

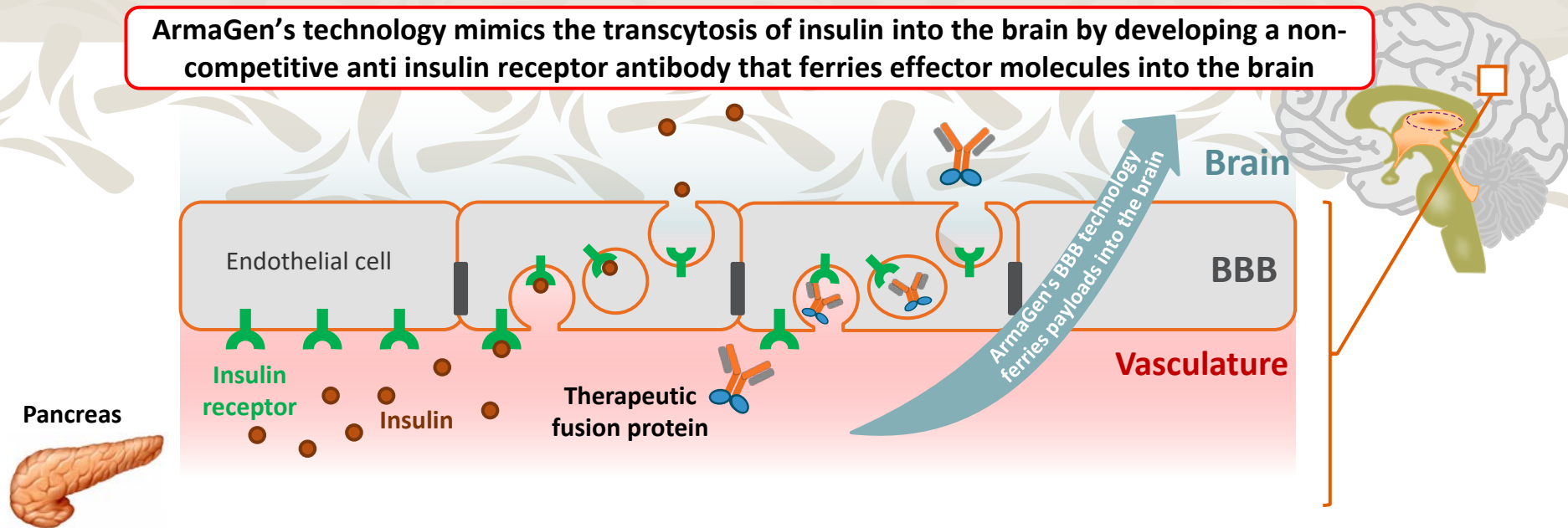
Derek Kelaita (Vice President, Business Development)

September 13, 2018

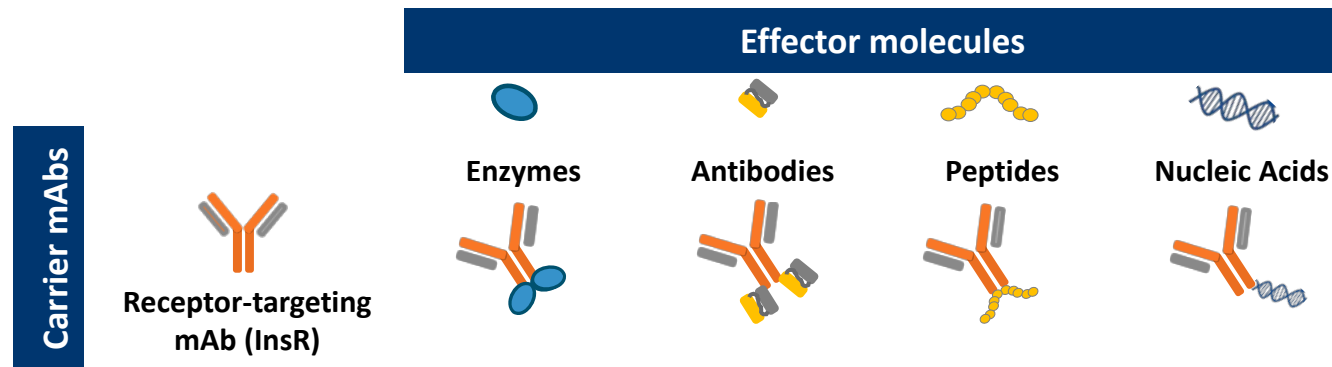


ArmaGen's Background

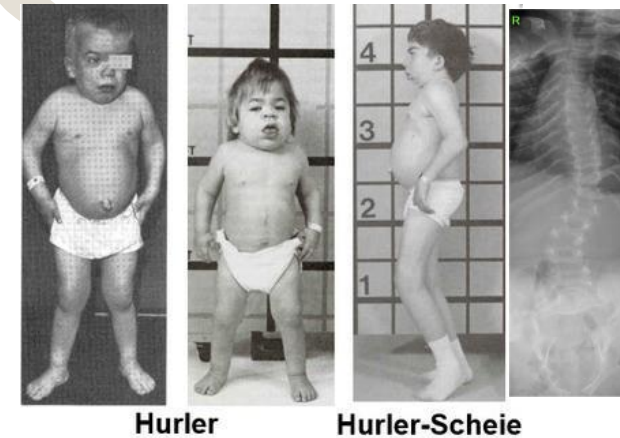
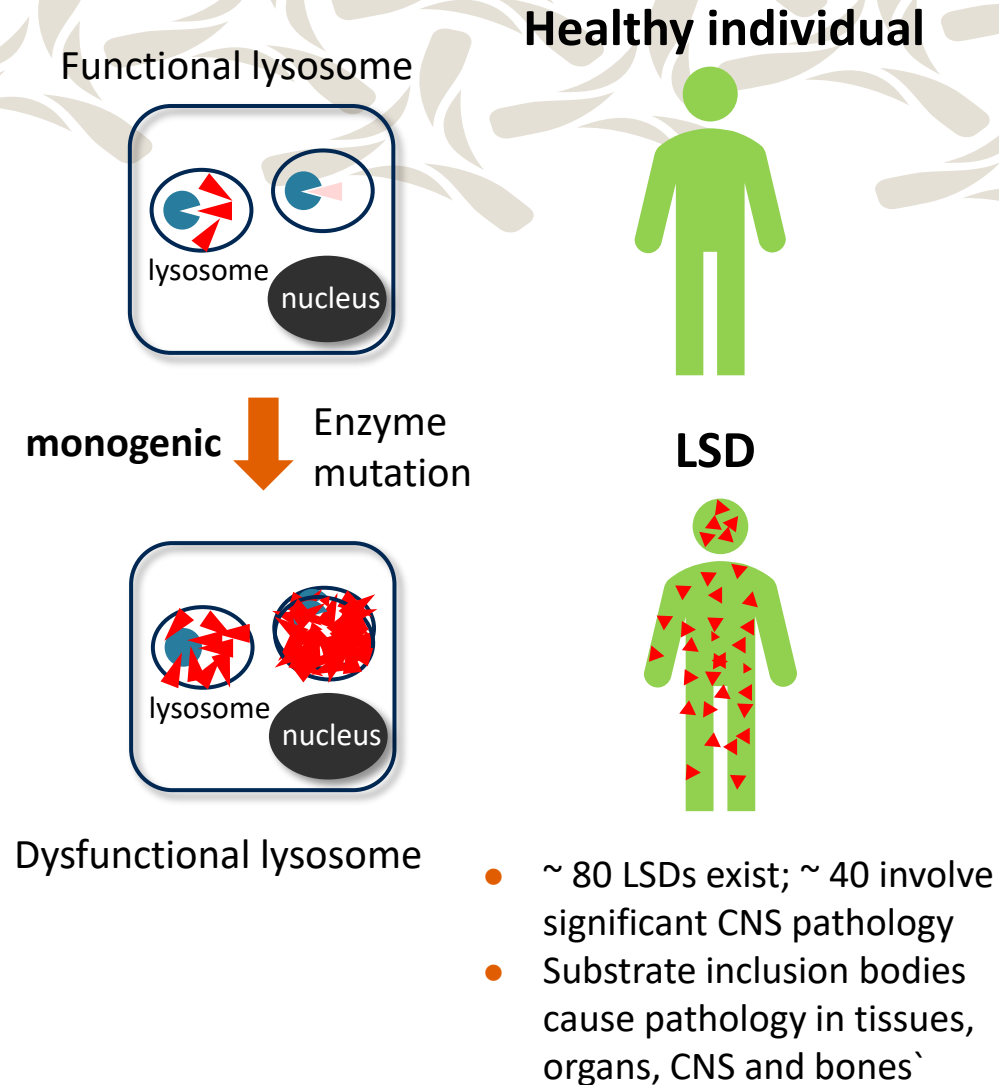
ArmaGen's technology mimics the transcytosis of insulin into the brain by developing a non-competitive anti insulin receptor antibody that ferries effector molecules into the brain



The platform enables the creation of novel combinations of receptor-targeting mAbs and large molecule effectors for the most difficult to treat diseases of the CNS



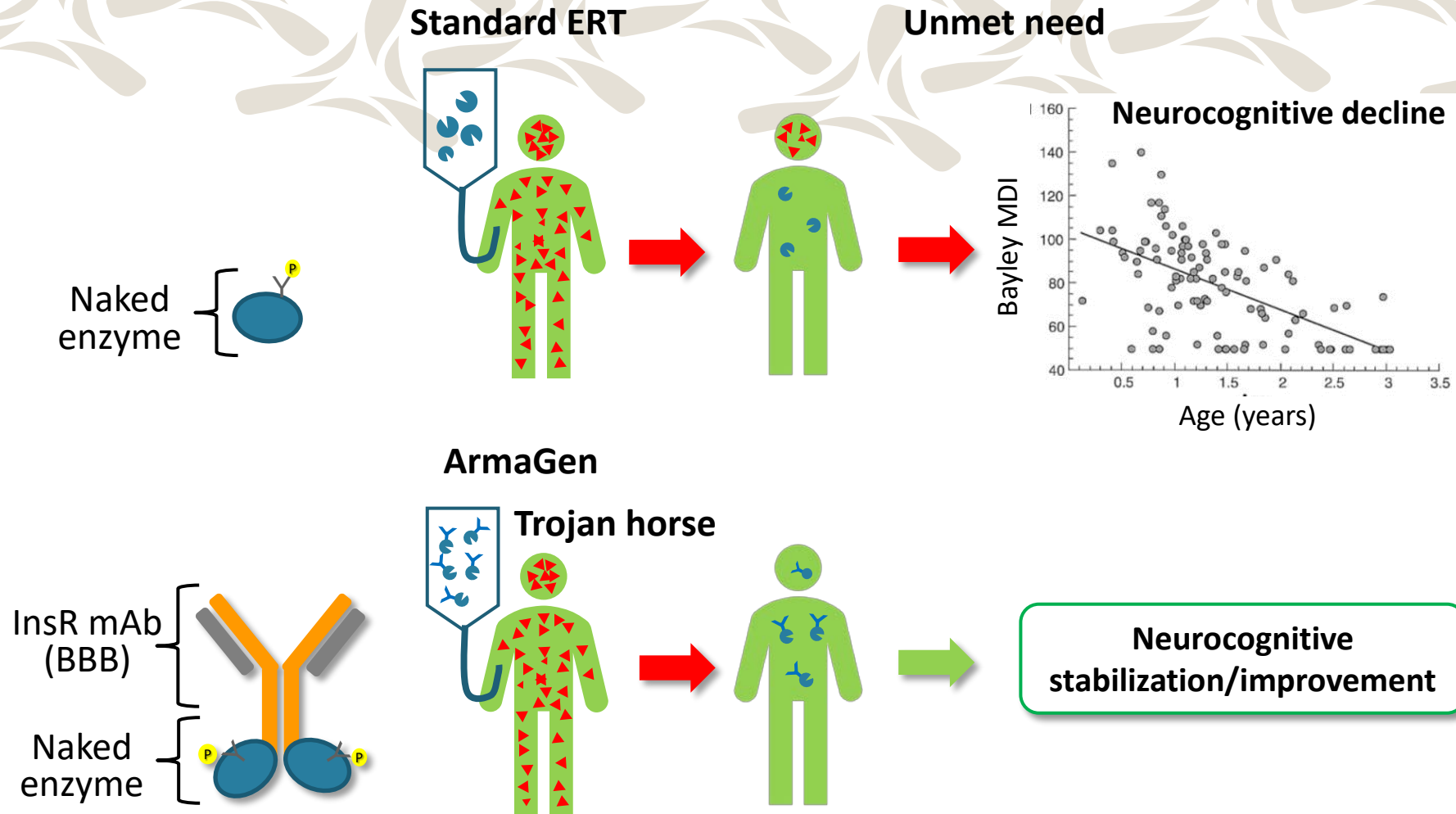
ArmaGen's Value Proposition – Medical Need in Lysosomal Storage Diseases



Symptoms

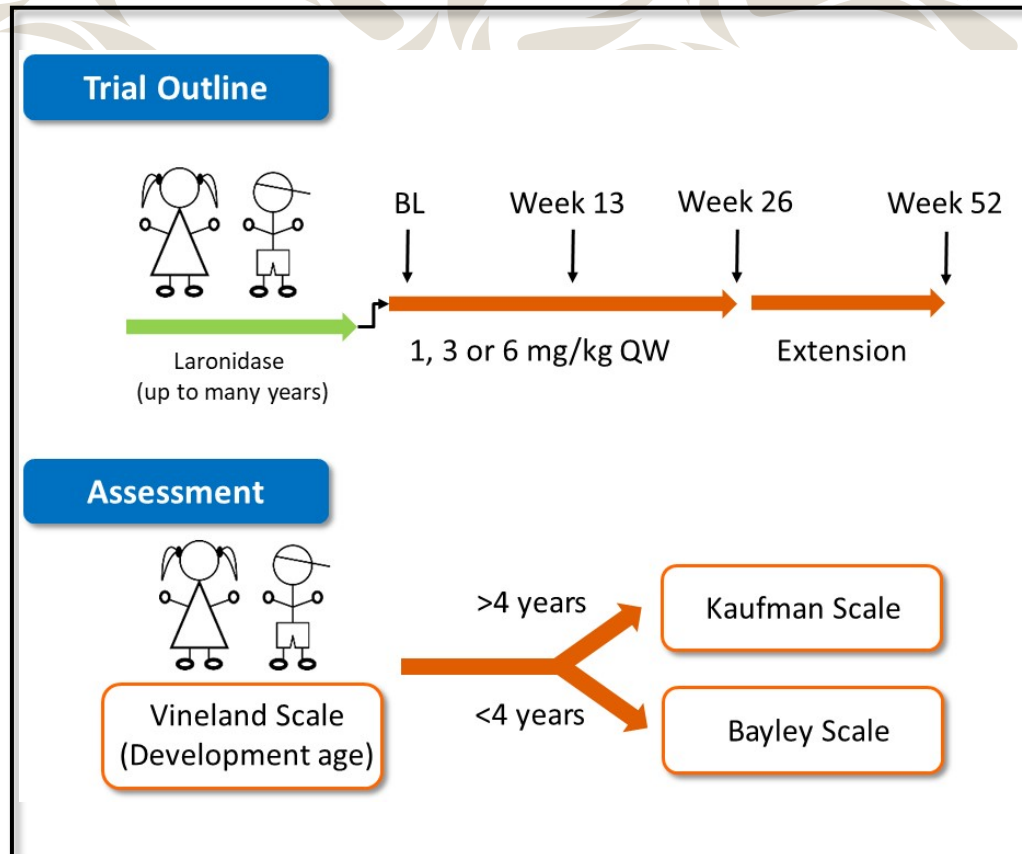
retarded cognitive development, skeletal deformities, low DQ, joint stiffness, corneal clouding, impaired hearing, cardiac dysfunction, retarded growth, pain, respiratory and ear infections

ArmaGen Addresses the Neurological and Somatic Symptoms in Lysosomal Storage Diseases





AGT-181-101 Proof of Concept Trial Outline in Pediatric MPS I Patients



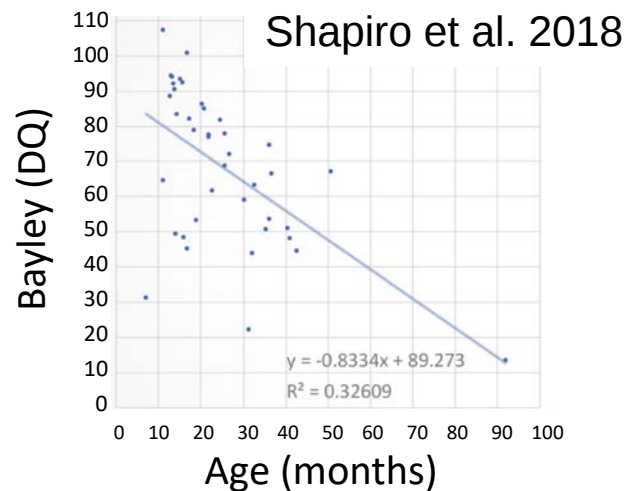
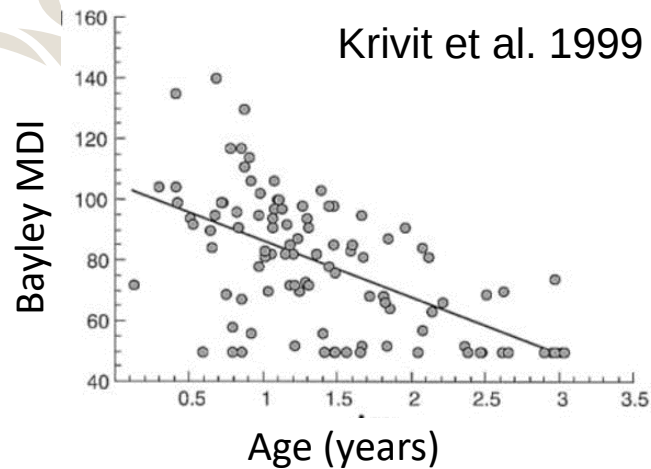
- Pediatric MPS I patients who had been on laronidase were immediately switched to AGT-181 and treated with weekly infusions of 1, 3 or 6 mg/kg for 6 months.

Endpoints investigated

- Safety and pharmacokinetic properties.
- Age-appropriate neurocognitive testing.
- Total urinary, plasma and CSF GAGs.
- Liver and spleen volume (MRI).
- Growth velocity, shoulder ROM.
- Neuroimaging (MRI and MRI DTI).
- 6MWT, FVC, mean left ventricular mass.

Cognitive Data in Trial AGT-181-101 in Context With The Natural History of MPS I

Natural history

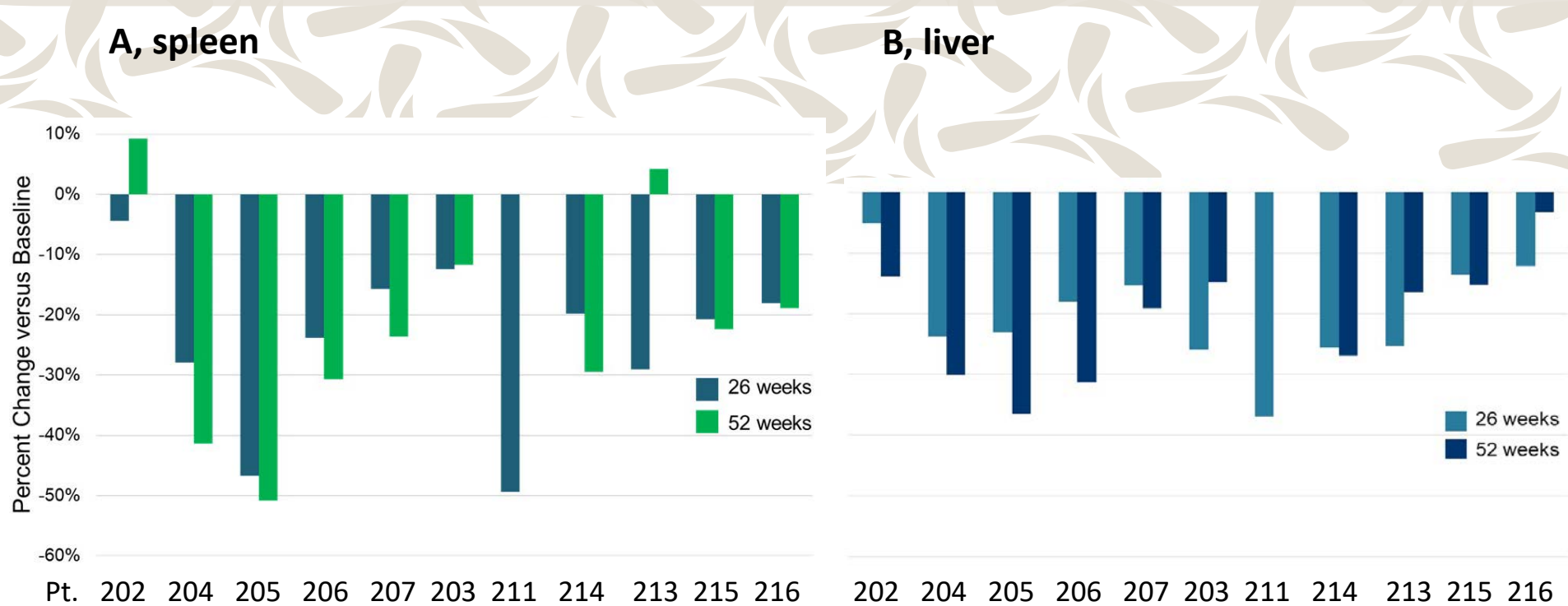


AGT-181-101 compared to Natural history

Study	Patients	DQ Change per year
Krivit et al. 1999	Severe untransplanted MPS I	-20.5
Shapiro et al. 2018	Severe untransplanted MPS I	>-10
AGT-181-101	Severe untransplanted MPS I	-1.2
AGT-181-101	Severe untransplanted MPS I attenuated	+3.4

Conclusion: A dramatic change in stabilization of DQ is observed in AGT-181 treated pediatric patients compared to the natural history of untransplanted untreated MPS IH patients

Unexpected Somatic Differentiation - Changes in Organ Volume



Hepato-splenomegaly is a sensitive marker of somatic disease control

- Improved organ volume control by AGT-181 over laronidase may be an indicator of improved uptake into the lysosome via the M6PR and insulin receptor (dual targeting).

Summary and Conclusions Trial AGT-181-101

Clinical Efficacy

- Treatment of severe MPS I patients with AGT-181 resulted in stabilization of DQ and improvement of neurocognitive function
- Unexpected somatic differentiation versus laronidase was observed: Further reduction in liver and/or spleen size, improvement in shoulder range of motion and growth velocity despite extensive pretreatment with laronidase

Clinical Safety

- AGT-181 has a favorable safety profile and is well tolerated at all doses tested allowing long-term weekly dosing of MPS I patients.

Conclusions

- Data supports advancement into Phase 3

In Preparation of Phase 3 Design

ArmaGen approached both FDA and EMA for regulatory guidance

- Goal was to seek advice on planning acceptable Phase 3 design for global study
- Specific areas of focus:
 - **Primary versus secondary endpoints** – which is which to demonstrate somatic and neurocognitive efficacy?
 - **Statistics:** how to calculate powering of a study when the phase 2 trial was uncontrolled and the effect size of the endpoint tool is unknown?
 - **Somatic endpoints:** What endpoint to choose if the target population is too impaired to conduct or does not even understand the accepted test? (6 minutes walk tests or lung capacity test)
 - **Use of biomarker (uGAG):** Can we use a biomarker response (for which we know the effect size) to at least calculate appropriate powering of the study? Approval would still be on other somatic and neurocognitive endpoints

Feedback from FDA and EMA to AGT-181 Clinical Development

Lack of consistency between FDA and EMA

FDA

- **Endpoints:** FDA encourages ArmaGen to use cognitive primary and somatic secondary endpoint
- **Statistics:** FDA expects efficacy to be demonstrated beyond reasonable doubt including appropriate powering of trial
- **Biomarker:** FDA does not accept uGAGs as their clinical impact on disease amelioration is unclear
- **Organomegaly:** FDA does not consider organomegaly as a clinically meaningful endpoint
- FDA suggested 2-year trial with interim analysis after one year with potential early termination or enrollment of more patients
- FDA recommended to seek input from EMA

EMA

- **Endpoints:** Instead of definition of a primary and secondary endpoint the EMA proposes to include a range of clinically meaningful endpoints and put into hierarchical order.
- **Statistics:** As long as endpoints all point in same direction, EMA less concerned about statistical power
- **Biomarker:** Use of uGAG control for statistical power calculation thereby becomes obsolete
- **Organomegaly:** EMA considers organomegaly as clinically meaningful somatic endpoint
- EMA encourages to enroll as many patients from Europe as possible and to be liberal on inclusion criteria regarding age and level of cognitive impairment



How a Rare Disease Center of Excellence Could Help

General areas of assistance:

- Provide context to FDA through deeper understanding of rare diseases.
- Coordinate/align positions between EMA and FDA regarding statistical requirements and generally accepted endpoints.
- Determine which requirements would be pre-approval vs post-approval.
- Clinical trial design. Relief/accommodations in order to accelerate rare disease development.

Act as catalyst to modernize CMC position in regards to biologics requirements to assist in commercialization.

- CMC represents one of the most expensive components of biologics development
- Commercial scale-up beyond GMP batch(es) for the clinical trial may not be required due to modest drug supply demand
- Sponsor may propose tighter specifications than usual for GMP material and work with FDA to develop criteria that define reasonable process robustness after NDA approval
- Use a pre-IND meeting to discuss an accelerated approval plan based on clinical data and CMC concessions including approval based on clinical GMP process
- Consider enhancement of CMC process robustness as post-approval commitment

Additional Comments

- Consider real world implications of regulatory decisions
- Venture-backed companies live and die based on FDA minutes
- “Successful” or “positive” meeting with FDA can have direct impact on whether or not a program is advanced
- Investors look for risk in any regulatory communications
- Greater insight into rare disease and any accommodations provided may enhance quality of final minutes

