

# Long-term administration of trailesinidase alfa enzyme replacement therapy (TA-ERT) results in profound and durable reduction of HS and stabilization of cognitive function and CGMV in patients with MPS IIIB

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## INTRODUCTION

- N-acetyl-alpha-glucosaminidase (NAGLU) mutation leads to NAGLU enzyme deficiency
- CSF heparan sulfate non-reducing end (HS-NRE) accumulation
- Normal cognition at birth
- Neuro developmental delay followed by progressive cognitive and functional regression
- Advanced stages:
  - loss of communication
  - bedridden state
  - feeding tube dependence
  - need for constant care
- Fatal in second decade of life
- No approved therapy - high unmet medical need

Figure 1: Neurotypical Development vs. Sanfilippo Syndrome

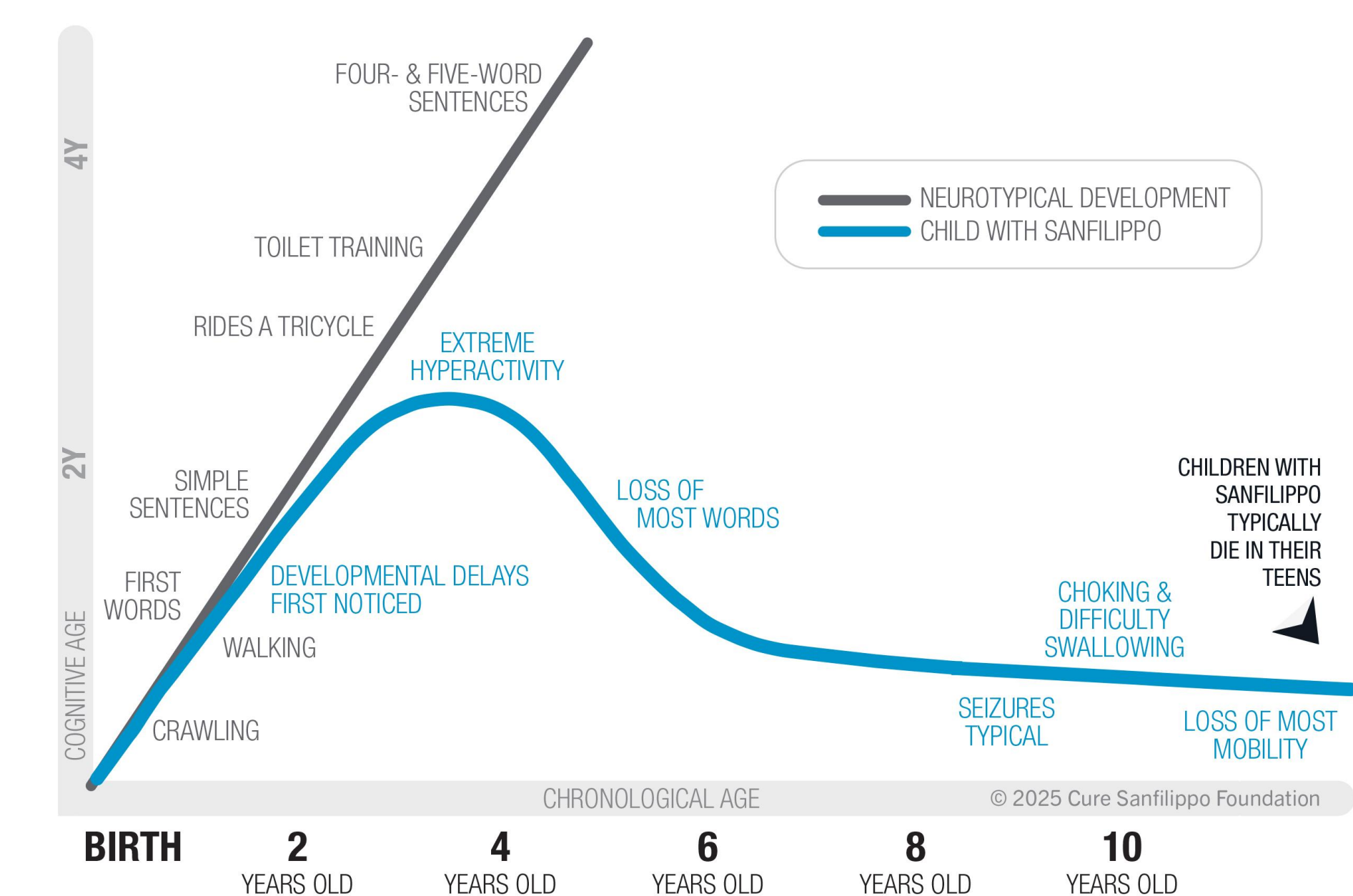


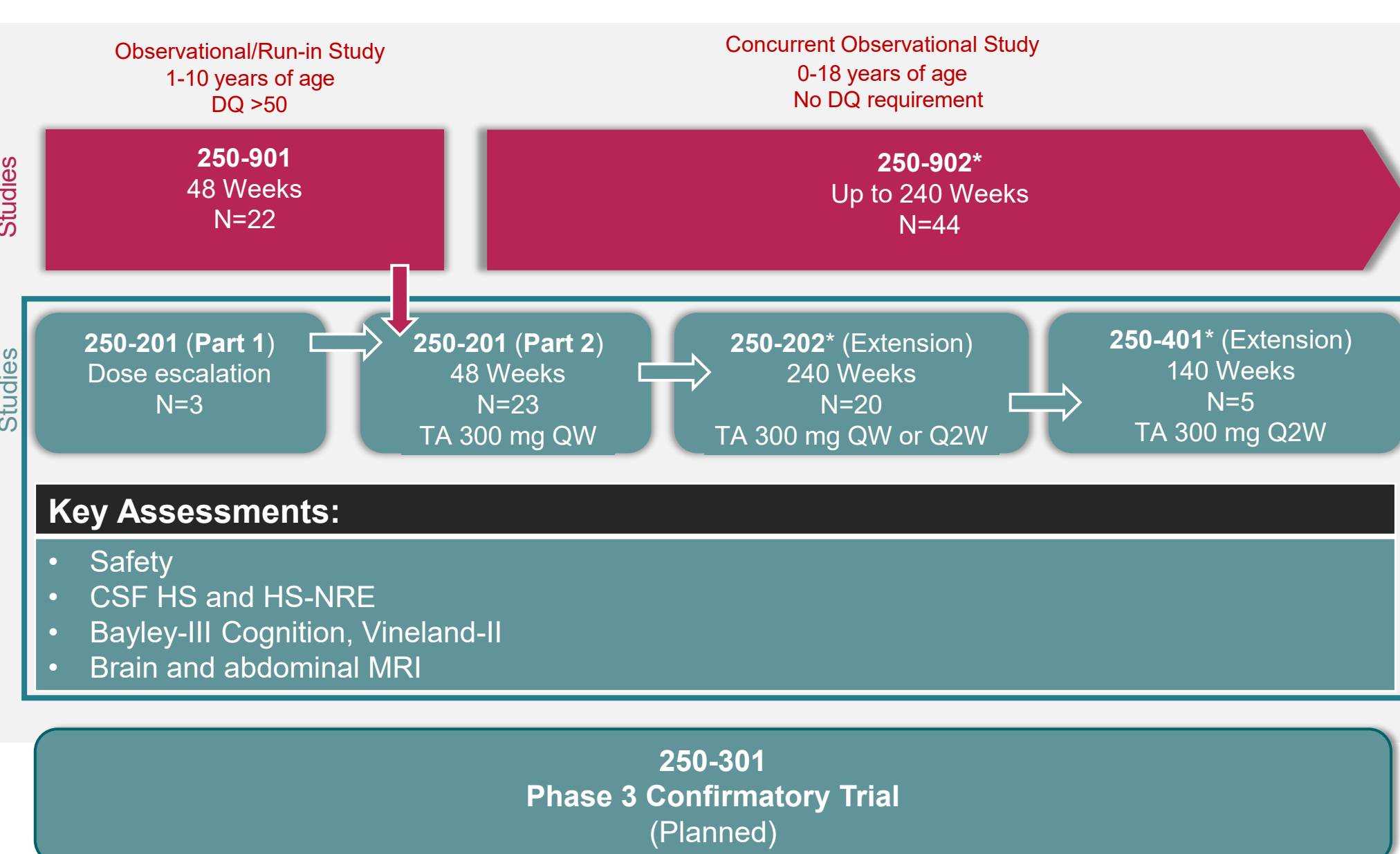
Figure represents studies of disease impact in rapidly-progressing forms of Sanfilippo Syndrome. Produced with permission from Cure Sanfilippo Foundation.

### Trailesinidase alfa enzyme replacement therapy:

- TA is a fusion protein of rhNAGLU and an IGF2 peptide.
- The IGF2 peptide enhances delivery of TA to lysosomes in neurons and other CNS cells.
- The internalization and delivery of TA to the lysosome is designed to restore NAGLU activity in children with MPS IIIB.

## METHODS

Figure 2. Observational Studies and TA Intervention Studies in MPS IIIB - Overview



\*Study was terminated. Interventional Studies = Studies 250-201+EXT (250-201, 250-202, 250-401).

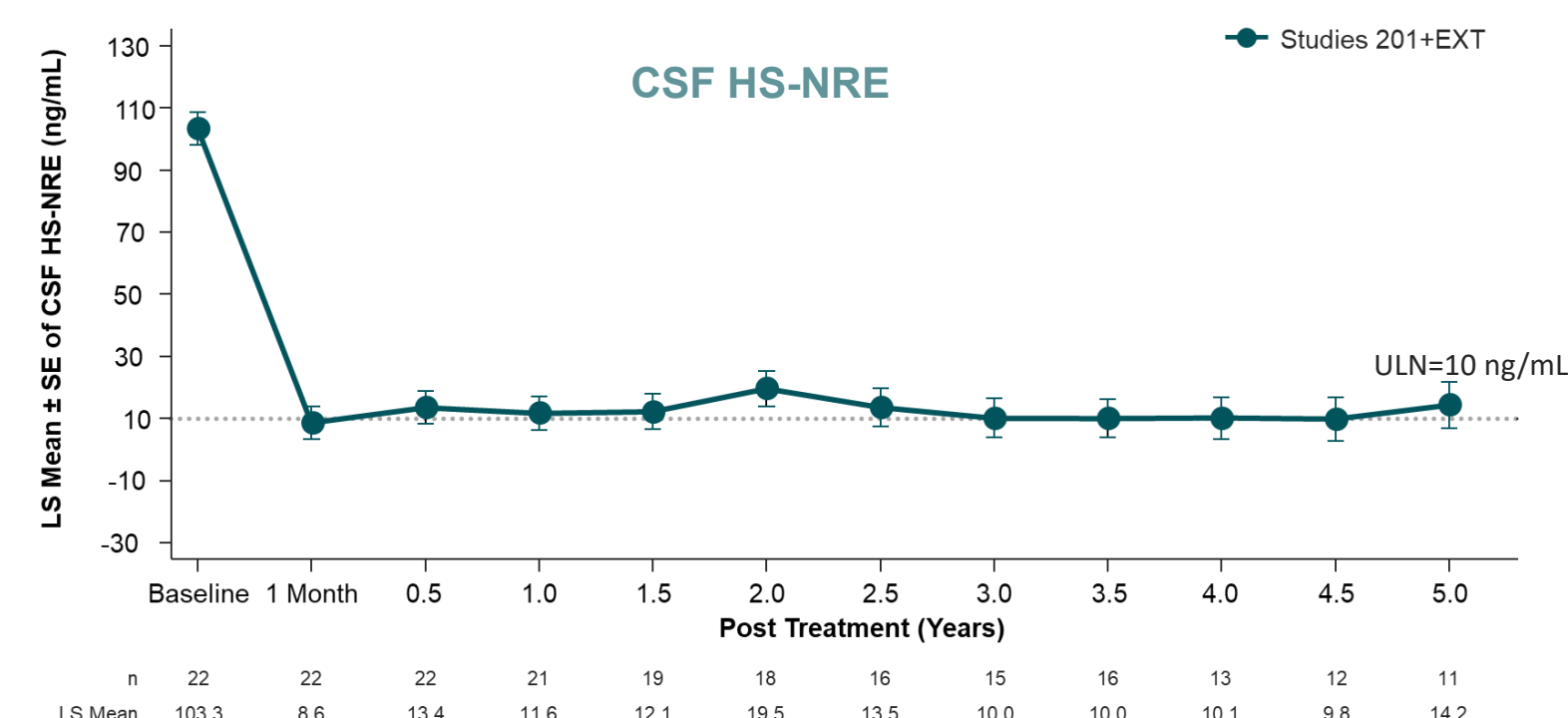
Table 1: Baseline Demographics and Characteristics in Untreated (Study 902) and TA-Treated (Study 201+EXT) Participants

	No DQ Inclusion Criterion Study 902 (NH) N=32 <sup>a</sup>	DQ>50 Inclusion Criterion Study 201+EXT N=22
<b>Age (years)</b>		
Mean (SD)	5.81 (2.20)	4.96 (2.03)
Median	6.08	5.08
<b>Sex n (%)</b>		
Male	17 (53.1)	13 (59.1)
<b>DQ (AEq/age)</b>		
Mean (SD)	26.0 (20.4)	55.4 (21.1)
Median	22.5	51.6
<b>Bayley-III Cognitive Raw Score</b>		
Mean (SD)	41.9 (17.76)	69.6 (15.20)
Median	40.0	69.0

<sup>a</sup>n=31 for Bayley-III Cognitive Raw Score. Bayley-III=Bayley Scales of Infant and Toddler Development, Third Edition; DQ=development quotient; NH=natural history; SD=standard deviation; TA=trailesinidase alfa. Table 5.3.5.3.1-1.2.2.1 (for 202) and Table 5.3.5.3.1-1.2.2.2

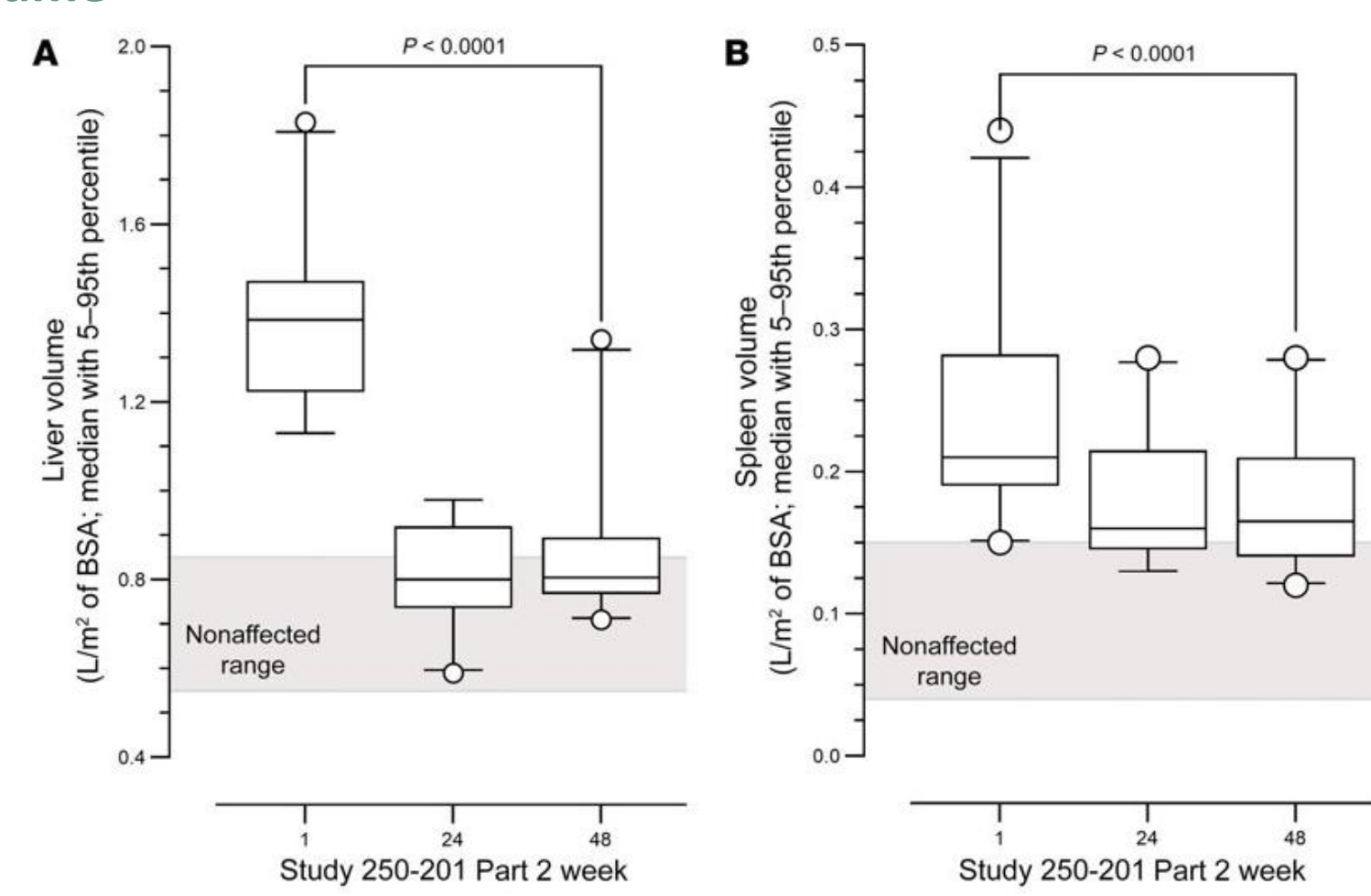
## RESULTS

Figure 3: Trailesinidase Alfa Rapidly Normalizes CSF HS and HS-NRE



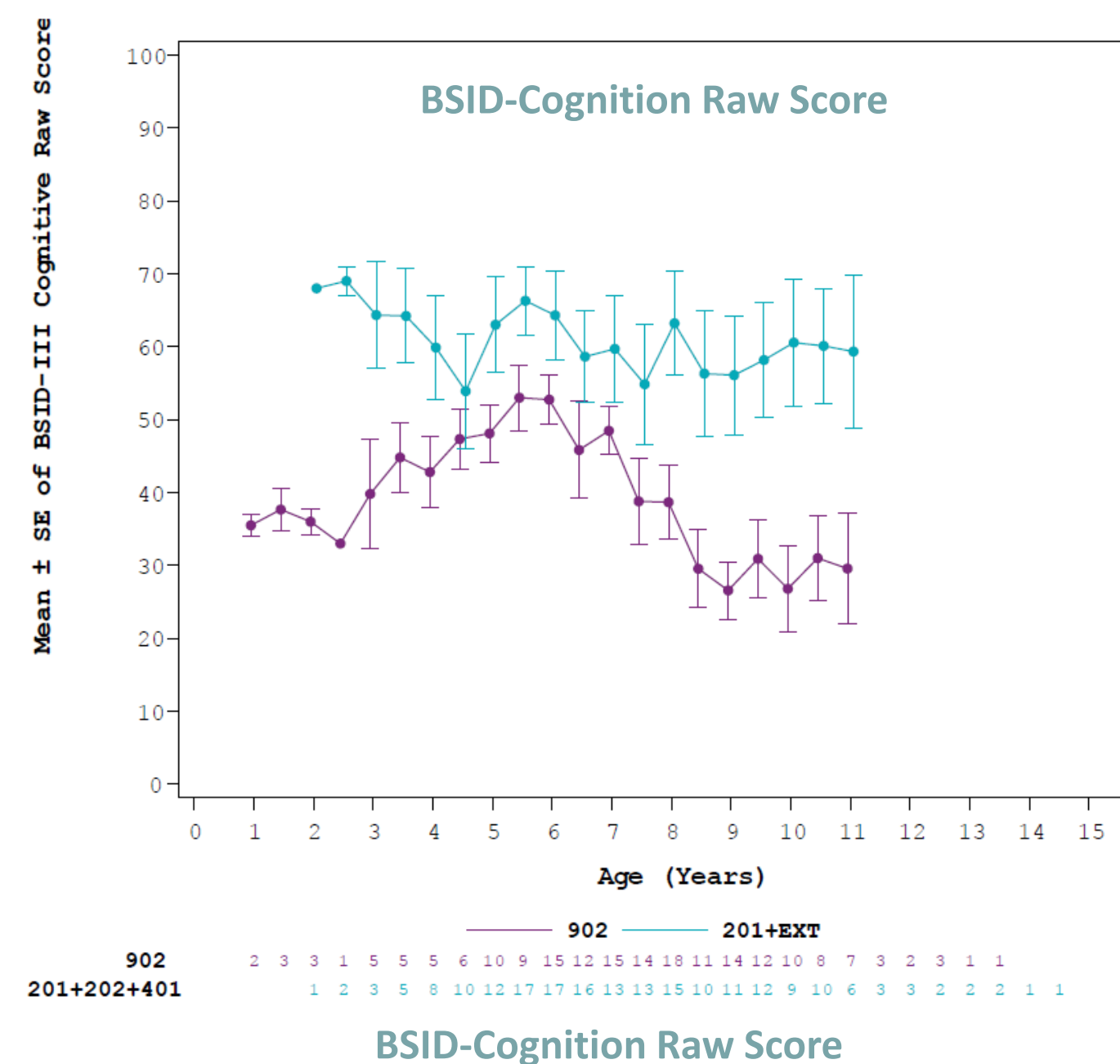
CSF=cerebrospinal fluid; HS=heparan sulfate; HS-NRE=heparan sulfate-nonreducing end; LS=least squares; SE=standard error; ULN=upper limit of normal. Source: Integrated Figure 5.3.5.3.1-2.1.5.1 and 5.3.5.3.1-2.1.5.2

Figure 4: Trailesinidase Alfa Treatment Rapidly Clears HS and Normalizes Liver and Spleen Volume



Liver (A), spleen (B) were measured by magnetic resonance imaging at Week 1 (Baseline) and Weeks 24 and 48. Liver and spleen volumes were adjusted for body surface area. Boxes represent the 5th to 95th percentiles with the median; dots represent values outside the 5th to 95th percentiles. BSA=body surface area; HS=heparan sulfate. Source: Muschol et al. 2023

Figure 6 and Table 2: Trailesinidase Alfa Stabilizes Cognitive Function



Chronological Age (Years)	Study 902 (N=32)	Study 201+EXT (N=22)	p-value 201+EXT vs. Study 902
4.0	42.8 (10.8)	59.8 (20.0)	0.111
4.5	47.3 (9.9)	53.9 (24.8)	0.550
5.0	48.1 (12.5)	63.0 (22.7)	0.080
5.5	53.0 (13.4)	66.2 (19.4)	0.080
6.0	52.7 (13.0)	64.2 (24.9)	0.108
6.5	45.8 (23.1)	58.6 (25.1)	0.179
7.0	48.4 (12.7)	59.6 (26.5)	0.183
7.5	38.7 (22.1)	54.8 (29.7)	0.122
8.0	38.6 (21.3)	63.2 (27.4)	0.007
8.5	29.5 (17.5)	56.3 (27.2)	0.014
9.0	26.5 (14.7)	56.0 (26.9)	0.005
9.5	30.9 (18.3)	58.1 (27.2)	0.008
10.0	26.8 (18.5)	60.5 (26.0)	0.004
10.5	31.0 (16.5)	60.1 (24.9)	0.013
11.0	29.5 (20.1)	59.3 (25.6)	0.038

BSID-III=Bayley Scales of Infant and Toddler Development, Third Edition; SE=standard error. Sources: Integrated Table 14.2.2.1.1.1; Integrated Table 14.2.2.1.1.3; TA ISE/ISS Final Analysis Figure 14.2.2.1.2.1

### Trailesinidase Alfa Safety Profile and Immunogenicity:

- 22 participants enrolled with follow-up lasting up to 6 years with ~6,000 TA doses administered
- 4 discontinuations occurred (3 due to hydrocephalus and 1 following infection)
- Device-related adverse events occurred at a rate of 0.02 per infusion with serious adverse events occurring at a rate of 0.01 per infusion<sup>1</sup>
- Hypersensitivity-related adverse events occurred at <0.01 per infusion and none were severe or serious<sup>1</sup>
- Anti-drug and neutralizing antibodies occurred but did not affect CSF TA exposure or CSF HS/HS-NRE levels<sup>2</sup>

## CONCLUSIONS

- MPS IIIB is an ultra-rare, serious, and fatal progressive neurodegenerative disease with no treatment options currently available.
- Weekly ICV 300 mg TA administration rapidly and durably normalized CSF HS-NRE levels, a surrogate endpoint that is reasonably likely to predict clinical benefit in MPS IIIB.
- TA treatment stabilized and preserved cognitive and non-cognitive outcomes, such as communication and motor skills, from the inexorable decline in these outcomes in untreated children.
- TA safety profile was consistent with that expected with an ICV-administered drug.

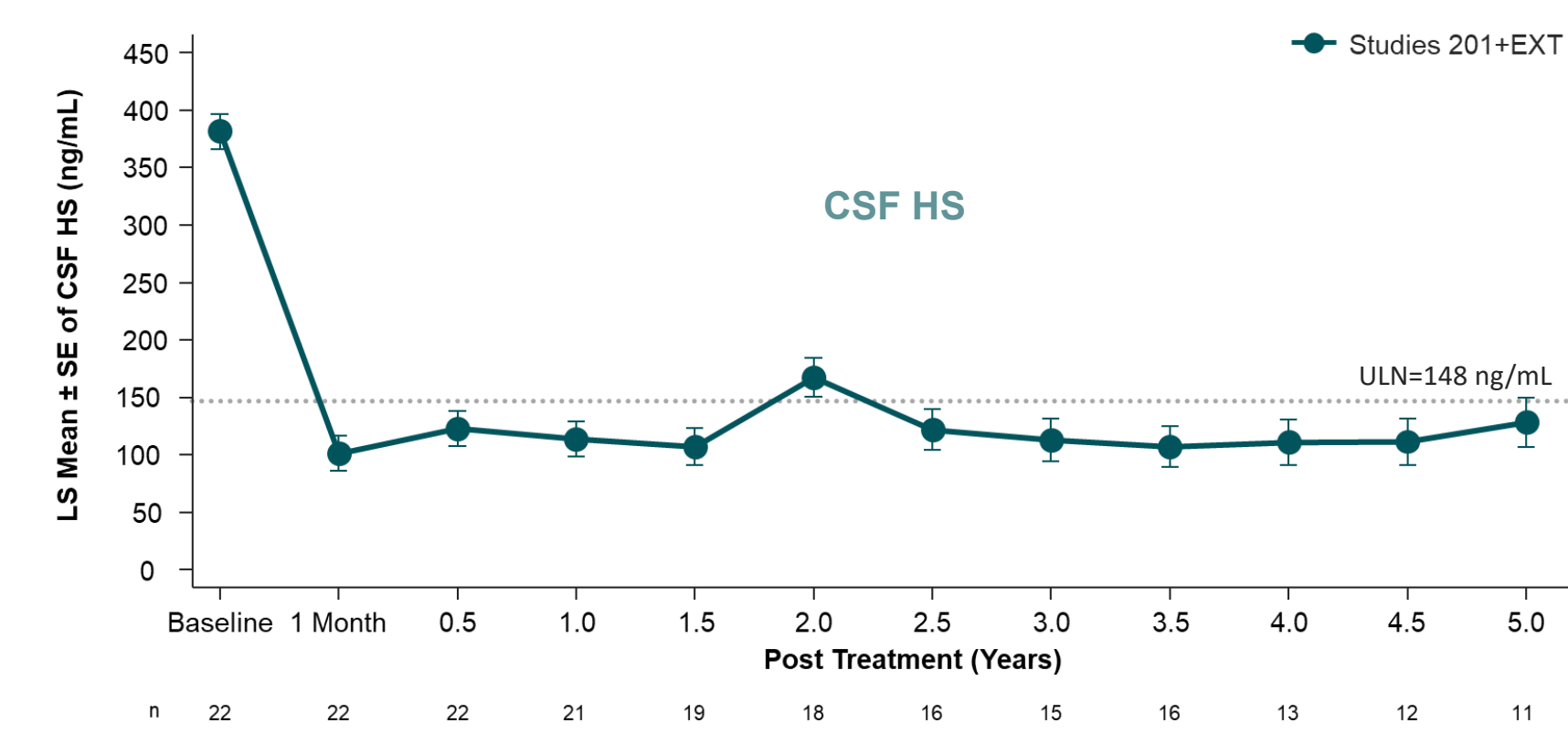
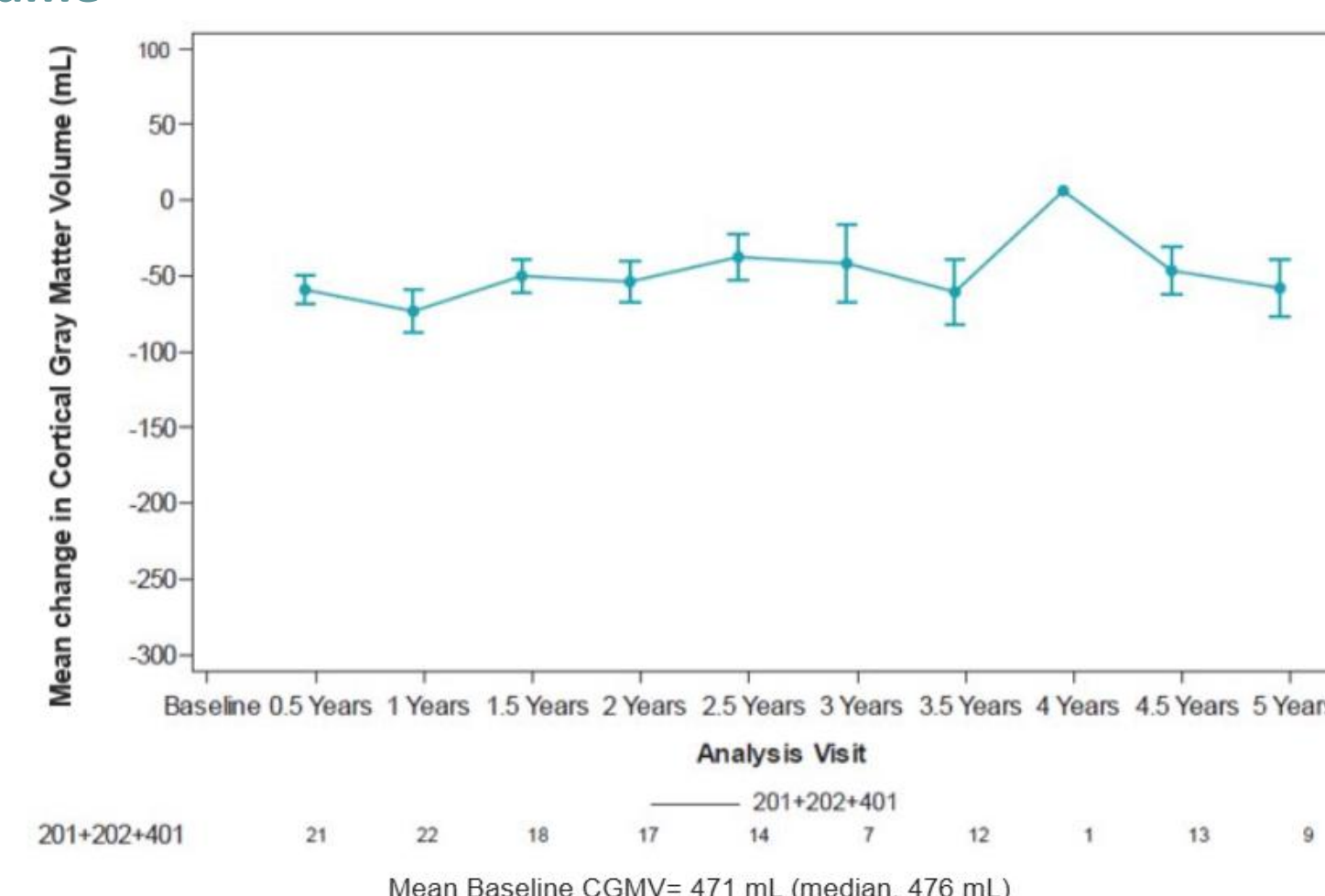
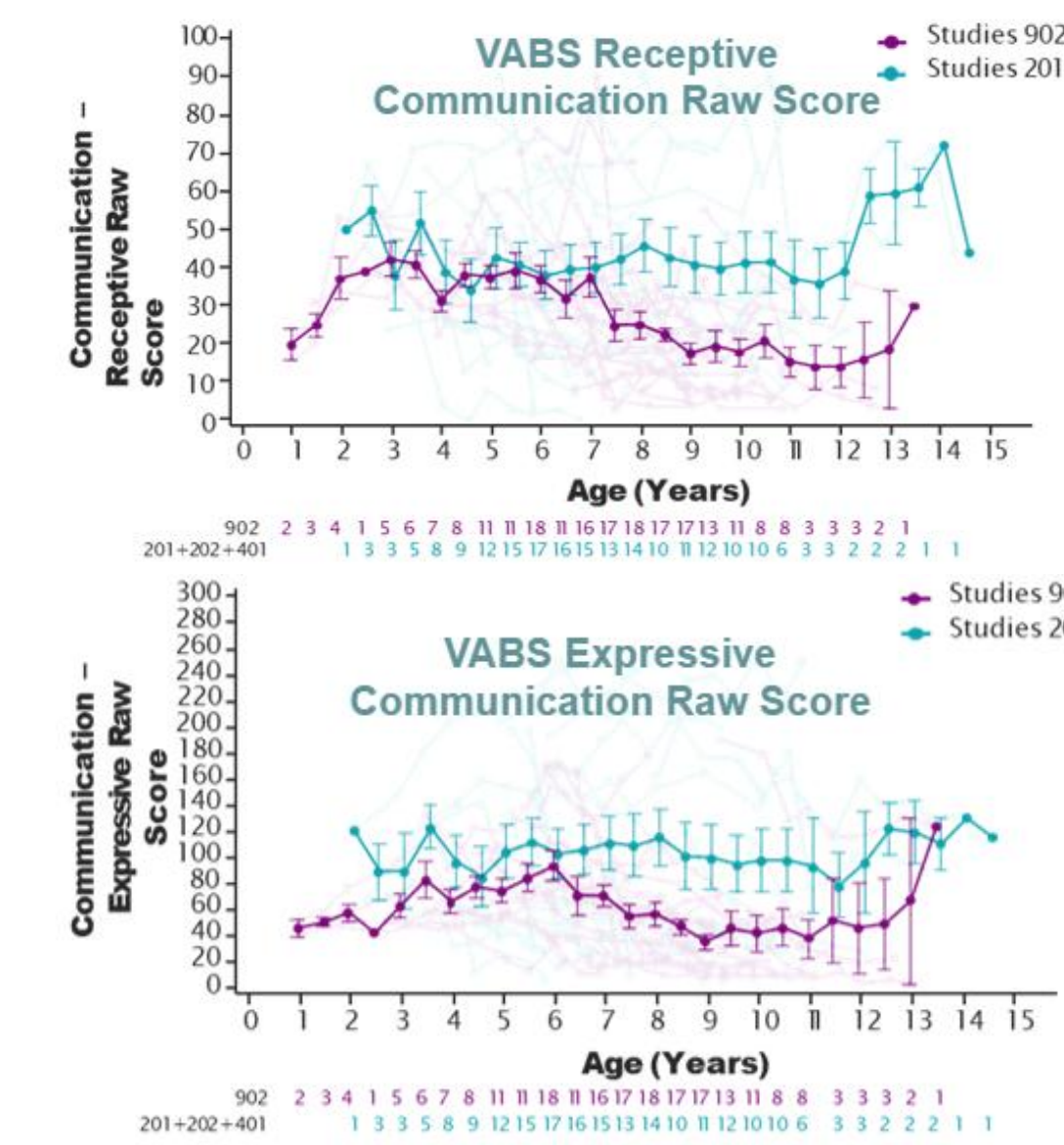


Figure 5: Trailesinidase Alfa Treatment Stabilizes Cortical Gray Matter Volume



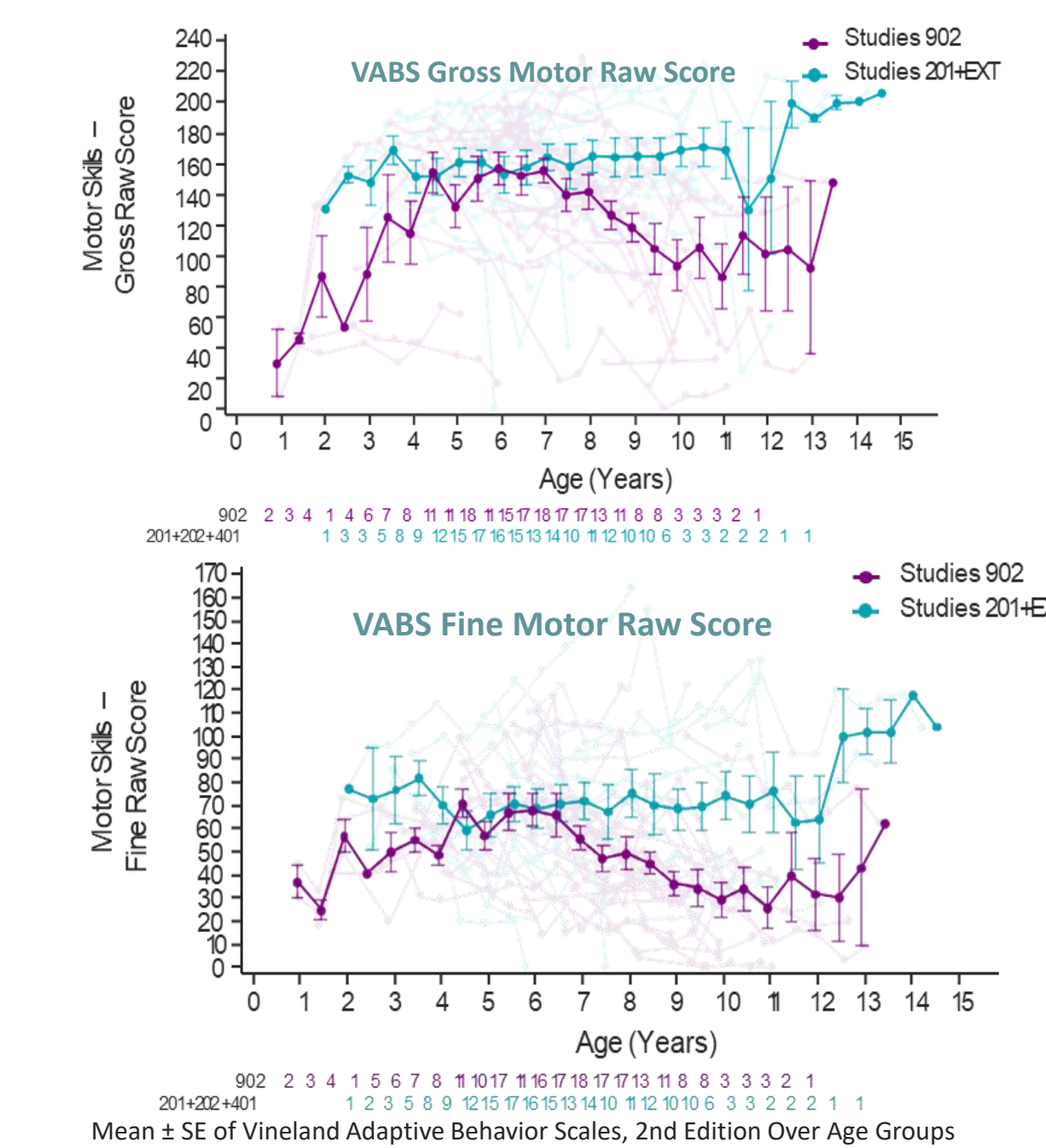
CGMV=cortical gray matter volume. Source: Figure 14.1000.18.2

Figure 7: Trailesinidase Alfa Stabilizes Communication in VABS-II



VABS=Vineland Adaptive Behavior Scales, Second Edition. Sources: Integrated Table 5.3.5.3.1-2.3.1.5.1; Integrated Table 5.3.5.3.1-2.3.1.5.3; Integrated Table 5.3.5.3.1-2.3.1.5.4; Integrated Table 5.3.5.3.1-2.3.1.5.5

Figure 8: Trailesinidase Alfa Stabilizes and Preserves Motor Skills



VABS=Vineland Adaptive Behavior Scales, Second Edition. Sources: Integrated Table 5.3.5.3.1-2.3.1.5.14; Integrated Table 5.3.5.3.1-2.3.1.5.15