Divergent Neurocognitive Outcomes in MPS IIIB Siblings: Tralesinidase Alfa Versus Supportive Management

Poster No. 064

Irene J. Chang, MD[1], Jacqueline Madden, PNP[2], Erin Jozwiak, NP[2], Saba Sile, MD[3], Ting Chang, PhD[3], Javier Szwarcberg, MD[3], Paul Harmatz, MD[2]

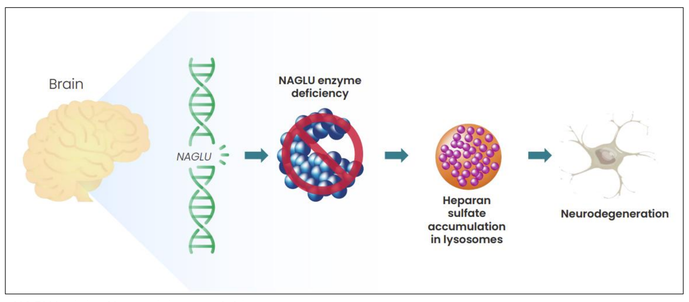
[1]Department of Pediatrics, Division of Medical Genetics, University of California San Francisco, San Francisco, CA, USA; [2]Department of Pediatrics, Division of Gastroenterology, University of California San Francisco (UCSF) Benioff Children's Hospital Oakland, Oakland, CA, USA; [3]Spruce Biosciences, South San Francisco, CA, USA

INTRODUCTION

Mucopolysaccharidosis type IIIB (MPS IIIB; Sanfilippo syndrome type B)

- MPS IIIB is an ultra-rare, fatal, progressive neurodegenerative genetic disease[1,2,3].
- MPS IIIB is caused by bialleic pathogenic variants in the *NAGLU* gene, resulting in deficiency of alpha-N-acetylglucosaminidase (NAGLU) needed for the degradation of heparan sulfate (HS) (Figure 1)[4].

Figure 1: HS Accumulation Is the Underlying Pathophysiology of MPS IIIB



NAGLU, alpha-N-aceytlglucosaminidase.

- Children with MPS IIIB present in early childhood with cognitive and speech delay, followed by developmental regression that includes loss of communication skills, motor deterioration, behavioral problems (hyperactivity, aggression, loss of impulse control), and sleep disturbances[5].
- Development peaks between 3 to 6 years of age before progressive decline begins[5].
- In the final stage of MPS IIIB, children lose the ability to communicate, are bed-ridden, require placement of feeding tubes for hydration and nutrition, and require constant attention.
- Children with MPS IIIB die in the second decade of life[6,7].

Tralesinidase alfa (TA) enzyme replacement therapy

- TA is a fusion protein of rhNAGLU (recombinant human NAGLU) and an insulin-like growth factor 2 (IGF2) peptide.
- The IGF2 peptide enhances delivery of TA to lysosomes in neurons and other central nervous system (CNS) cells.
- The internalization and delivery of TA to the lysosome is designed to restore NAGLU activity in children with MPS IIIB.

METHODS

Two male siblings were diagnosed with non-attenuated, severe MPS IIIB.

- Sibling 1: participated in TA clinical trial Studies 250-201 and Extensions (Study 250-201 + EXT)
- Sibling 2: clinical observations were made during routine clinical visits. This sibling did not participate in natural history (NH) or clinical trials.

Study 250-201 + EXT

- The primary objectives of the studies were safety, tolerability, efficacy, and impact on cognitive function.
- TA 300 mg weekly was delivered via intracerebroventricular (ICV) administration for up to 6 years.
- Assessments during the study included:
  - HS and HS-NRE (HS non-reducing end) levels in cerebrospinal fluid (CSF)
  - Cognitive function, using the Bayley Scales of Infant Development, 3rd Edition (BSID-III)
  - Behavior and skills, using the Vineland Adaptive Behavior Scales, 2nd Edition (VABS-II)
  - ICV- and treatment-related adverse events (AEs)

Baseline characteristics of participants in Study 250-201 were compared to untreated participants in the NH observational Study 250-902 (Table 1).

- Sibling 1's baseline age at start of treatment was 5.9 years, baseline DQ was 56.4 (by BSID), and baseline cognitive raw score was 72.

Table 1: Baseline Characteristics of Participants in Studies 250-902 and -201

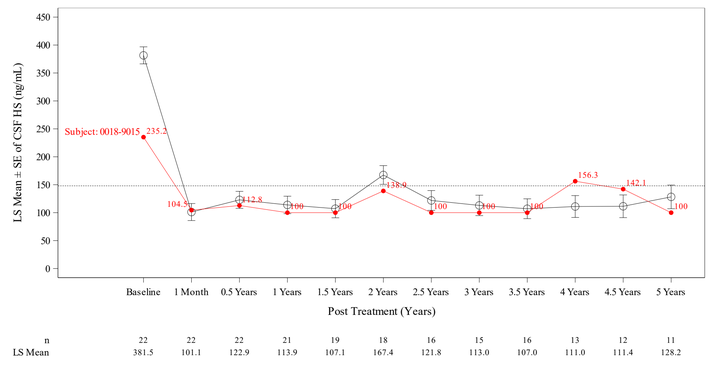
	No DQ Inclusion Criterion	DQ>50 Inclusion Criterion
	Study 250-902 (NH; N=32)	Study 250-201 (N=22)
Age (years)		
Mean (SD)	5.81 (2.200)	4.96 (2.03)
Median	6.08	5.08
Sex, n (%)		
Male	17 (53.1%)	13 (59.1)
DQ (AEq/age)		
Mean (SD)	26.0 (20.4)	55.4 (21.1)
Median	22.5	51.6
Bayley-III Cognitive Raw Score		
Mean (SD)	41.9 (17.76)	69.6 (15.20)
Median	40.0	69.0

AEq=age equivalence; DQ=development quotient ; n=number of participants; N=total number of participants; NH=natural history; SD=standard deviation.

RESULTS

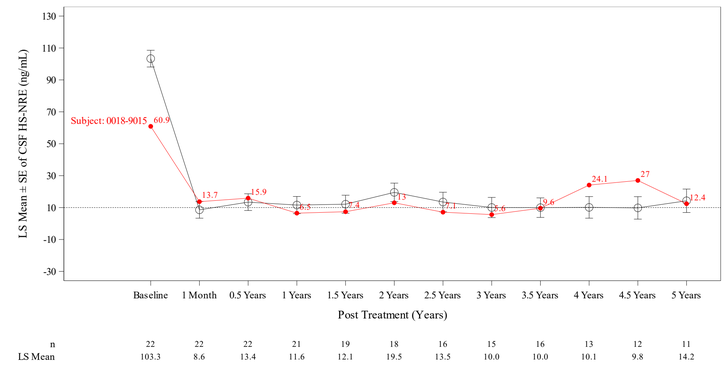
Overall in Study 250-201 + EXT and specifically in the treated sibling, TA rapidly and durably normalized CSF HS (Figure 2) and HS-NRE (Figure 3).

Figure 2: TA Treatment Reduced and Durably Normalized CSF HS



CSF, cerebrospinal fluid; HS, heparan sulfate; LS, least squares ; SE, standard error; TA, Tralesinidase alfa.
Black: mean levels in Study 250-201 + EXT. Red: Treated participant (Sibling 1). The dashed line represents the 95th percentile of the upper limit of normal of 148 ng/mL. Values below the normal limit of quantitation (LLOQ) were replaced by the limit of quantitation (LOQ) value of 100 ng/mL.

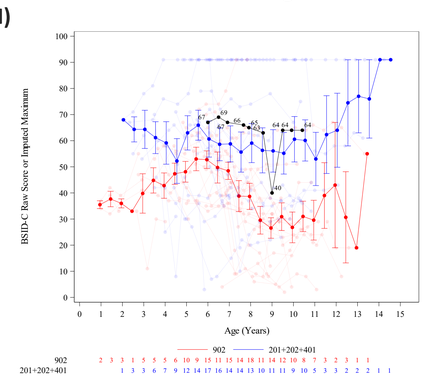
Figure 3: TA Treatment Reduced and Durably Normalized CSF HS-NRE



CSF, cerebrospinal fluid; HS-NRE, heparan sulfate non-reducing end; LS, least squares ; SE, standard error; TA, Tralesinidase alfa.
Black: mean levels in Study 250-201 + EXT. Red: Treated participant (Sibling 1). The dashed line represents the 95th percentile of the upper limit of normal of 10 ng/mL. Values below the normal limit of quantitation (LLOQ) were replaced by the limit of quantitation (LOQ) value of 5 ng/mL.

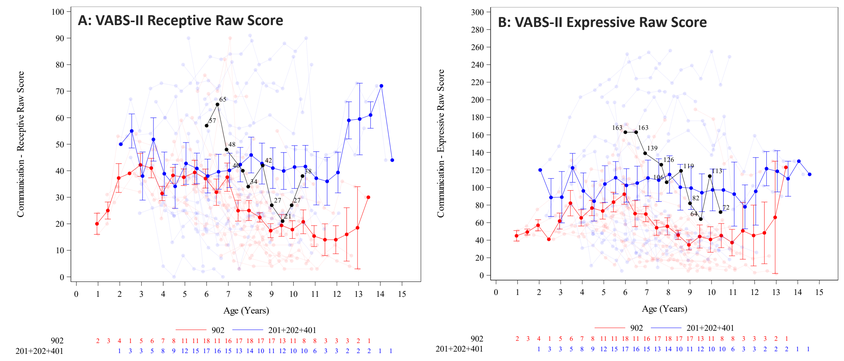
Overall in Study 250-201 + EXT and specifically in the treated sibling, TA preserved cognition (Figure 4), communication (Figure 5), and motor skills (Figure 6) and prevented the age-dependent decline in these outcomes that were seen in Study 250-902, the observational study.

Figure 4: TA Treatment Preserved Cognitive Function (BSID-III)



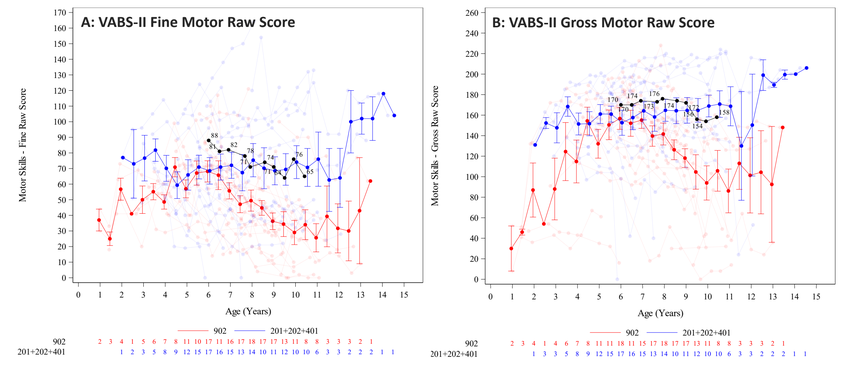
BSID-C, Bayley Scales of Infant Development, 3rd Edition – Cognitive; BSID-III, Bayley Scales of Infant Development, 3rd Edition; TA, Tralesinidase alfa.
The scores of the treated participant (Sibling 1; black line) are superimposed on the mean BSID-C scores from the natural history Study 250-902 (red) and Study 250-201 + EXT (blue). Numbers at the bottom represent number of participants assessed at each age group. If a participant qualified for the Kaufman Assessment Battery for Children, 2nd Edition, Non-Verbal Index (KABC-II NVI), a maximum BSID-III cognitive raw score of 91 was imputed.

Figure 5: TA Treatment Preserved Communication Skills (VABS-II)



TA, Tralesinidase alfa; VABS-II, Vineland Adaptive Behavior Scales, 2nd Edition.
The scores of the treated participant (Sibling 1; black line) are superimposed on the mean VABS-II scores from the natural history Study 250-902 (red) and Study 250-201 + EXT (blue). Numbers at the bottom represent number of participants assessed at each age group.

Figure 6: TA Treatment Preserved Motor Skills (VABS-II)



TA, Tralesinidase alfa; VABS-II, Vineland Adaptive Behavior Scales, 2nd Edition.
The scores of the treated participant (Sibling 1; black line) are superimposed on the mean VABS-II scores from the natural history Study 250-902 (red) and Study 250-201 + EXT (blue). Numbers at the bottom represent number of participants assessed at each age group.

Safety

In the clinical trials, the treated sibling reported the following AESIs, most of which were related to study treatment and none of which led to study treatment discontinuation:

- CSF eosinophilia (non-serious Grade 1),
- CSF pleiocytosis (serious Grade 2; non-serious Grade 1),
- nausea (non-serious Grade 1),
- pyrexia (non-serious Grade 1), and
- vomiting (serious Grade 2 [not-related]; non-serious Grades 1 and 2).

No treatment-related AEs of seizures or weakness were observed during treatment.

In an age-matched (10-12 years of age) comparison, the treated sibling had better clinical, cognitive, language, and motor functions compared to the untreated sibling (Table 2).

Table 2: Clinical Observations in the Treated and Untreated Siblings Between 10 to 12 Years of Age

	Sibling 1		Sibling 2
Treatment status; age at observation	**On treatment; 10.5 years of age**	**Off treatment x 1 month; 12.1 years of age**	**Untreated; 11.7 years of age**
Language	Has a vocabulary of several words; can make one-word requests and follow simple directions	Speaks a few words; makes eye contact and waves; parents report his receptive language skills exceed his expressive language skills	Nonverbal; will grab or push things away, but is otherwise unable to indicate preferences; not able to follow directions
Self-care	Toilet trained; can put on his own clothing and feed himself using a fork and spoon	Toilet trained, does not require diapers; can feed himself finger foods	No longer toilet trained, wears diapers; is dependent for toileting, dressing, and feeding
Fine motor	Can complete a puzzle, use an iPad, pick up small objects, and stack blocks	Can manipulate an iPad	Will touch or grasp items, but does not use them purposefully
Gross motor	Can run, climb, walk, and throw a ball	Ambulatory	Ambulatory, but poor coordination and difficulty changing positions such as getting up from a chair

Sources: Sibling 1 on treatment, VABS assessments; Sibling 1 post-treatment, clinic notes; Sibling 2, clinic notes and Individualized Education Programs (IEPs). Consent to share information was obtained from parent.

CONCLUSIONS

- Tralesinidase alfa rapidly and durably normalizes CSF HS-NRE, a surrogate endpoint that is reasonably likely to predict clinical benefit in MPS IIIB.
- In children with MPS IIIB, tralesinidase alfa preserves cognition, communication, and motor skills relative to the age-dependent decline seen in untreated children.
- The sibling treated with tralesinidase alfa displayed superior cognitive, language, and motor functioning relative to the untreated sibling at the same age.

Acknowledgements:

The authors wish to thank the participating and the non-participating siblings and their family and caregivers. We also thank the investigator, the clinical staff, and personnel at the study site.

References:

1. Huang W, Cheng YS, Yang S, Swaroop M, Xu M, Huang W, et al. Disease modeling for mucopolysaccharidosis type IIIB using patient derived induced pluripotent stem cells. Exp Cell Res. 2021;407(1):112785.
2. Muenzer J, Ho C, Lau H, Dant M, Fuller M, Boulos N, et al. Community consensus for Heparan sulfate as a biomarker to support accelerated approval in Neuronopathic Mucopolysaccharidoses. Mol Genet Metab. 2024;142(4):108535.
3. Rouse CJ, Jensen VN, Heldermon CD. Mucopolysaccharidosis type IIIB: a current review and exploration of the AAV therapy landscape. Neural Regen Res. 2024;19(2):355-9.
4. Wagner VF, Northrup H. Mucopolysaccharidosis Type III. 2019 Sep 19. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.
5. Okur I, Ezgu F, Giugliani R, Muschol N, Koehn A, Amartino H, et al. Longitudinal natural history of pediatric subjects affected with mucopolysaccharidosis IIIB. J Pediatr. 2022;249:50-58.e2.
6. Kim MS, Yang A, Noh ES, Kim C, Bae GY, Lim HH, et al. Natural history and molecular characteristics of Korean patients with mucopolysaccharidosis type III. J Pers Med. 2022;12(5):665.
7. Lavery C, Hendriksz CJ, Jones SA. Mortality in patients with Sanfilippo syndrome. Orphanet J Rare Dis. 2017;12(1):168.

Corresponding author:
Irene Chang (Irene.chang@ucsf.edu)

Presented at:
22nd Annual WORLDSymposium 2026
February 2-6, 2026
San Diego, CA, USA