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

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Allievex thanks PIs, site staff, participating families and patients!

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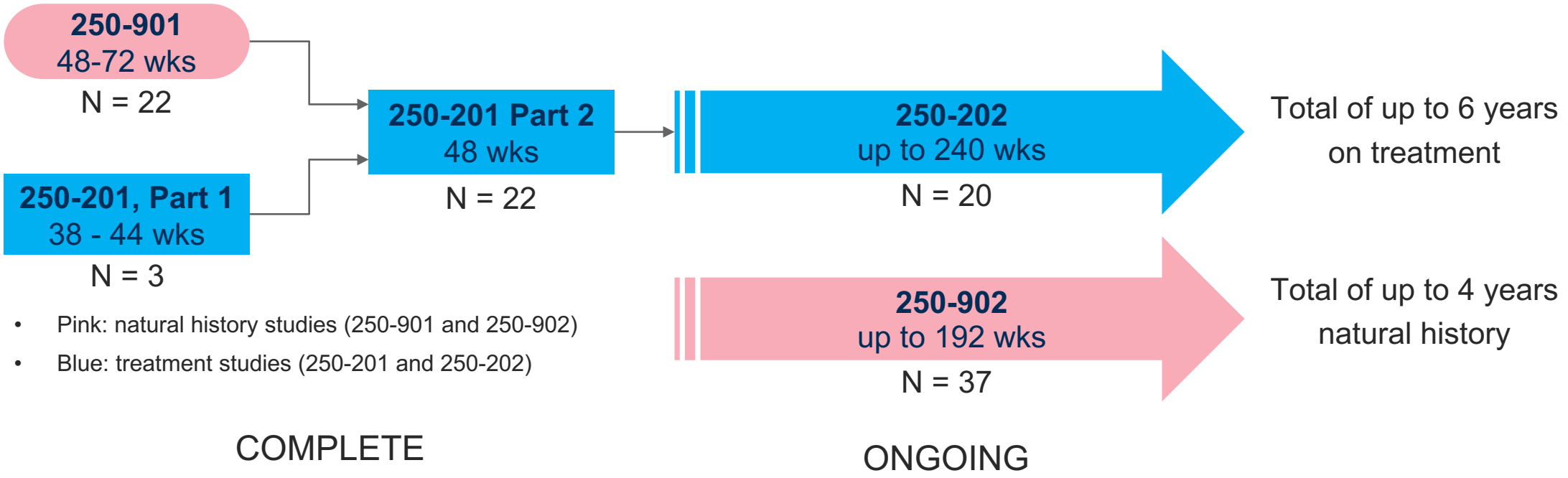
Disclosures

- This study was funded by BioMarin Pharmaceutical and Allievex Corporation

- Personal disclosures
  - I receive monetary and stock compensation from Allievex Corporation in my capacity as Chief Medical Officer
  - My wife is an employee of Ultragenyx Pharmaceutical
  - We own stock in BioMarin Pharmaceutical and Ultragenyx Pharmaceutical

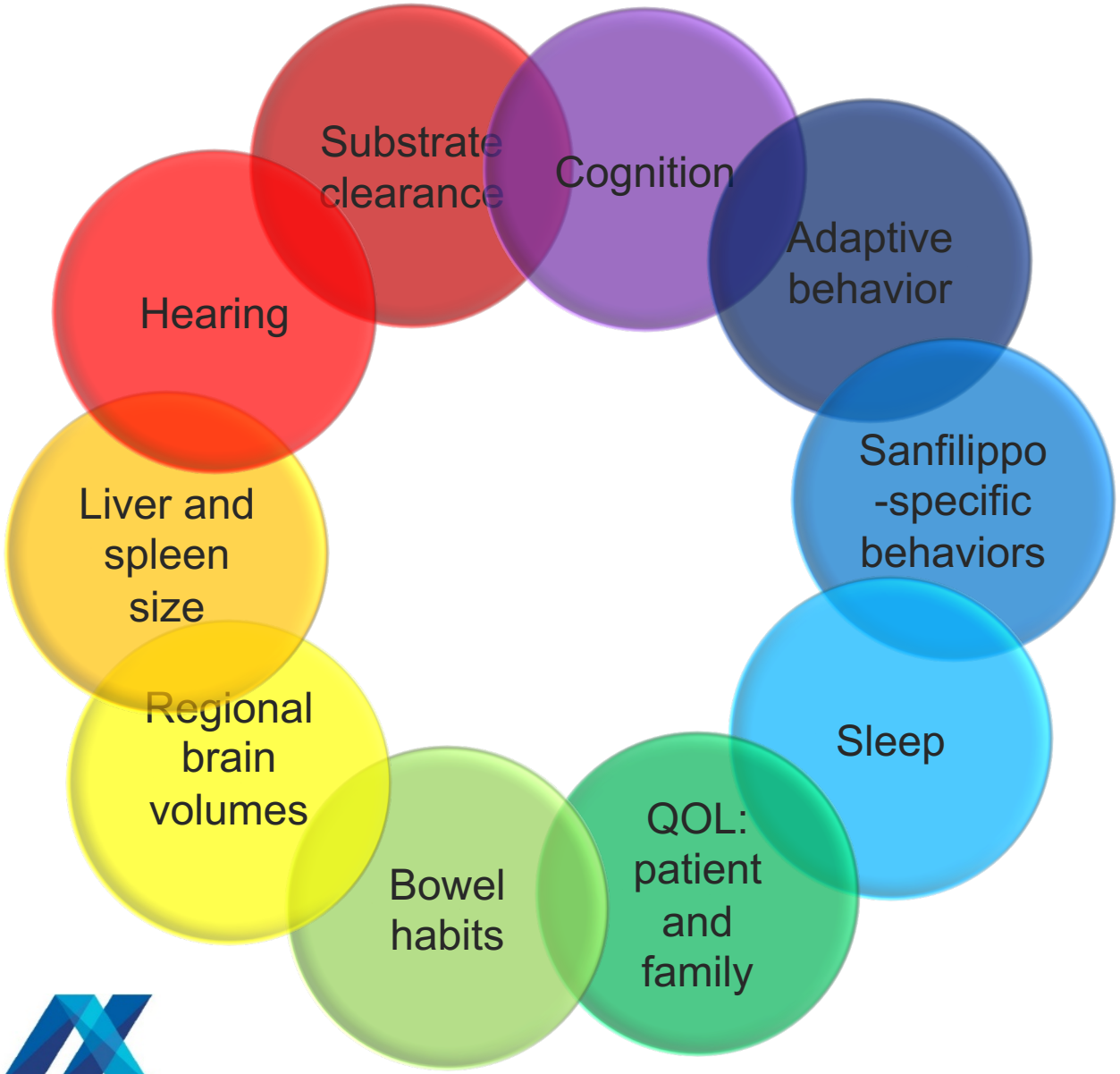
- This presentation shares information about an investigational drug which has not yet been approved

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: 144 weeks (up to 4 years)
  - Within-subjects: 48 weeks (1 year)

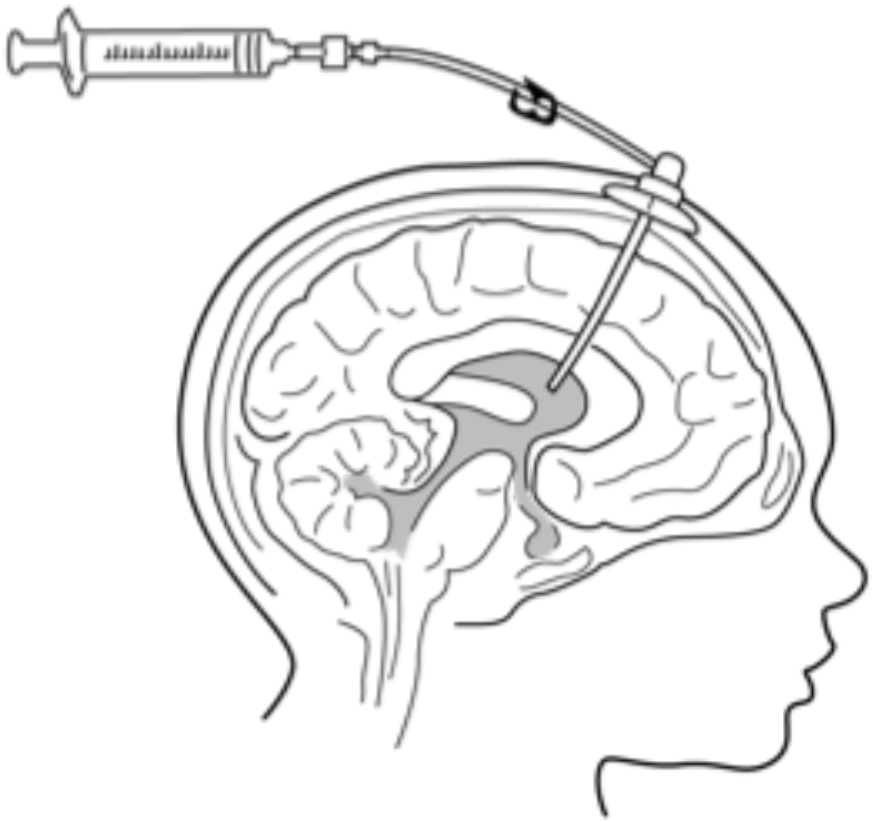
Collecting data on multiple disease-relevant endpoints



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

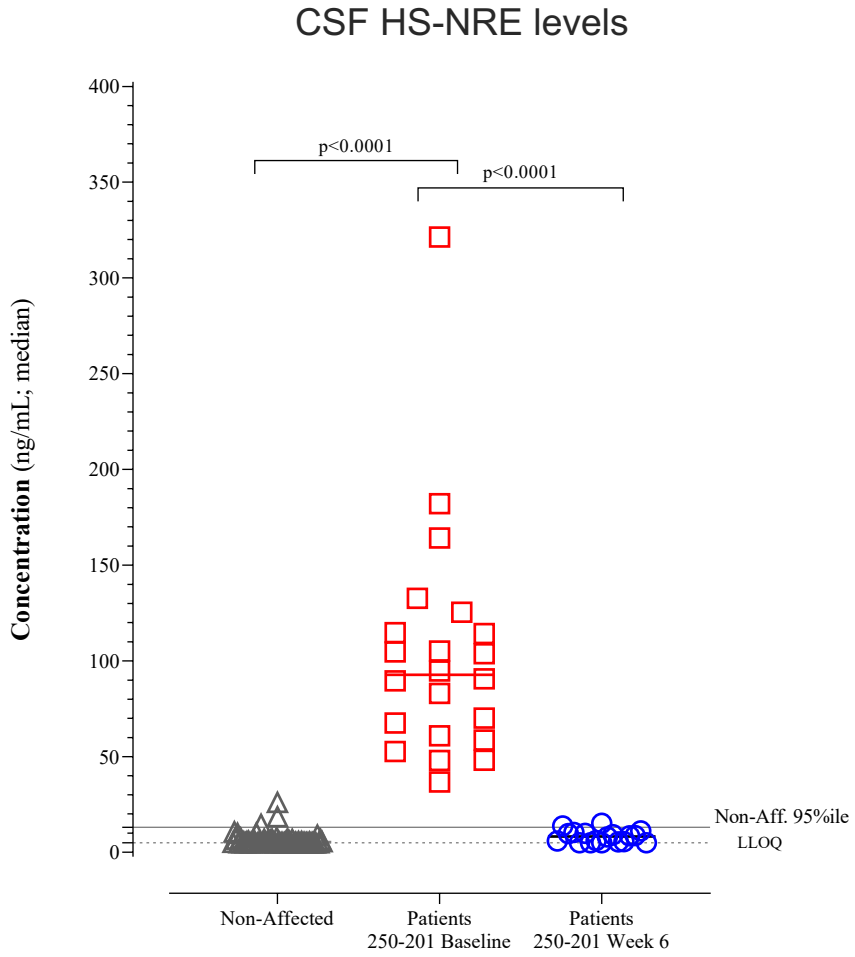
Intracerebroventricular administration of tralesinidase alfa

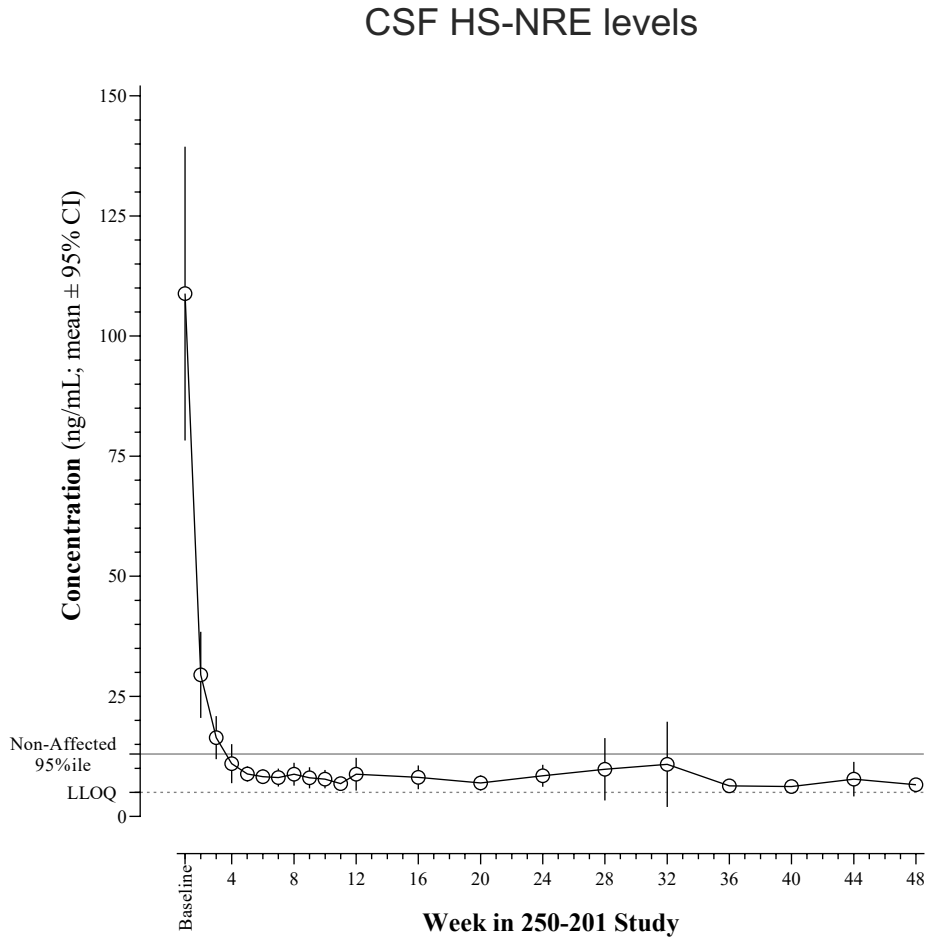
- Fusion protein of recombinant human NAGLU and human insulin-like growth factor 2 (rhNAGLU-IGF2)
- Bypasses the blood-brain barrier
- Infusion time 5-10 minutes
- 300 mg ICV weekly



Treatment normalizes CSF HS-NRE, the substrate that accumulates in Sanfilippo B

Within-subjects comparison

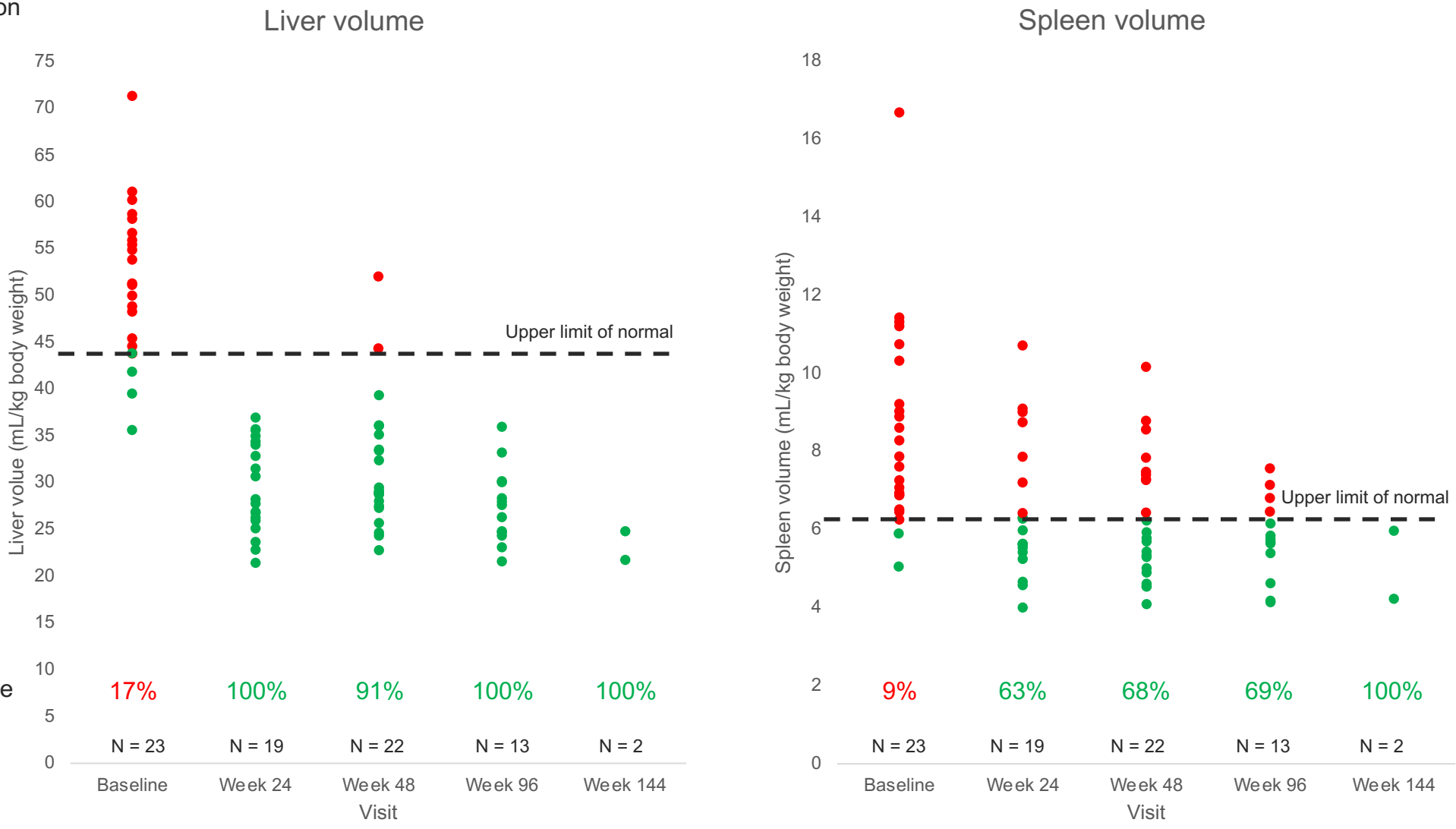




Normalization of CSF HS-NRE (< 95%ile of non-affected controls) is prerequisite for and likely predictive of maximal clinical benefits

Treatment normalizes liver and spleen volumes as assessed by MRI

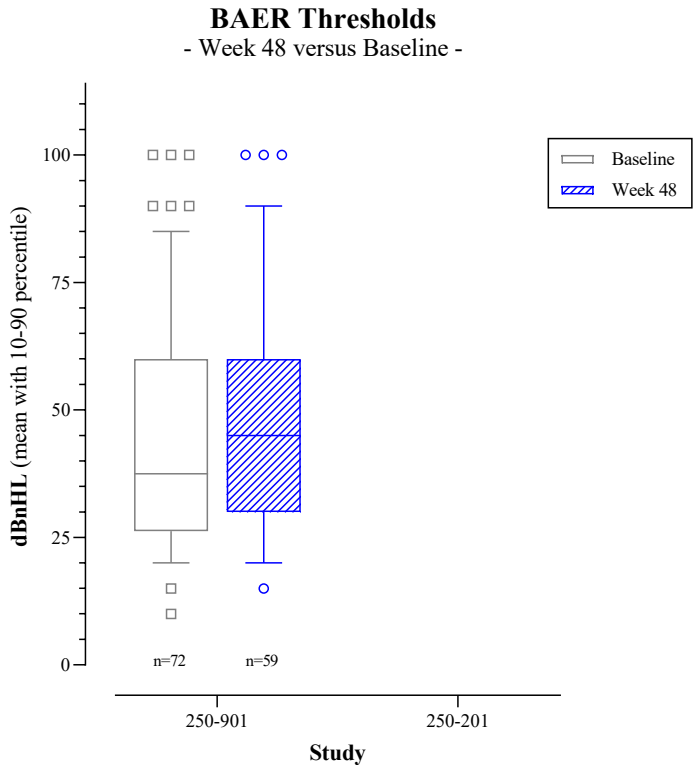
Within-subjects comparison



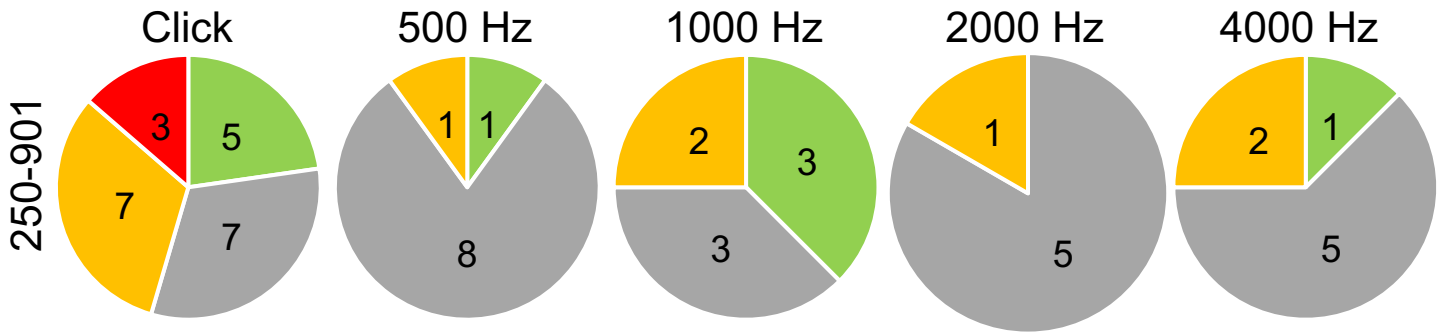
ICV tralesinidase alfa clears HS-NRE throughout the body

Hearing worsens over time in Sanfilippo B patients

Within-subjects comparison



250-901: thresholds worsen by 7.5 dBnHL/year



Worse by 2 classes | Worse by 1 class | No change | Better by 1 class | Better by 2 classes

Clinical hearing classifications

Normal: ≤20 dBnHL

Mild: >20 and ≤40 dBnHL

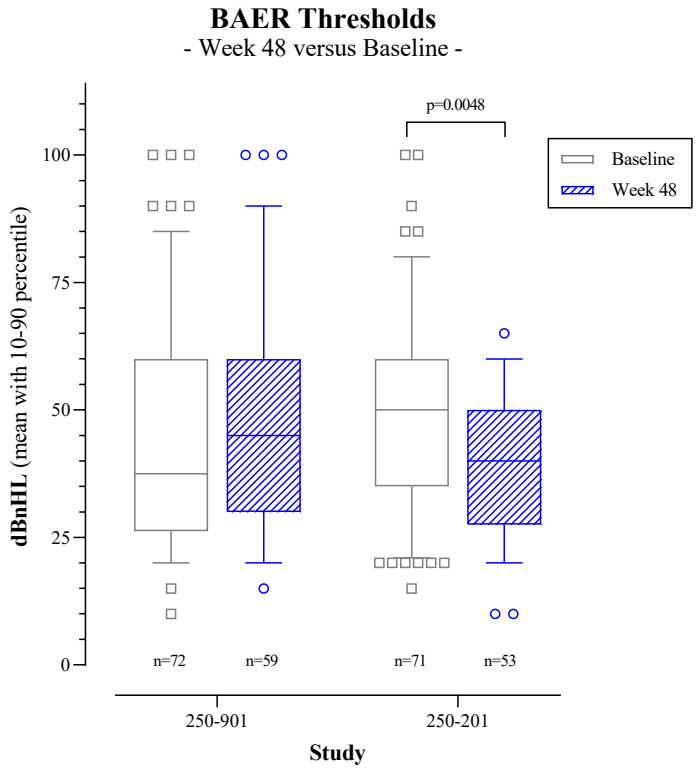
Moderate: >40 and ≤60 dBnHL

Severe: >60 and ≤80 dBnHL

Profound: >80 dBnHL

Hearing improves on treatment

Within-subjects comparison



250-901: thresholds worsen by 7.5 dBnHL/year

250-201: thresholds improve by 10 dBnHL/year

Clinical hearing classifications

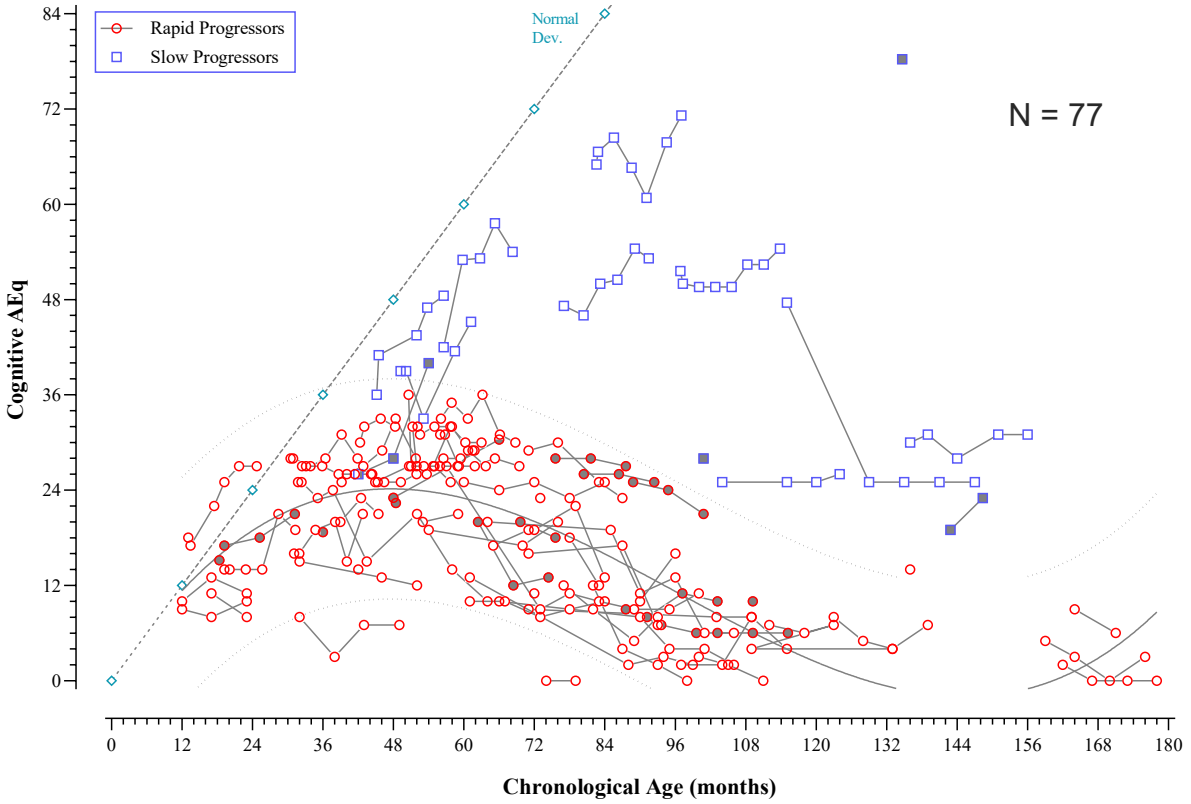
Normal:	≤20 dBnHL
Mild:	>20 and ≤40 dBnHL
Moderate:	>40 and ≤60 dBnHL
Severe:	>60 and ≤80 dBnHL
Profound:	>80 dBnHL

- 1 of 2 patients who started treatment with hearing aids no longer uses them

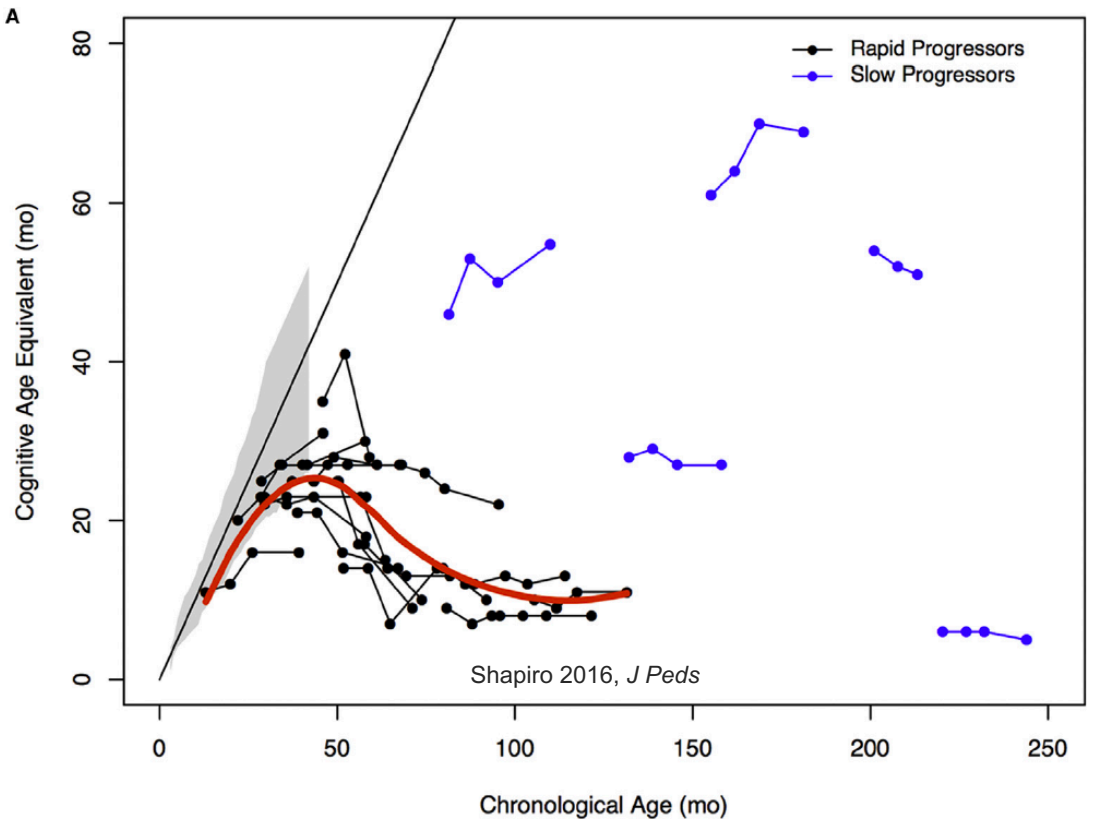
Hearing worsens in natural history but improves with treatment

Cognitive function declines over time in Sanfilippo patients

Sanfilippo B



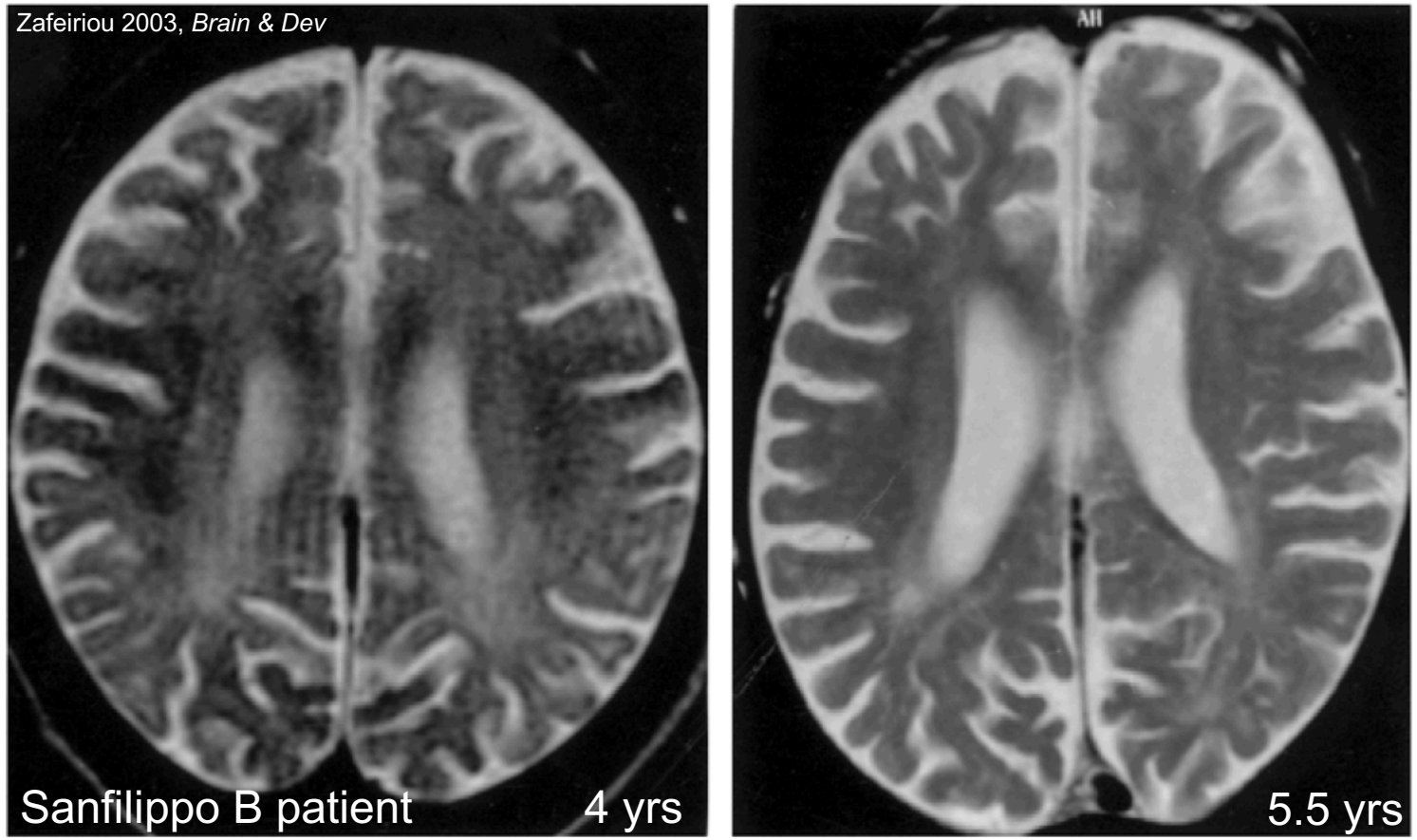
Sanfilippo A



Open circles and squares: 250-901 and 250-902
Closed circles and squares: Valstar 2011, *Orphanet J Rare* Dis; Whitley 2018, *J* Peds; Zafeiriou 2003, *Brain & Dev*

Natural history predicts progressive cognitive decline over time

Loss of brain mass is linked to loss of cognitive function

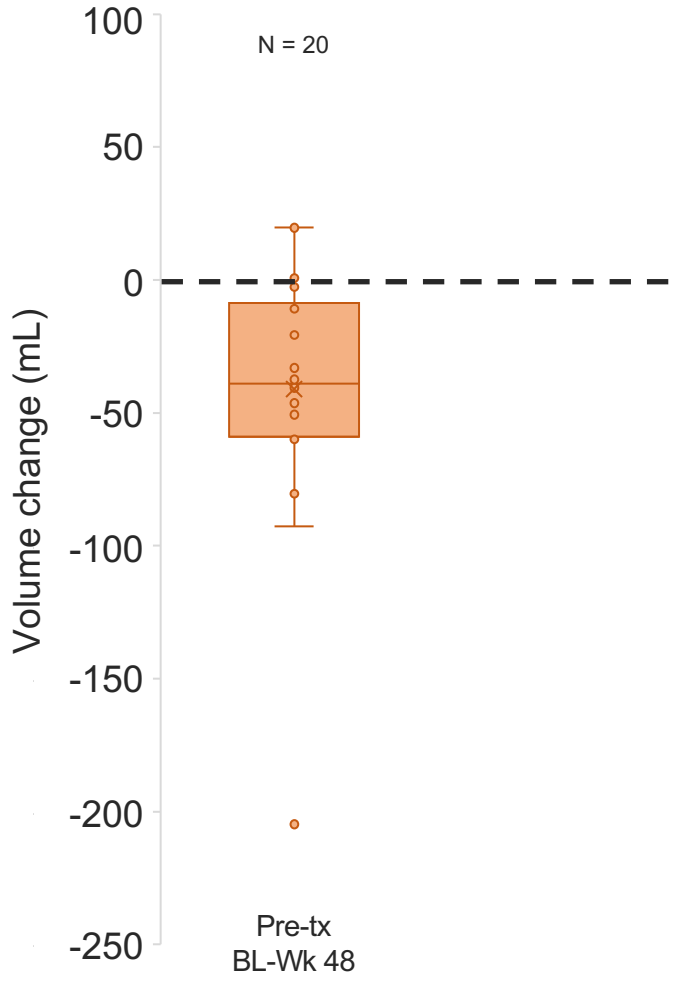


Cortical gray matter volume loss per year

- Sanfilippo A patients: ~41 mL (*Shapiro 2016*)
- Sanfilippo B patients: ~33 mL (*Whitley 2018*)

Sanfilippo B patients lose brain mass over time

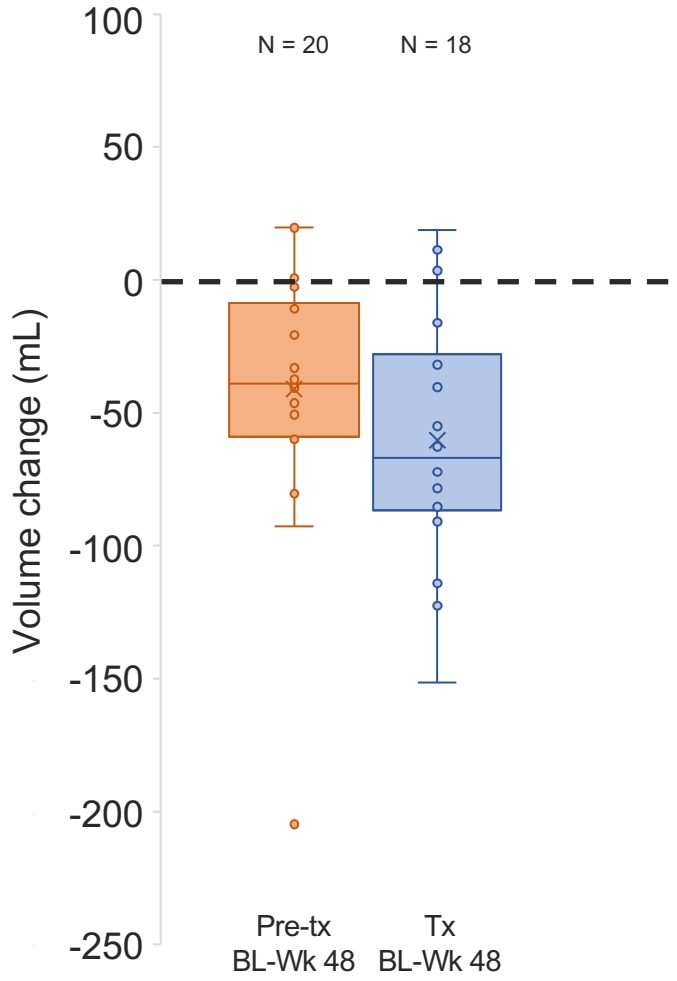
Within-subjects comparison



- Natural history
  - Baseline to Week 48 (1 yr) – subjects lose 41 mL of cortical GM volume

Cortical gray matter volume loss accelerates in the 6 months of treatment

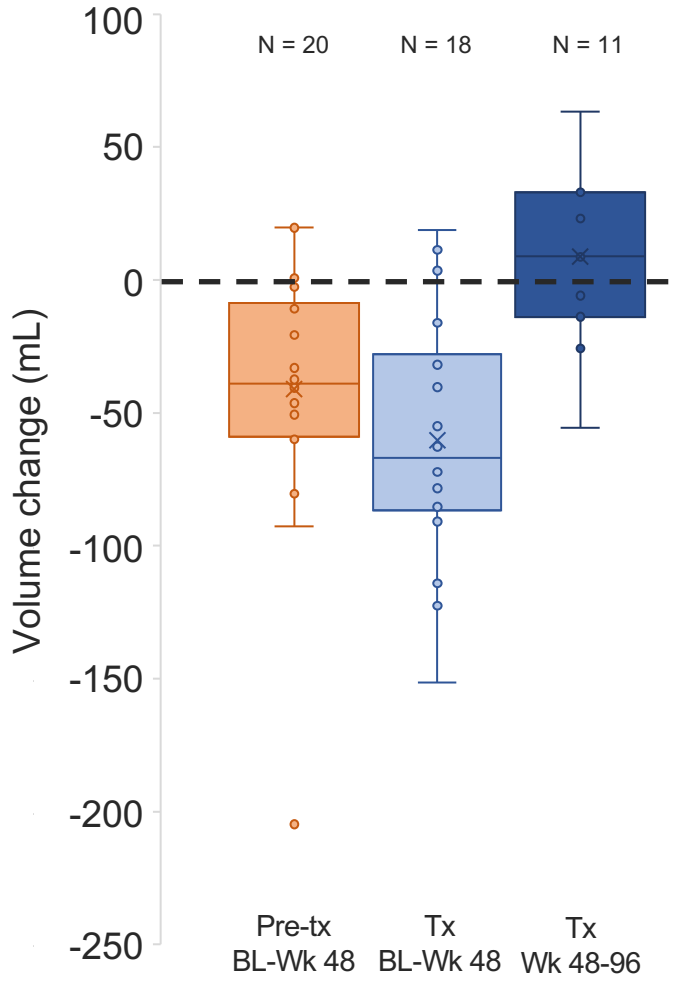
Within-subjects comparison



- Natural history
  - Baseline to Week 48 (1 yr) – subjects lose 41 mL of cortical GM volume
- Treatment
  - First 24 weeks (6 mo) of treatment – loss accelerates to ~60 mL
    - Likely represents rapid HS-NRE clearance from the brain
  - Second 24 weeks (6 mo) of treatment – gain of ~3.5 mL

Cortical gray matter volume increases in the second year of treatment

Within-subjects comparison

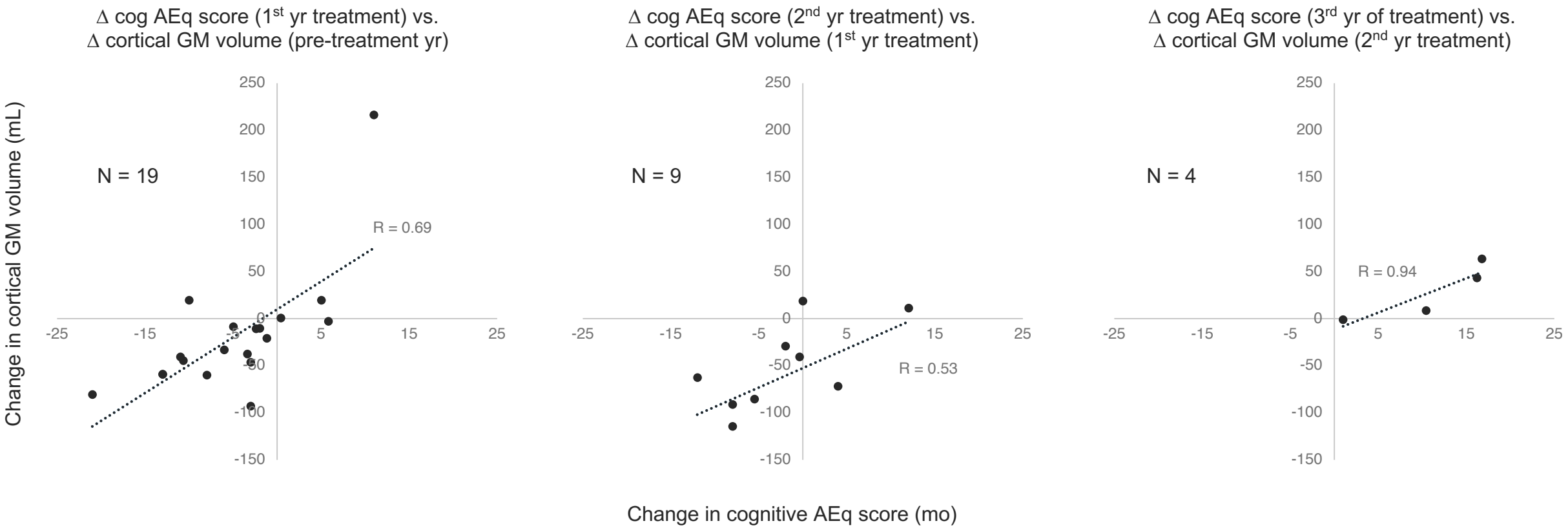


- Natural history
  - Baseline to Week 48 (1 yr) – subjects lose 41 mL of cortical GM volume
- Treatment
  - First 24 weeks (6 mo) of treatment – loss accelerates to ~60 mL
    - Likely represents rapid HS-NRE clearance from the brain
  - Second 24 weeks (6 mo) of treatment – gain of ~3.5 mL
  - Weeks 48 – 96 (2nd yr) of treatment – gain of ~9 mL

Treatment-related increase in brain volume in a neurodegenerative disease is unique and suggests reversal of underlying disease pathology

Cortical gray matter volume correlates with cognitive function

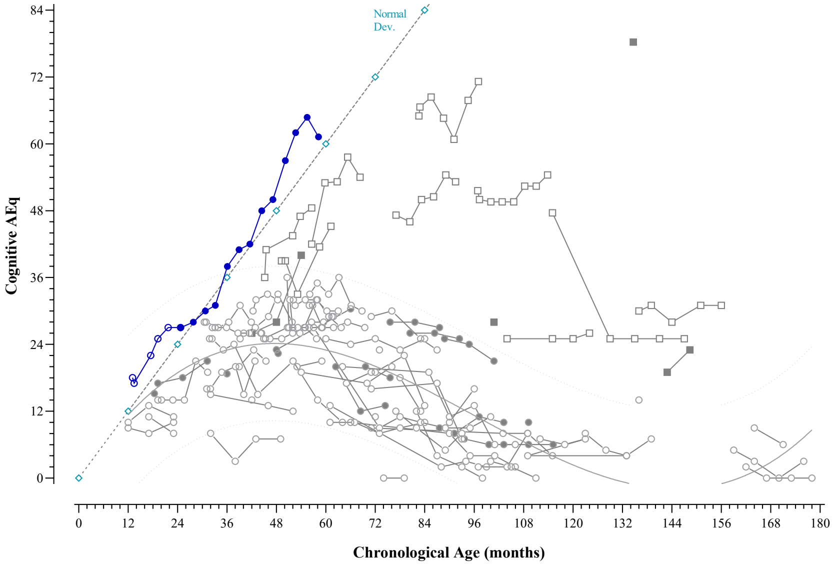
Within-subjects comparison

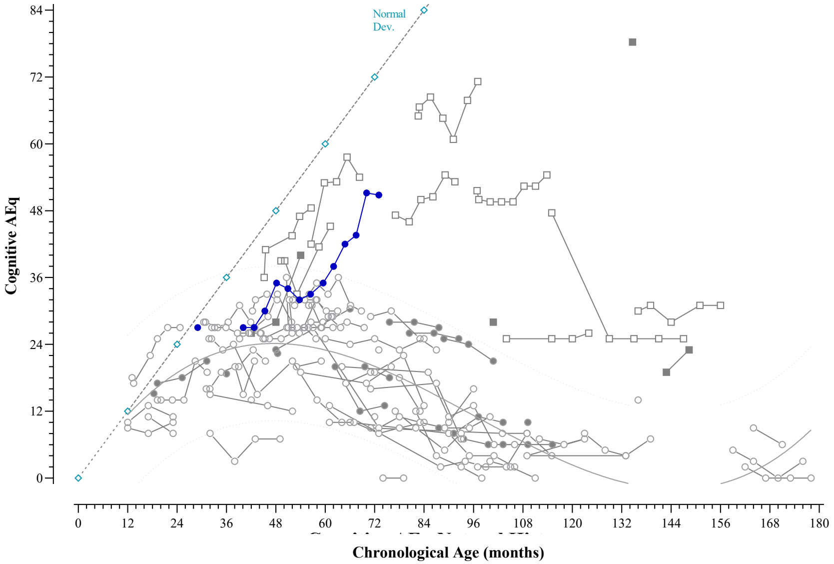


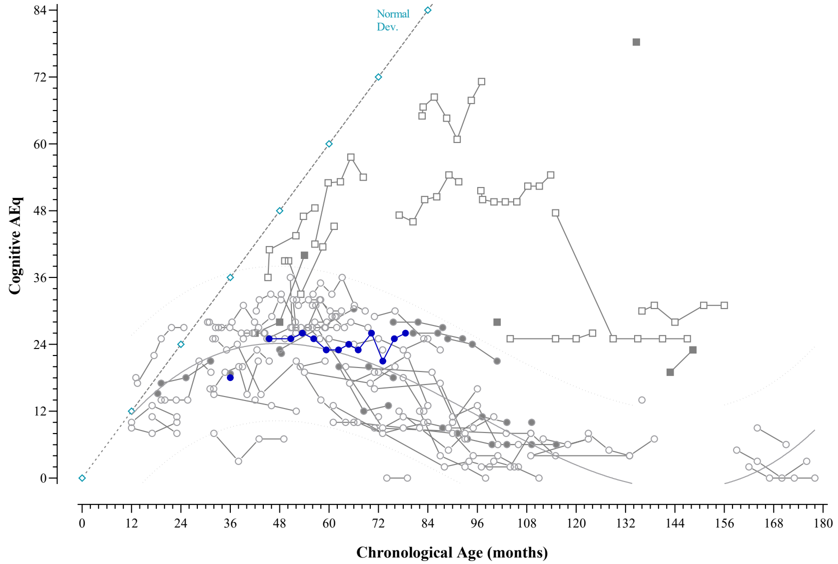
- **Changes in cortical volume predict subsequent changes in cognition**
- Delay between brain volume and cognition changes – **clinical improvement takes time**

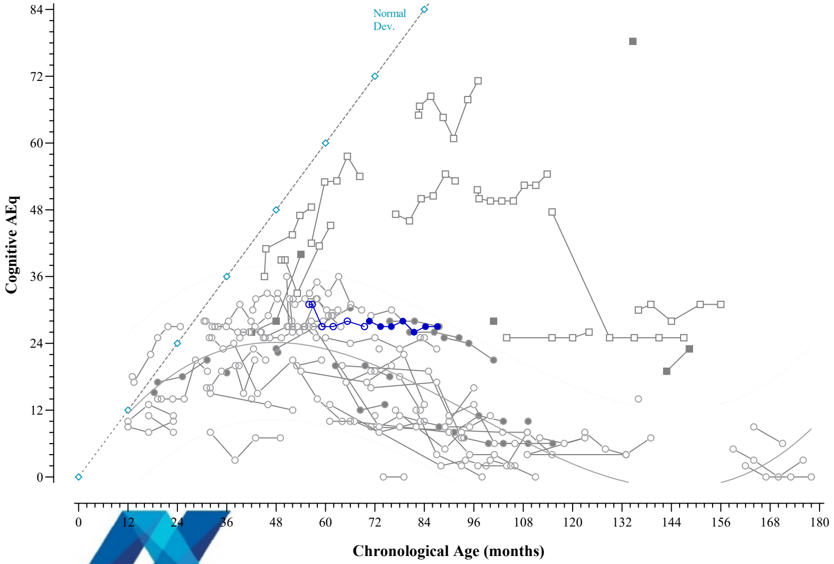
Cognitive function in treated rapid progressors deviates from natural history

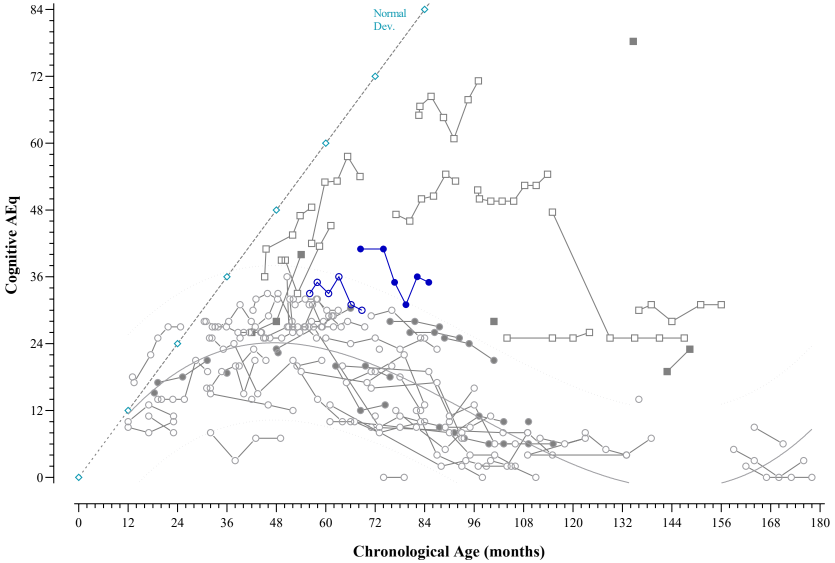
Between-subjects comparison











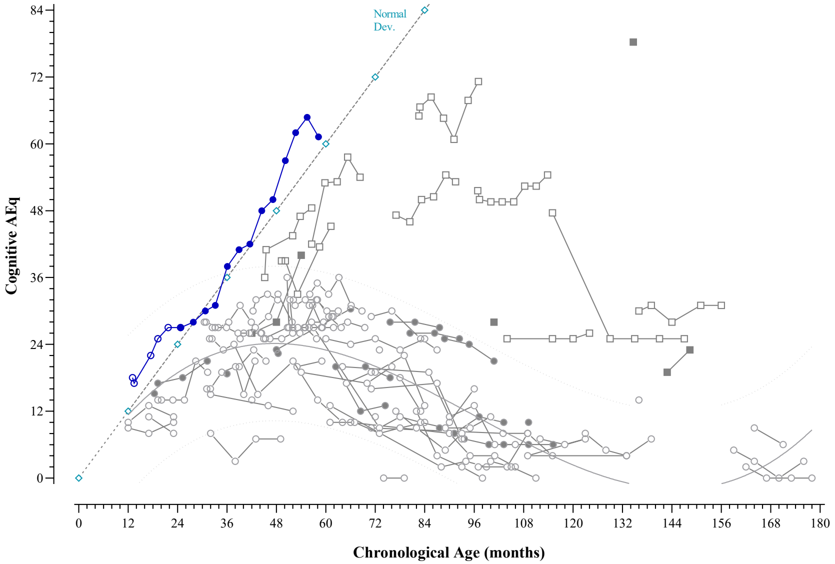
Cognitive (BSID-III, KABC-II)

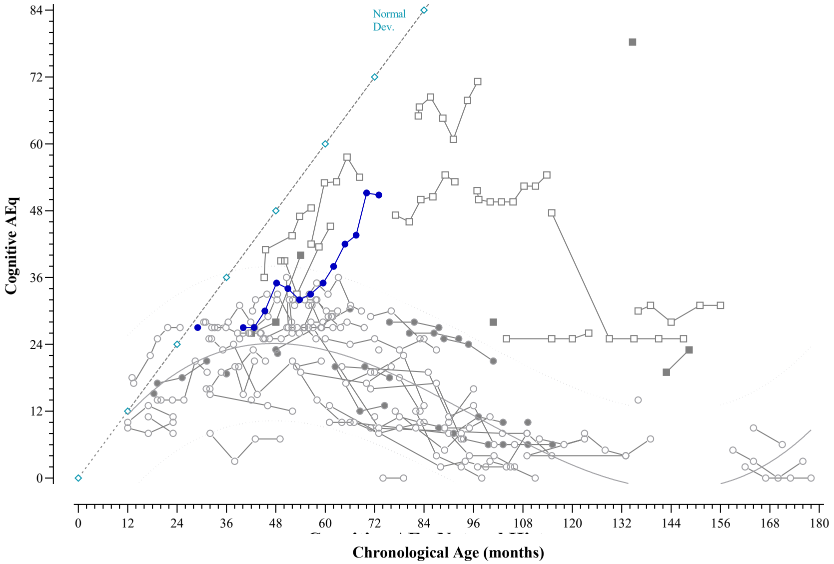
Duration	Natural history mean change (SD, N)	Treated mean change (SD, N)
2 years	-4.88 (5.96, 8)	-3.71 (16.56, 8)
3 years	-	22.02 (13.22, 3)

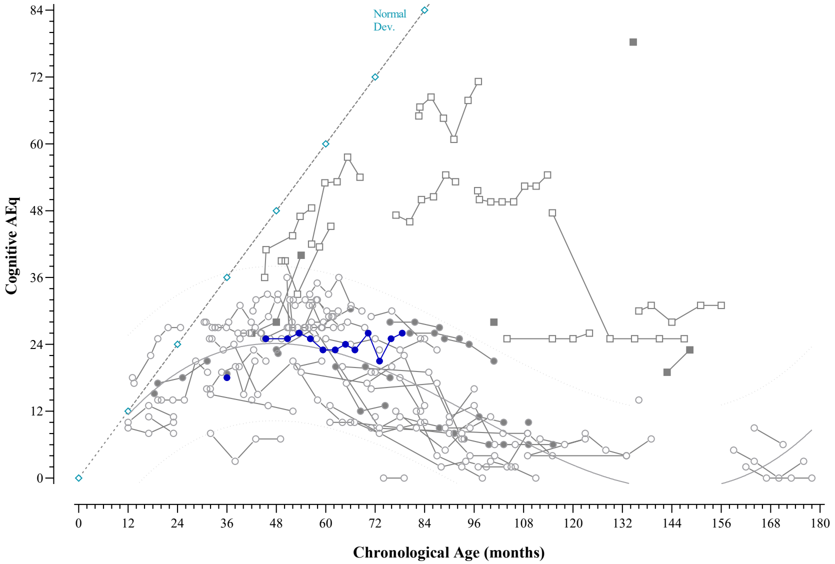
38% (5/13) of treated rapid progressors outperform predicted natural history trajectory

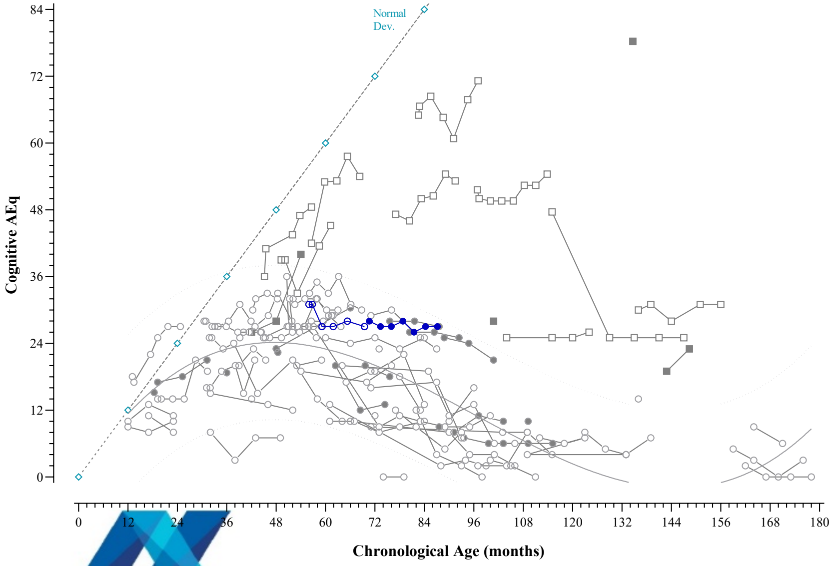
Adaptive behavior function in treated rapid progressors deviates from natural history

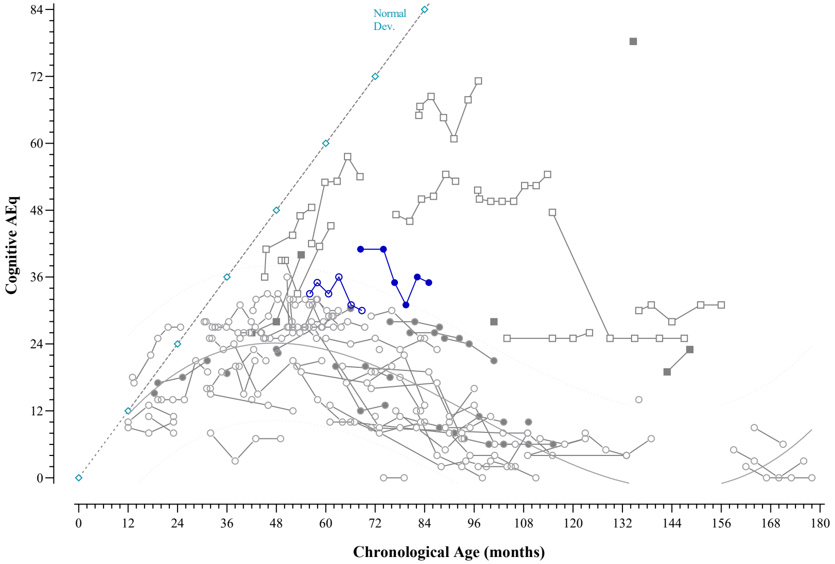
Between-subjects comparison











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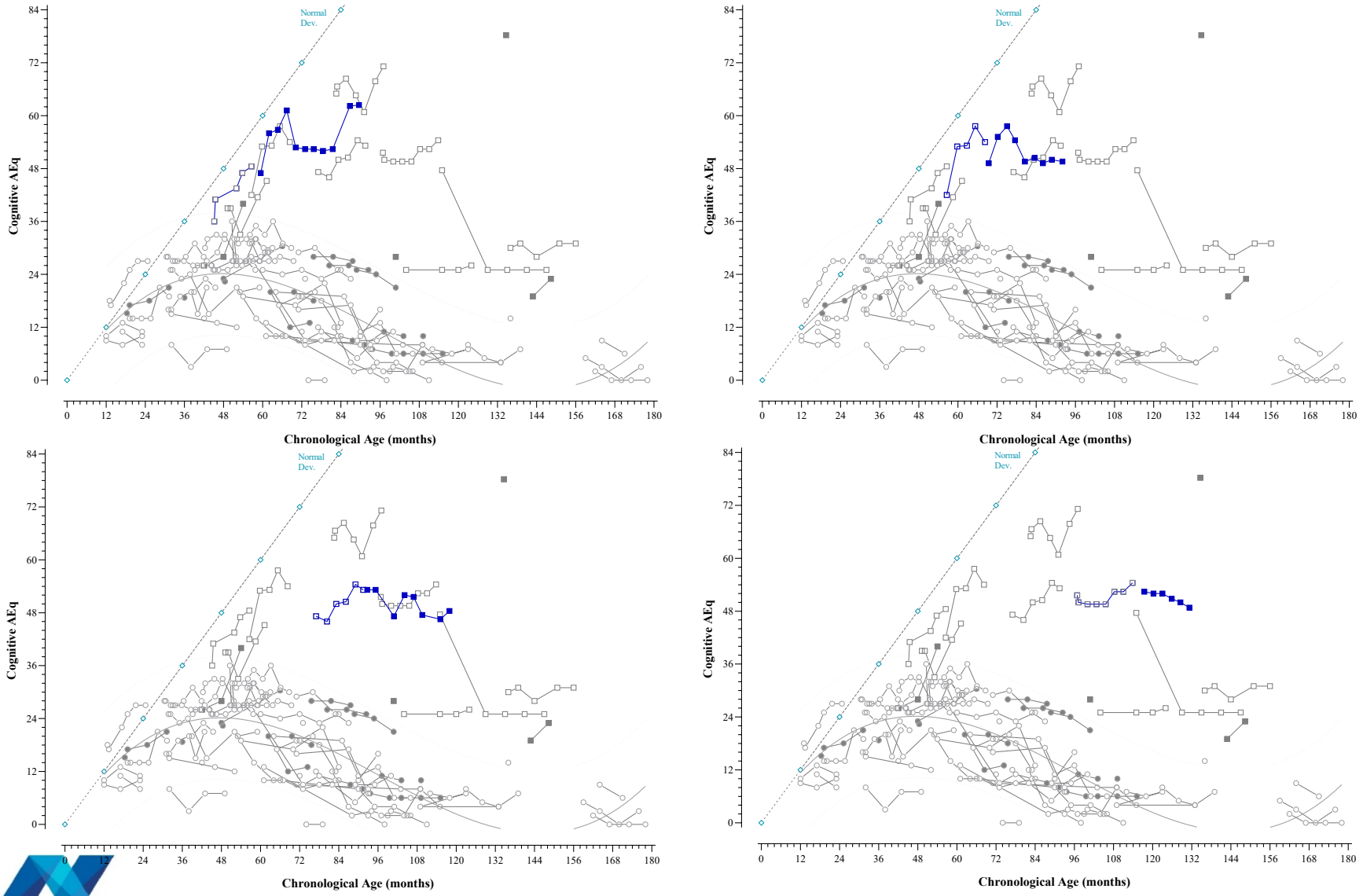
2 years	-4.88 (5.96, 8)	-3.71 (16.56, 8)
3 years	-	22.02 (13.22, 3)

Adaptive behavior (VABS-II)

Duration	Natural history mean change (SD, N)	Treated mean change (SD, N)
2 years	-4.00 (6.20, 9)	-2.25 (18.94, 8)
3 years	-	16.00 (12.73, 2)

Cognitive function is stable in all treated slow progressors

Between-subjects comparison



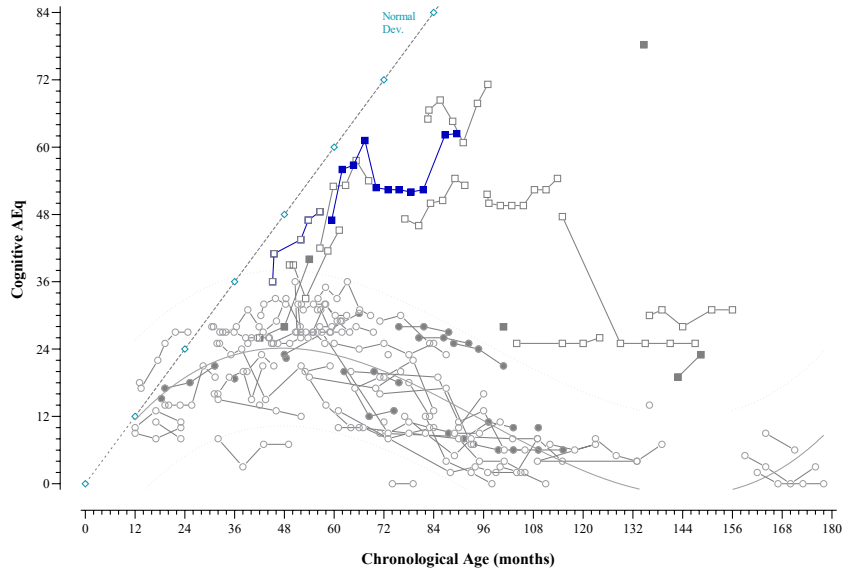
Cognitive (BSID-III, KABC-II)

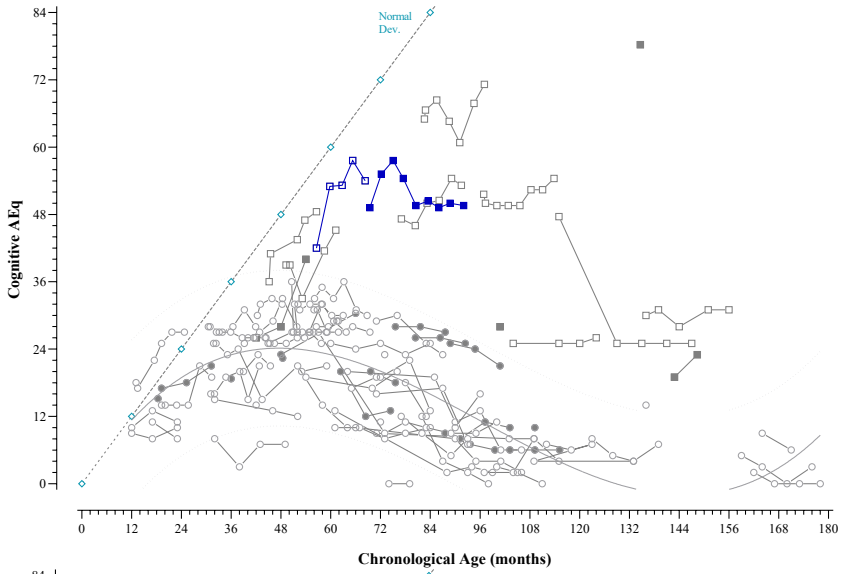
Duration	Treated mean change (SD, N)
2 years	-0.30 (6.08, 3)

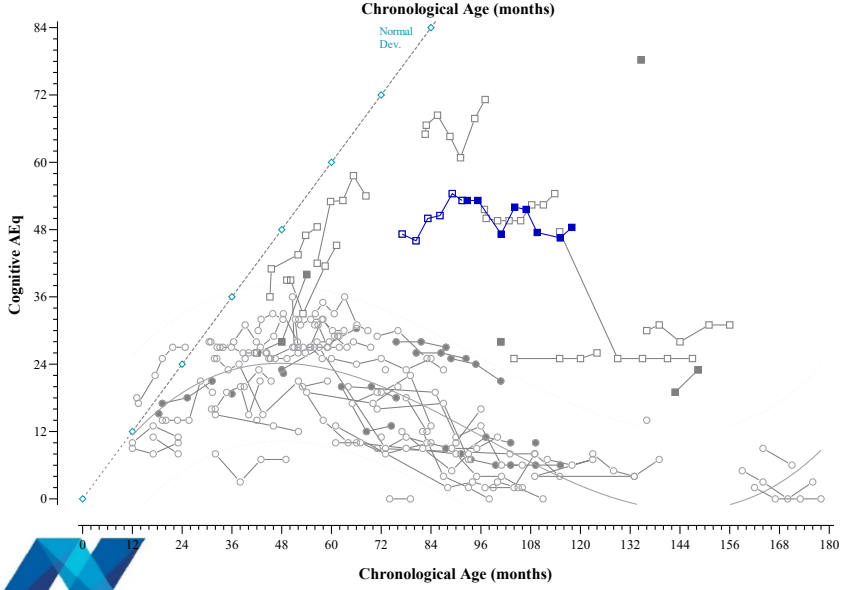
100% (4/4) of slow progressors have stable cognitive function on treatment

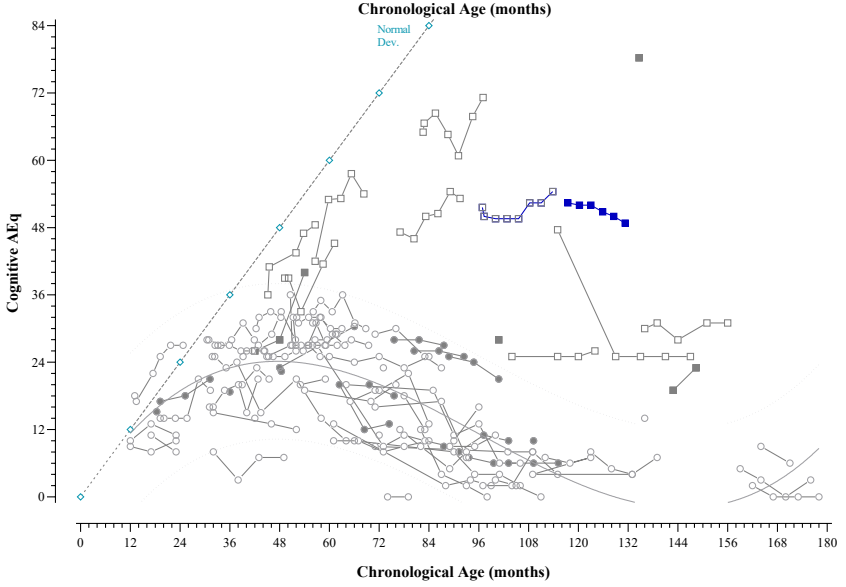
Adaptive behavior function is stable in treated slow progressors

Between-subjects comparison









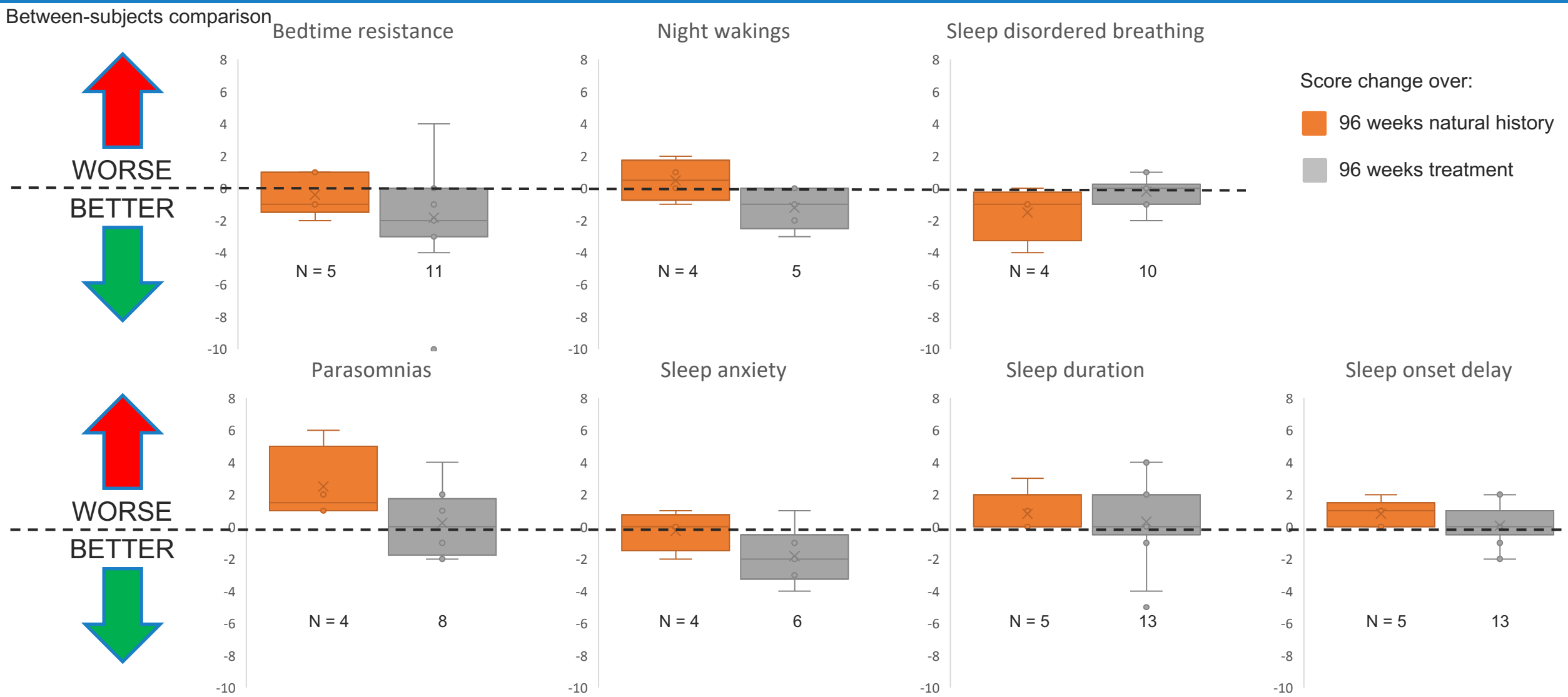
Cognitive (BSID-III, KABC-II)

Duration	Treated mean change (SD, N)
2 years	-0.30 (6.08, 3)

Adaptive behavior (VABS-II)

Duration	Treated mean change (SD, N)
2 years	-1.00 (11.53, 3)

Sleep problems improve or remain stable on treatment (CSHQ)



- 6/7 measures are directionally better on treatment than natural history

Sleep improves on treatment

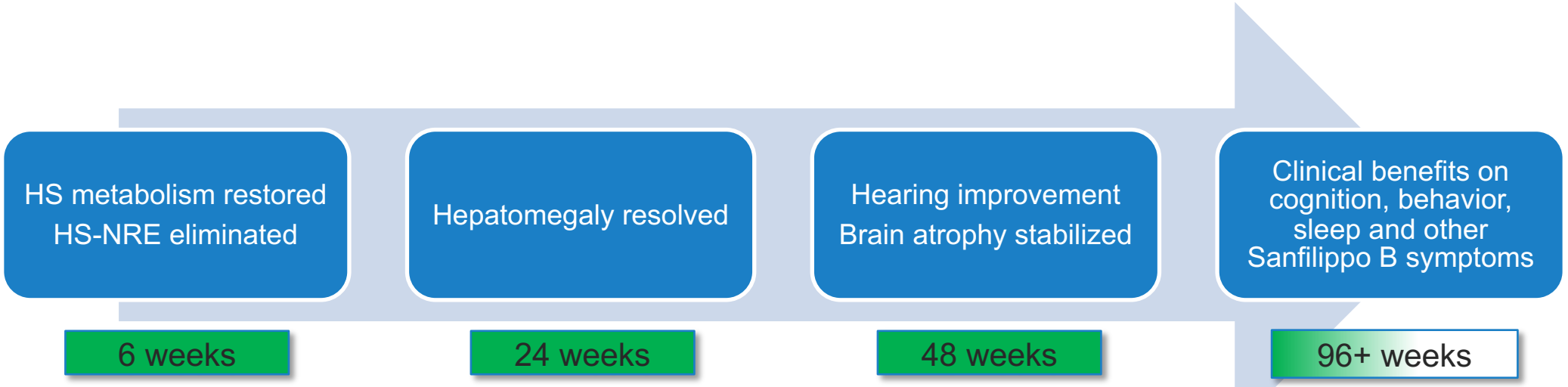
Tralesinidase alfa is generally safe and well-tolerated

Combined Safety Profile	
Safety population	22
Total doses administered	>2352 (>95% of scheduled)
Longest exposure to date	>224 weeks
Treatment-emergent AEs	939 (< 5% on a per-dose basis, ~95% mild to moderate)
Device-related Treatment-emergent SAEs (16)	Cerebrospinal fluid leakage (2), device malfunction (3), device related infection (4), extravasation of IP/CSF (3), device dysfunction (2), headache (1), wound Infection (1)
Drug-related Treatment-emergent SAEs (15)	Angioedema (1), consciousness fluctuating (1), hydrocephalus (1), pleocytosis (8), pyrexia (1), vomiting (3)
Study discontinuations (9)	Pre-treatment: withdrawal of consent (3) Treatment: device related infection (1), hydrocephalus (2), subdural hygroma (1), withdrawal of consent (2)

Data as of October 19, 2020

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

Summary



- Treatment is associated with improvement or stability of function across domains in within-subjects and between-subjects comparisons
- 250-902 natural history and 250-202 treatment extension studies are ongoing

THANK YOU!

Hope to see you (in person) at WORLD Symposium 2021!