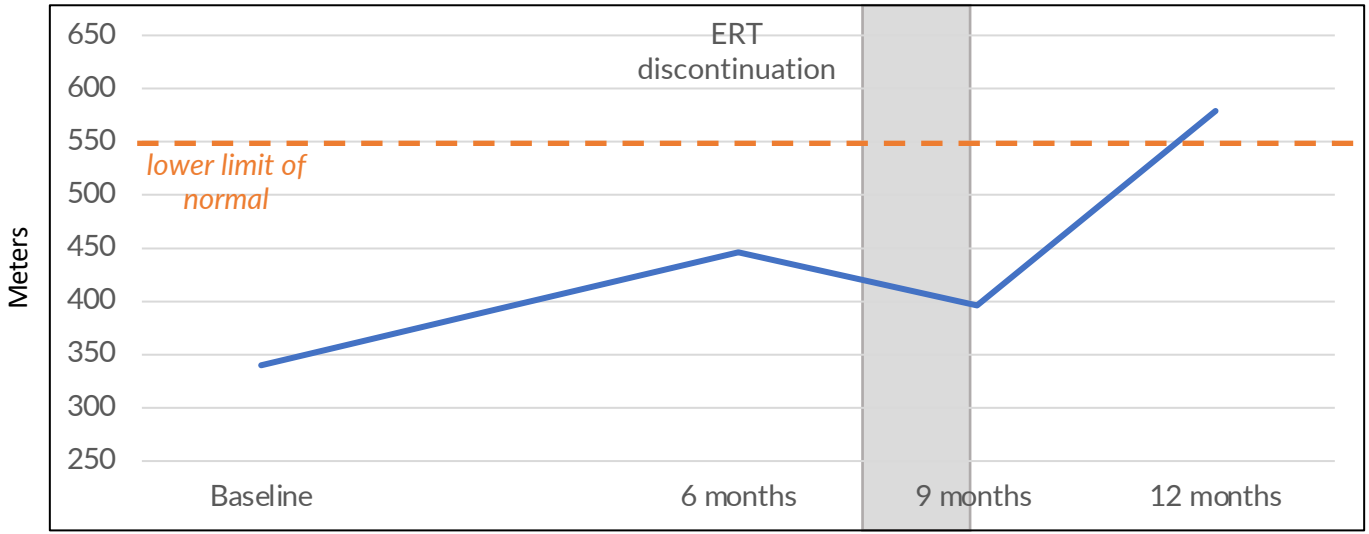
Luciferase expression; brain

(-) control



Note: These data are from two different experiments. Data from both studies selected for representative purposes.

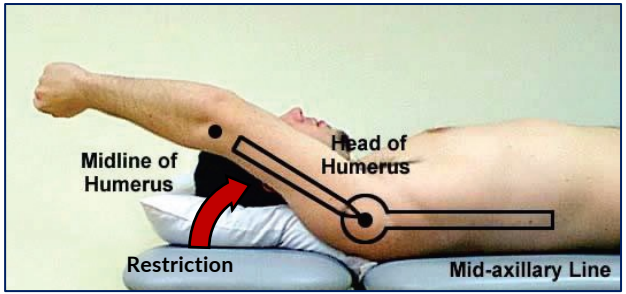
At one year, the patient has normalized the clinical endpoint of 6MWT



- 239-meter (70%) improvement in 6MWT at one year
- 30 meters is generally considered clinically meaningful
  - Laronidase was approved on a 20-meter improvement

6MWT = six-minute walk test
Baseline and 12-month measured in duplicate

At 12 months, clinical improvement was noted in the endpoint of shoulder flexion; significant for the patient

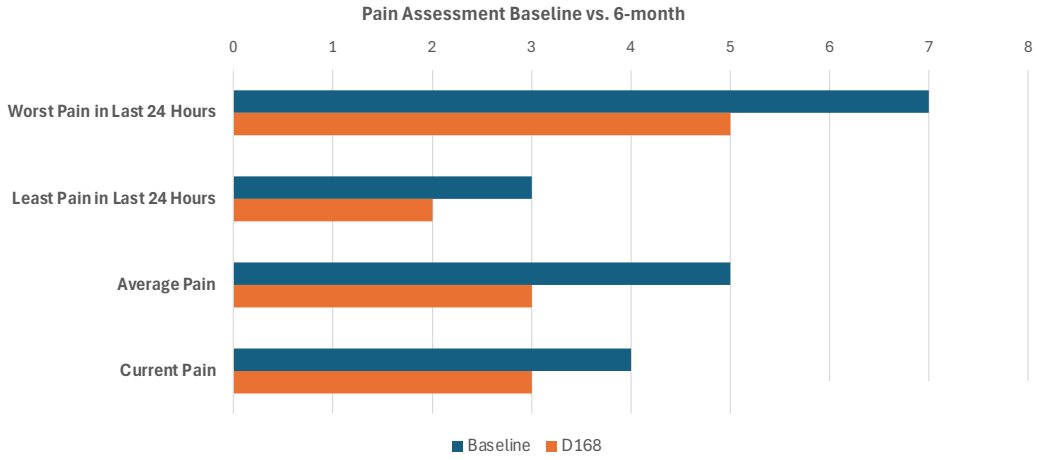


Assessment	Measurement		Screening*	6-month	9-month	12-month*	Improvement from Screening @ 12 mo.	
							Degrees	%
Shoulder ROM	Active range of motion restriction	Left Arm	61	37	34	36	26	42%
		Right Arm	54	35	35	35	19	35%
	Passive range of motion restriction	Left Arm	48	34	30	32	16	33%
		Right Arm	43	32	30	31	12	28%
	Average improvement		N/A	17	19	19		

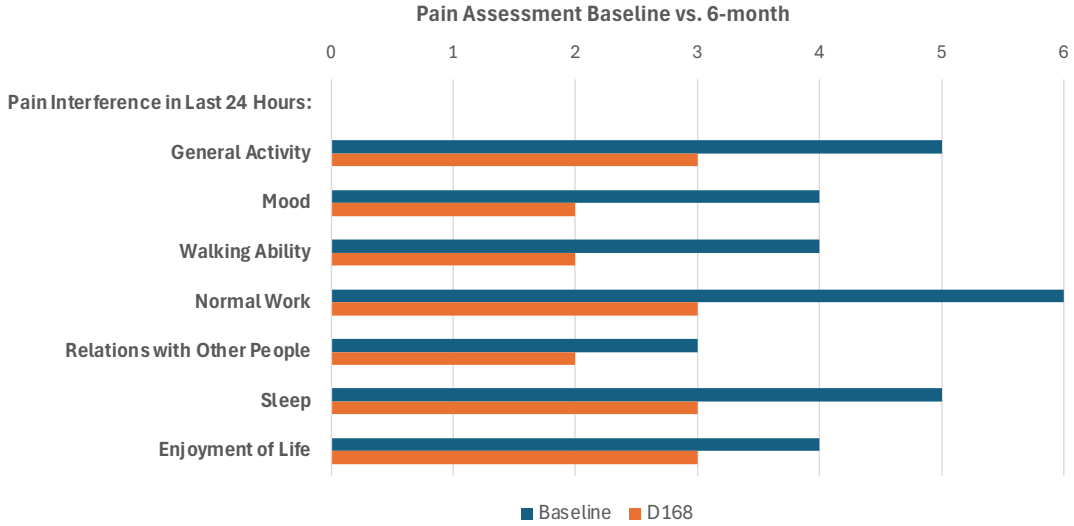
*Average of 2 measures at this time point

- Shoulder ROM – increased ~19° (at 12 months) in current trial vs. 10° in laronidase pivotal trial
- Shoulder flexion improved at 6, 9, and 12 months, even after the ERT discontinuation period

Patient reported outcomes all trending positive



"…Patient reports improved range of motion in general, particularly in shoulders and hips. This has improved patients ADLs by allowing the patient to more easily reach their back in the shower, and sit cross-legged, which they were unable to do previously. Sleeping well."



- Scale is from 1 to 10, lower is better
- Pain has improved over all measures at six months
- Pain is interfering less with daily life and activities at six months
- QoL survey: Improved or stayed the same on 33/36 measures at six months vs. baseline

Conclusions

- Safety and initial activity in an adult with low-dose ISP-001 (2.5 x 10^7 cells/kg) and ERT:
  - CSF heparan sulfate – biomarker for accelerated approval – reduced by 25% at 6 months
  - GAGs in urine normalized; then rose somewhat after discontinuing ERT
  - Plasma IDUA readouts confounded by ERT and potentially endogenous IDUA
- Functional improvements observed at 6, 9, and 12 months
  - 6MWT at 12 months of 579 meters was 70% over baseline, bringing this patient into the normal range
  - Positive patient-reported outcomes, QOL survey, pain assessment at six months
- Next anticipated dose 10^8 cells/kg

Acknowledgements

IMMUSOFT

- Sean Ainsworth, CEO
- Rob Hayes, CSO
- Robert Sikorski, CMO
- R. Scott McIvor, CDO
- Jake Wesley
- Chris Hampe
- Glen Grandea
- Kole Meeker
- Joelle Solan
- Cassidy Papia
- Erik Olson

UNIVERSITY OF MINNESOTA

- Paul Orchard
- Lauren Matzke
- Alli Travis

GRANT FUNDING

- California Institute for Regenerative Medicine (CLIN2-14416)
- National Institutes of Health (NIH R44 GM115192)