In-depth analyses of cognition, motor, communication, and adaptive natural history disease course in participants with MPS IIIB

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Background and objectives

- Mucopolysaccharidosis (MPS) IIIB is an ultra-rare lysosomal storage disorder caused by deficiency of the α-*N*-acetylglucosaminidase (NAGLU) enzyme, resulting in accumulation of heparan sulfate (HS) within lysosomes and progressive neurodegeneration[1, 2].
- Neurodegeneration manifests as developmental and speech delay, resulting in severe intellectual disability, and other neurologic manifestations such as autism spectrum disorder, behavioral problems, and sleep disturbance[1, 2].
- This study (NCT03227042) aimed to characterize disease progression in pediatric patients with severe, non-attenuated MPS IIIB in terms of neurocognitive function, adaptive skills, behavior, quality of life, sleep disturbances, family impact, and biochemical measures of disease burden.

Methods

- Prospective, multicenter, multinational, noninterventional, longitudinal natural history study in participants aged ≤18 years with MPS IIIB confirmed by deficient NAGLU enzyme activity.
- Neurocognitive function and adaptive skills were assessed for up to 240 weeks using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) and the Vineland Adaptive Behavior Scales, Second Edition (VABS-II). The VABS-9 composite score was derived from 3 domains of the VABS-II (communication, daily living skills, socialization).
- The BSID-III has been validated for children aged 1–42 months, but was also used in older children with MPS IIIB if developmental functioning remained within this range.
- Behavior, sleep, quality of life (QoL), and family impact were evaluated using the Sanfilippo Behavior Rating Scales, Children's Sleep Habits Questionnaire, Infant-Toddler Quality of Life (ITQOL) questionnaire, and Pediatric Quality of Life Inventory™ (PedsQL) Family Impact Module.
- Neurocognitive, adaptive skills, behavioral, sleep, QoL, and family impact outcomes were summarized descriptively by chronological age and/or by visit.
- Urinary HS and HS non-reducing end (HS-NRE) levels, normalized to urine creatinine, were measured for up to 72 weeks and summarized by visit.
- The Full Analysis Set included all enrolled participants who carried *NAGLU* allelic variants associated with a severe, non-attenuated MPS IIIB phenotype.

Results

- Among 44 enrolled participants, 40 carried *NAGLU* allelic variants associated with severe MPS IIIB and were included in the analysis **(Table 1)**. Mean follow-up was 39.9 months (~3.3 years).
- Baseline medical history, concomitant medication use, and physical examination findings were consistent with the known clinical profile of severe MPS IIIB.
- Urinary HS and HS-NRE levels, normalized to creatinine, were at least sevenfold above the upper limit of normal at all time points over a 72-week (~1.4-year) observation period.
- Mean BSID-III cognitive raw score increased, albeit at a slower rate than expected for typical development, until approximately 60–66 months of age (maximum mean score of 53 at 66 months), plateaued between 60 and 78 months, and subsequently decreased to a mean score of 33 by 132 months of age **(Figure 1)**.
- BSID-III and VABS-II fine and gross motor skills, communication, daily living skills, and socialization domain scores as well as VABS-9 composite score showed a pattern similar to cognitive scores **(Figure 1)**.
- Behavior and sleep assessments remained relatively stable throughout the study, whereas QoL assessments showed declines across several ITQOL and PedsQL domains over time.
- Most longitudinal data were derived from individuals aged 5–11 years, limiting interpretation outside this age range.
- Eight participants reported ≥1 serious adverse event, including 1 death at 13.5 years of age considered due to disease progression; seizures were reported in 7 participants.

Table 1. Demographics and baseline characteristics

	Total (N=40)[a]
Age at enrollment, months	
Mean (SD)	82.2 (37.7)
Median (min, max)	76.0 (12.0, 164.0)
Sex, n (%)	
Male	22 (55.0)
Female	18 (45.0)
Ethnicity, n (%)	
Hispanic or Latino	11 (27.5)
Not Hispanic or Latino	29 (72.5)
Age at onset of initial presenting symptoms, months (n=38)	
Mean (SD)	19.7 (15.4)
Median (min, max)	16.0 (2.0, 72.0)
BSID-III cognitive raw score (n=37)	
Mean (SD)	41.4 (18.6)
Median (min, max)	39.0 (3.0, 72.0)
BSID-III cognitive AEq score, months (n=37)	
Mean (SD)	13.7 (8.4)
Median (min, max)	11.0 (0.5, 31.0)
VABS-9 composite raw score (n=39)	
Mean (SD)	279.8 (187.5)
Median (min, max)	216.0 (35.0, 697.0)
VABS-9 composite AEq score, months (n=39)	
Mean (SD)	16.6 (11.1)
Median (min, max)	13.0 (2.0, 44.0)

[a]n=40 for all variables unless indicated otherwise. AEq: age-equivalent; max: maximum; BSID-III: Bayley Scales of Infant and Toddler Development, Third Edition; HS: heparan sulfate; HS-NRE: heparan sulfate non-reducing end; min: minimum; N: number of participants in the analyses set; n: number of participants in each category; SD: standard deviation; VABS-9: Vineland Adaptive Behavior Scales, Second Edition composite score including communication, daily living skills, and socialization

Figure 1. Mean BSID-III and VABS-II raw scores by chronological age



Time points at the end of the observation period where analyses included ≤2 participants are not included in the graphs. Once a participant reached the BSID-III ceiling, raw scores were imputed at the ceiling value.
BSID-III: Bayley Scales of Infant and Toddler Development, Third Edition; n: number of participants; NA: not applicable; SE: standard error; VABS-II: Vineland Adaptive Behavior Scales, Second Edition; VABS-9: VABS-II composite score including communication, daily living skills, and socialization.

Conclusions

- This prospective, longitudinal natural history study characterizes the age-dependent trajectory of cognitive and adaptive skill acquisition and subsequent decline in individuals with severe, non-attenuated MPS IIIB.
- These findings may facilitate earlier recognition and diagnosis of MPS IIIB through improved disease characterization and may inform future evaluation of cognitive and adaptive outcomes in clinical trials.

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