Tralesinidase alfa (AX 250) enzyme replacement therapy for Sanfilippo Syndrome Type B

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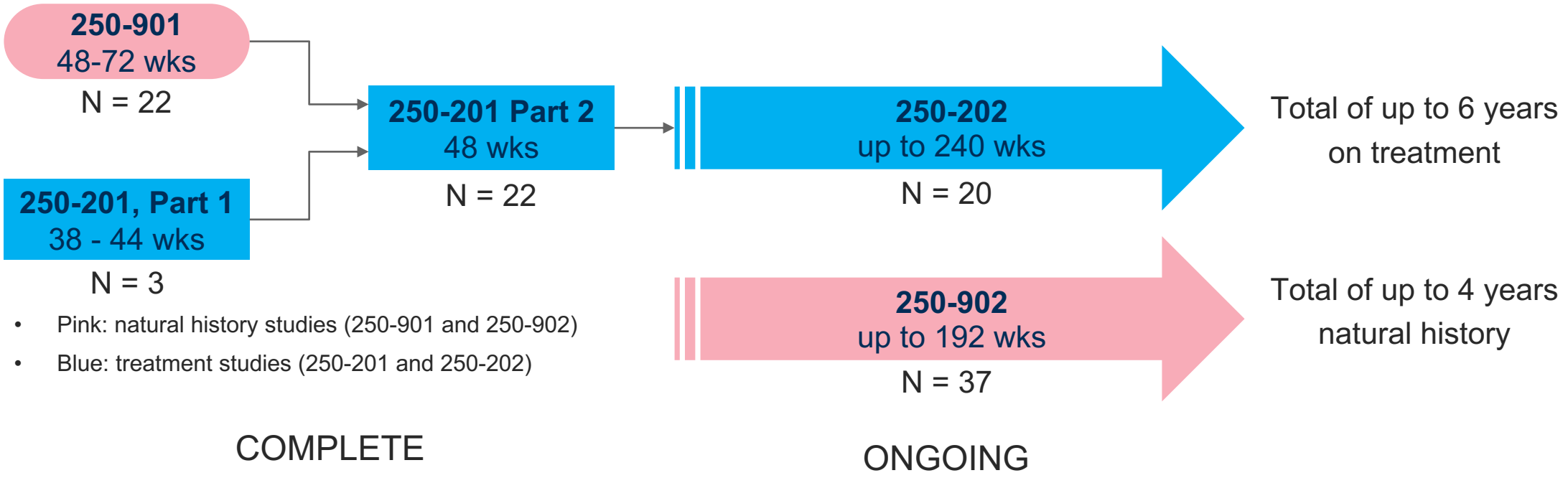
Disclosures

- This study was funded by BioMarin Pharmaceutical and Allievex Corporation

- Nicole Muschol has the following financial relationships to disclose:
  - Consultant for BioMarin, Lysogene, Sanofi/Genzyme, Shire/Takeda, Sobi
  - Grant/research support from BioMarin, Sanofi/Genzyme, Shire/Takeda
  - Honoraria and travel grants from Alexion, Amicus, BioMarin, Chiesi, Sanofi/Genzyme, Shire/Takeda

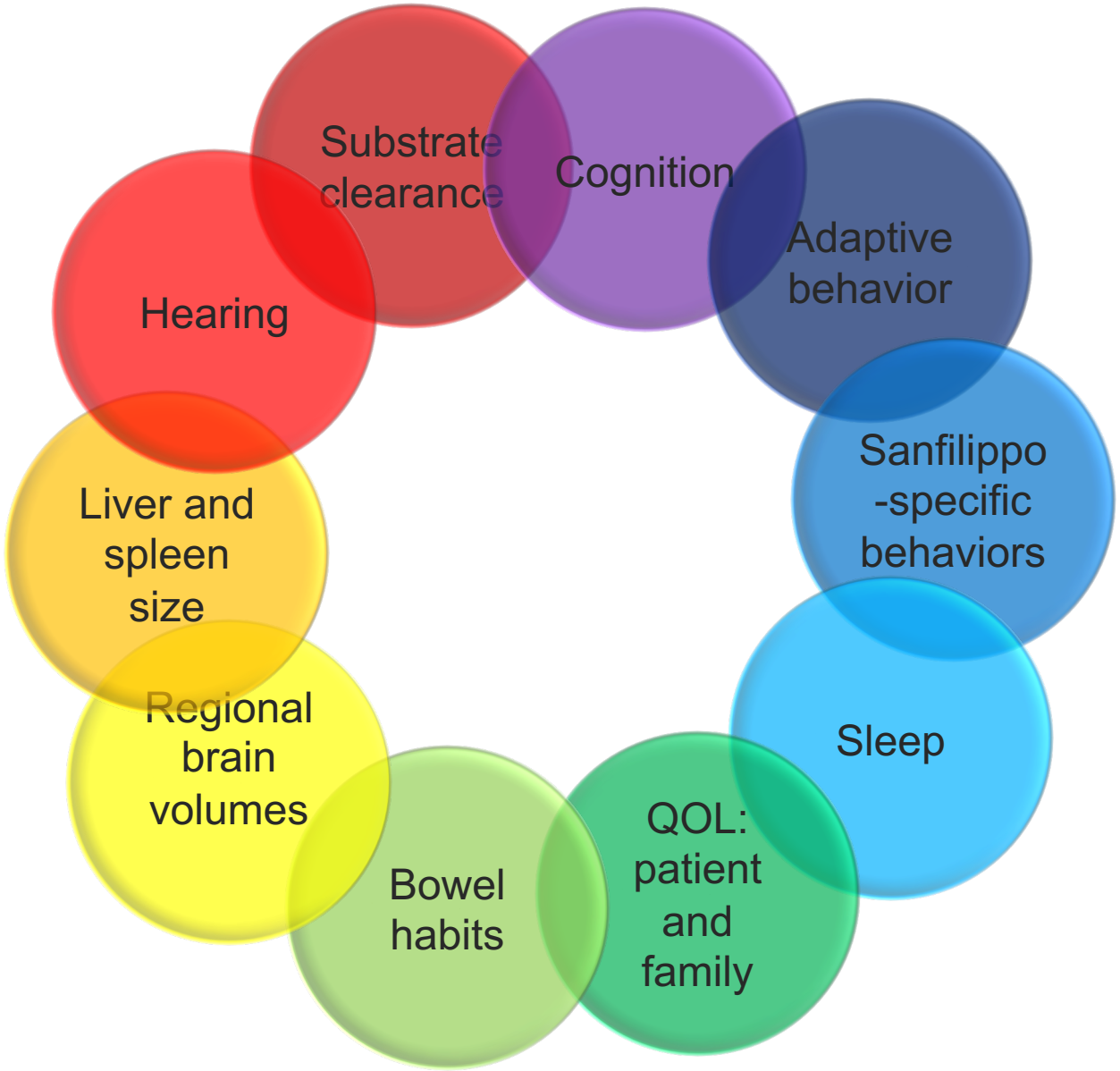
- This presentation shares information about an investigational drug which has not yet been approved

Tralesinidase alfa clinical program studies and design



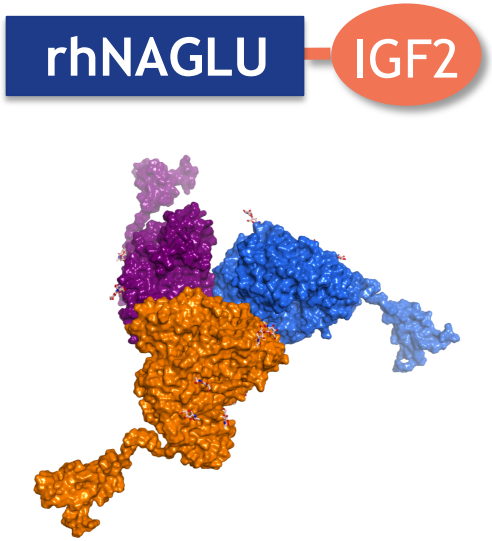
- Largest, longest-running, most comprehensive Sanfilippo B natural history and treatment studies to date
- Clinical program allows between- and within-subjects comparisons to study efficacy
  - Between-subjects: up to 4 years
  - Within-subjects: 48 weeks (1 year)

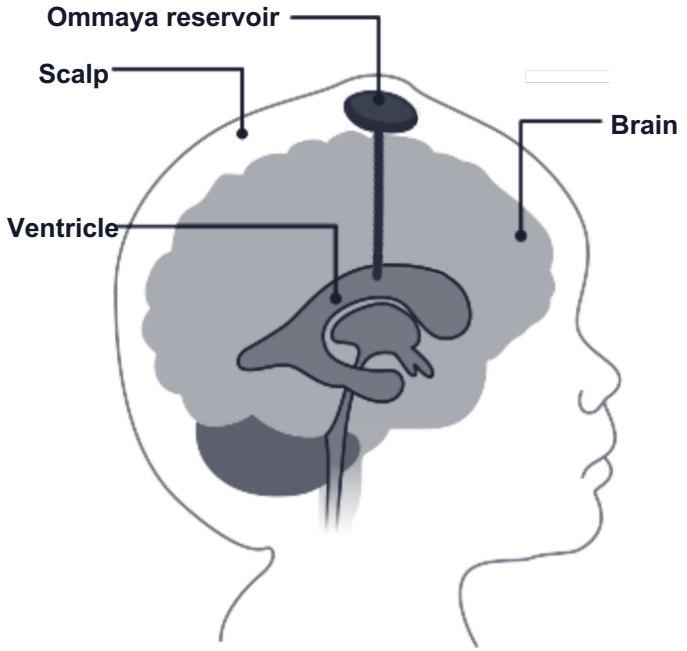
Natural history and treatment data on multiple disease-relevant endpoints



- Selection of clinical endpoints reflects caregiver, advocacy group and expert clinician input
- Multidomain approach accounts for heterogeneous nature of disease symptoms

Intracerebroventricular administration of tralesinidase alfa ERT



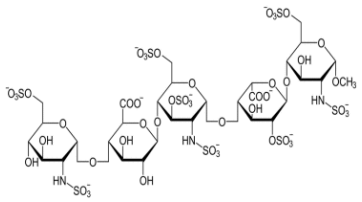


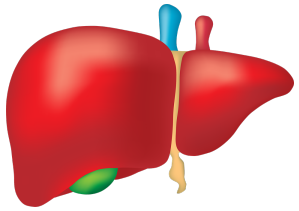
- Novel fusion of recombinant human alpha-N-acetylglucosaminidase (rhNAGLU) and insulin-like growth factor 2 (IGF2)
- IGF2 tag enhances cellular uptake and lysosomal targeting while minimizing off-target effects

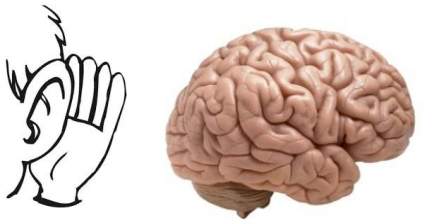
- Administered via Ommaya reservoir – technique used for over 50 years
- Bypasses the blood-brain barrier
- Infusion time 5-10 minutes
- 300 mg ICV weekly

Treatment goals and expected sequence of events

- Effective treatments will slow (good), stabilize (better) or reverse (best) disease symptom progression







Biochemical evidence of drug activity (HS-NRE clearance)

Substrate clearance from tissues (decrease in visceral organ size)

Physiological and structural changes in target organs (improvements in hearing, brain atrophy)

Clinical benefits (cognition, behavior, sleep, QoL)

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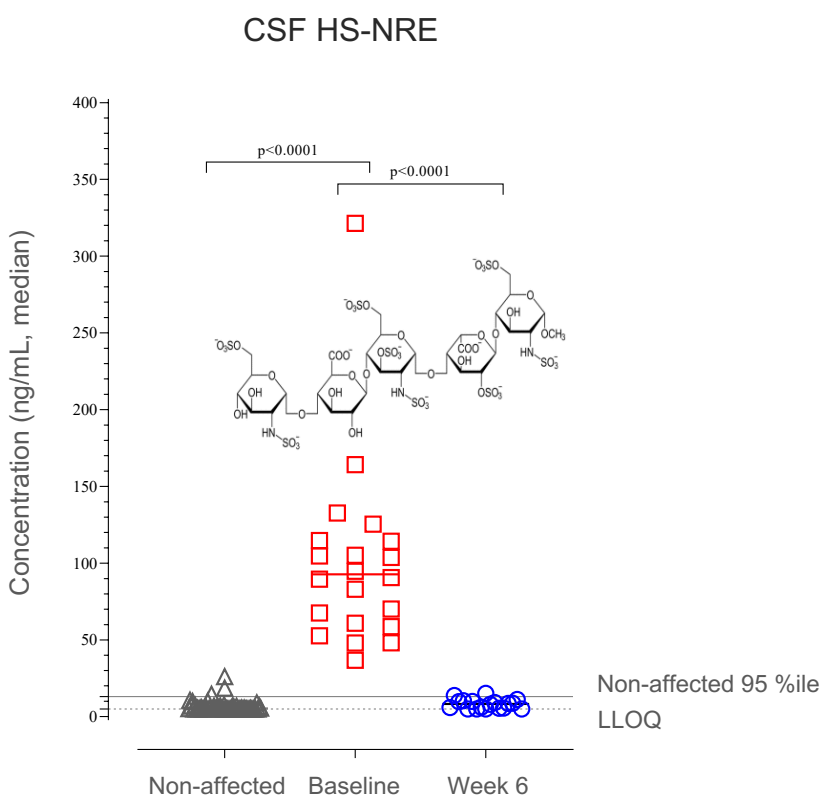
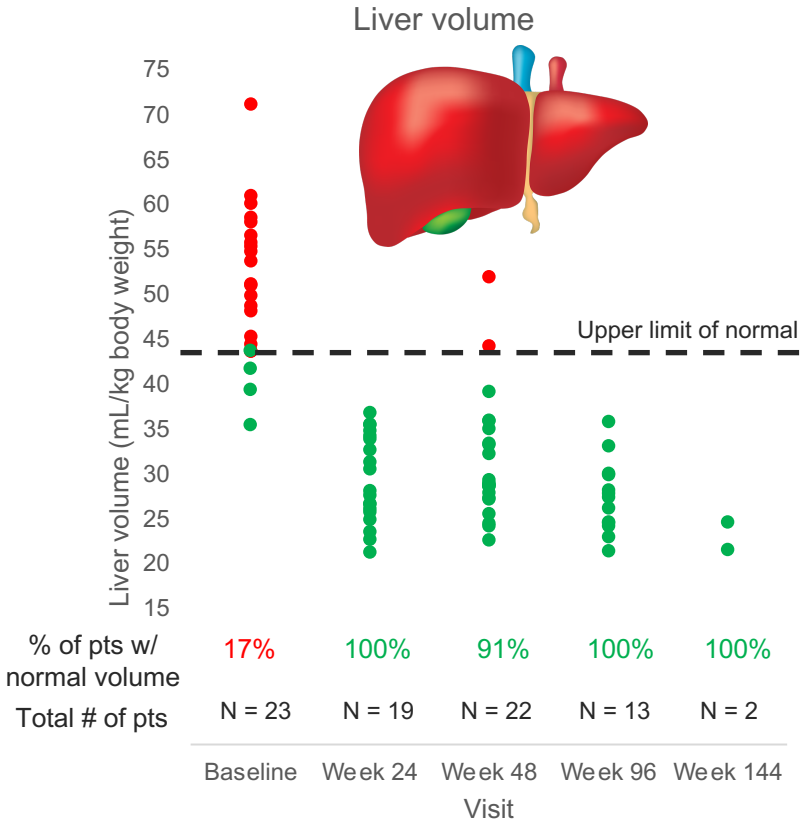
Tralesinidase alfa treatment normalizes HS-NRE and liver size

Biochemical evidence of drug activity (HS-NRE clearance)

Substrate clearance from tissues (decrease in visceral organ size)



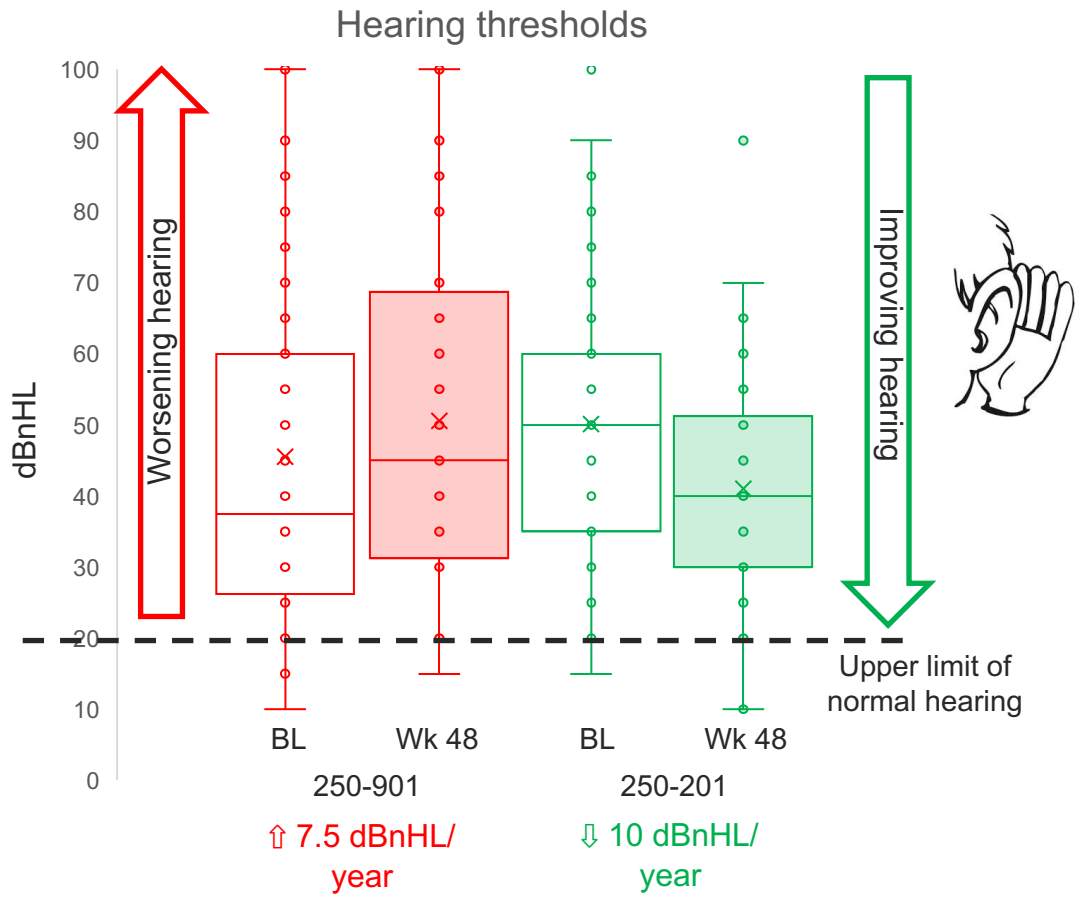
Normalization of CSF HS-NRE is prerequisite for and likely predictive of maximal clinical benefits



ICV tralesinidase alfa clears HS-NRE throughout the body

HS-NRE normalization predicts improved hearing

Physiological and structural changes in target organs (improvements in hearing, brain atrophy)



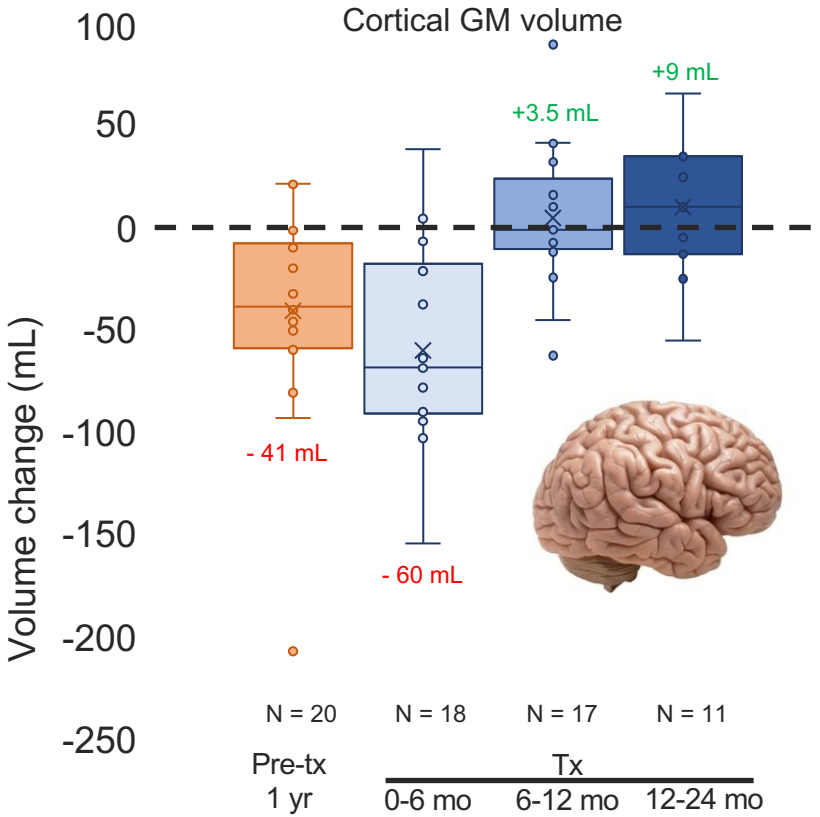
- 1 of 2 patients no longer uses hearing aids

Hearing improves with treatment

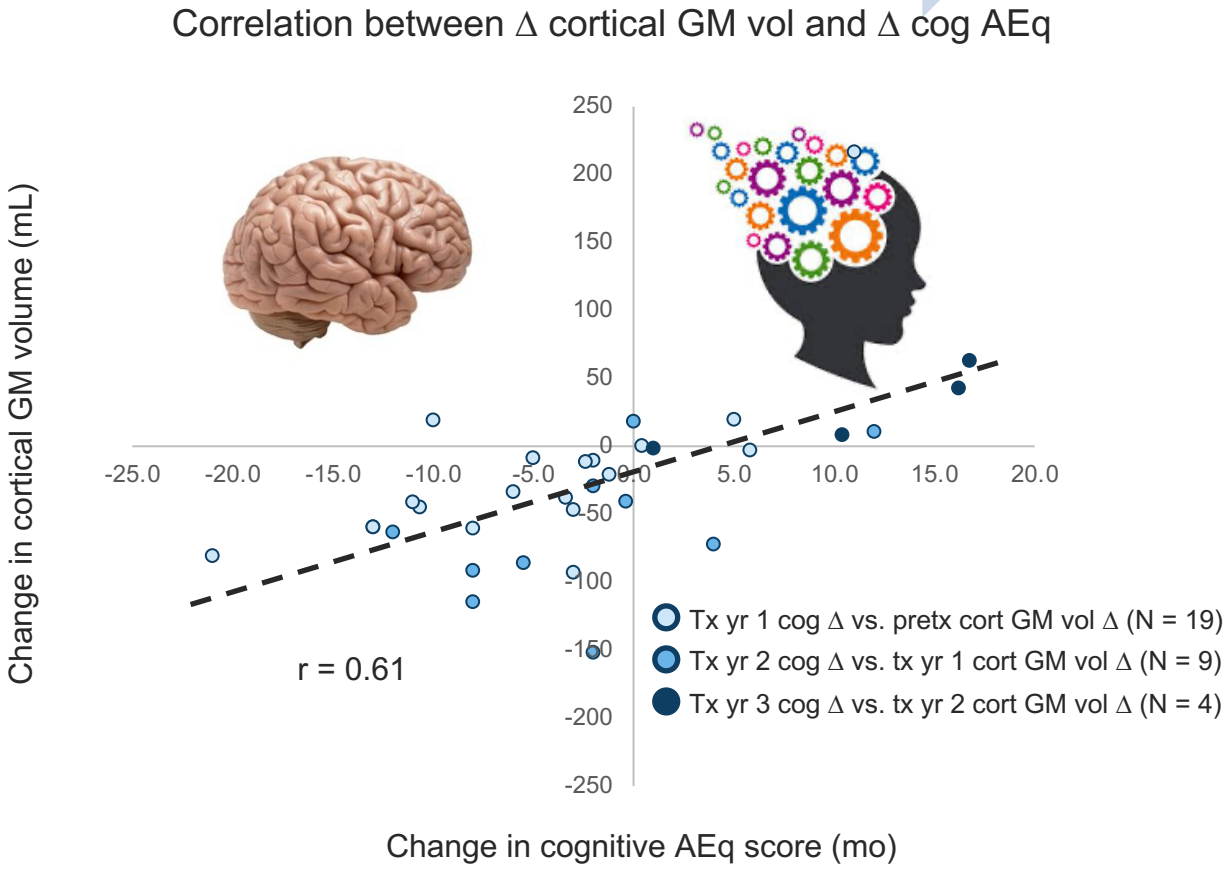
HS-NRE normalization predicts increases in brain volume and improved cognition

Physiological and structural changes in target organs (improvements in hearing, brain atrophy)

Clinical benefits (cognition, behavior, sleep, QoL)



Increase in brain volume is unique and suggests reversal of underlying disease pathology

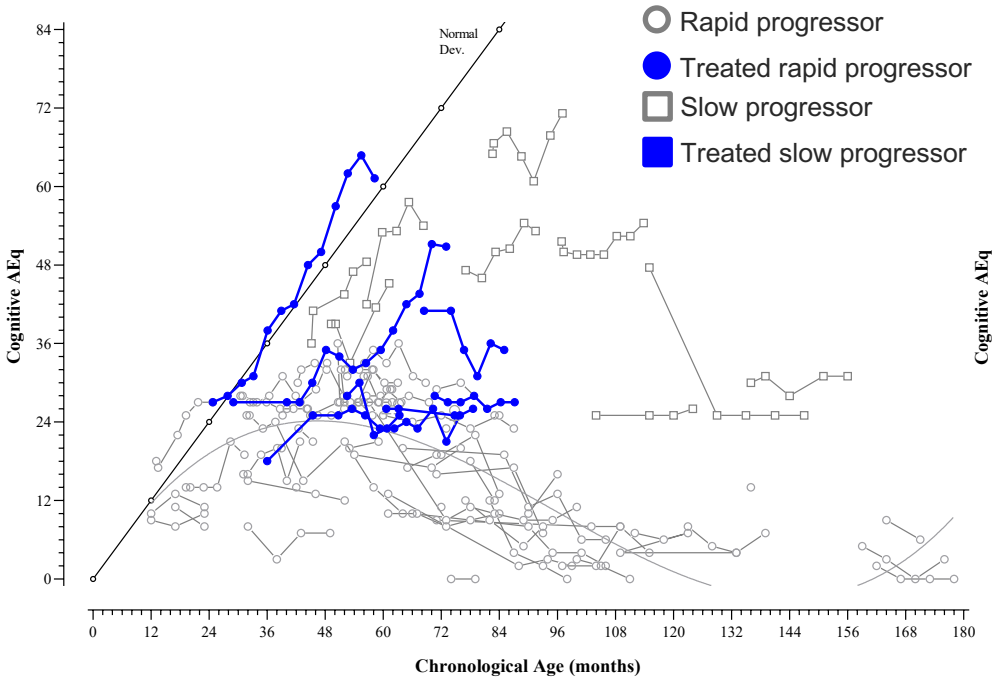


- **Changes in cortical volume predict changes in cognition**
- **Clinical improvement takes time (2 – 3 years)**

Cognitive function improves or remains stable with treatment

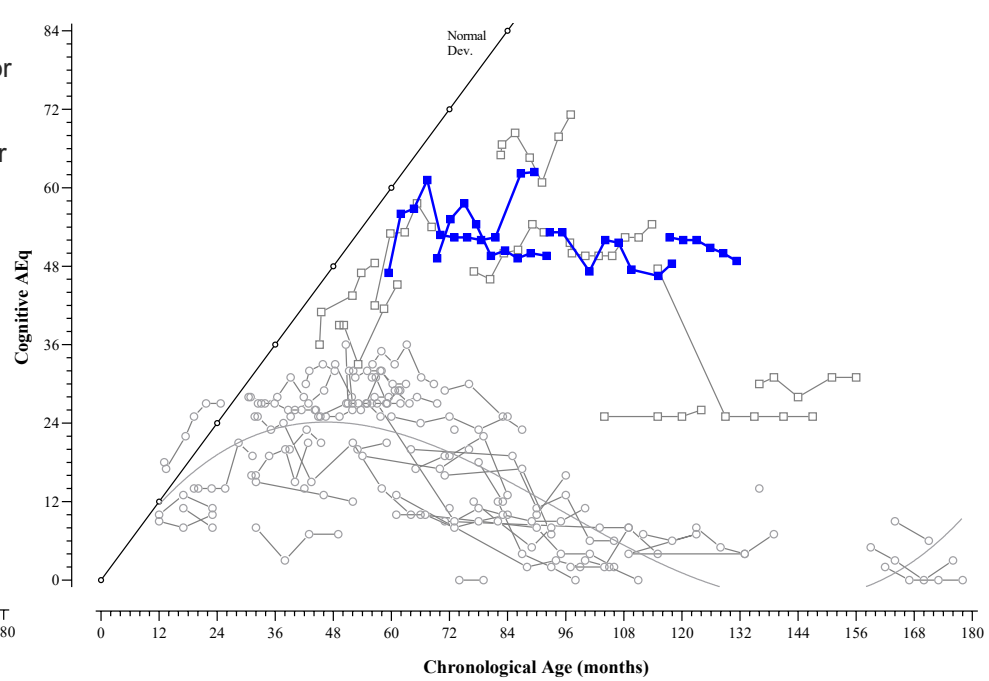
Clinical benefits (cognition, behavior, sleep, QoL)

Rapid progressors



39% (7/18) of treated rapid progressors are stable or outperform predicted natural history trajectory

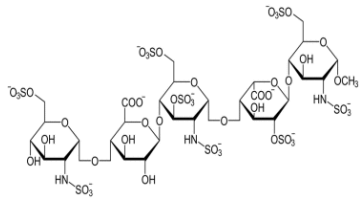
Slow progressors

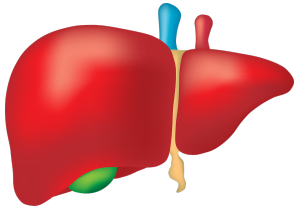


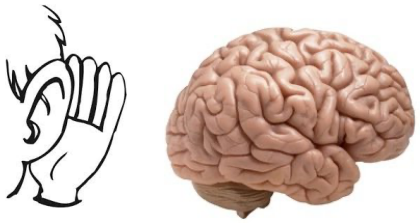
100% (4/4) of slow progressors have stable cognitive function on treatment

- See poster #168 for additional treatment data

Tralesindase alfa treatment summary







HS metabolism restored HS-NRE eliminated	Hepatomegaly resolved	Hearing improvement Brain atrophy stabilized	Clinical benefits on cognition, behavior, sleep and other Sanfilippo B symptoms
6 weeks	24 weeks	48 weeks	96+ weeks

Time on treatment

Tralesindase alfa treatment drives improvement or stability of function across domains

Tralesinidase alfa is generally safe and well-tolerated

Combined Safety Profile	
Safety population	22
Total doses administered	>2311 (~96% of scheduled)
Longest exposure to date	>4 years
Drug-related AEs	<10% of doses ~94% CTCAE grade 1 or 2 Most common (68% of total): fever, headache, vomiting
Drug-related SAEs (15 total)	<1% of doses CTCAE grade 2 or 3 Most common (53% of total): CSF pleocytosis
Device-related SAEs (16 total)	<1% of doses CTCAE grade 1 – 3 Most common (69% of total): infection, malfunction
Treatment discontinuations (6 total)	AE-related (4), withdrawal of consent (2)

Data as of November 5, 2020

AEs and SAEs are consistent with mode of administration and ERTs in general

Thank you to PIs, site staff, participating families and patients!

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