

Interim analysis of a phase 1/2 study of weekly intravenous tvidenofusp alfa in mucopolysaccharidosis type II

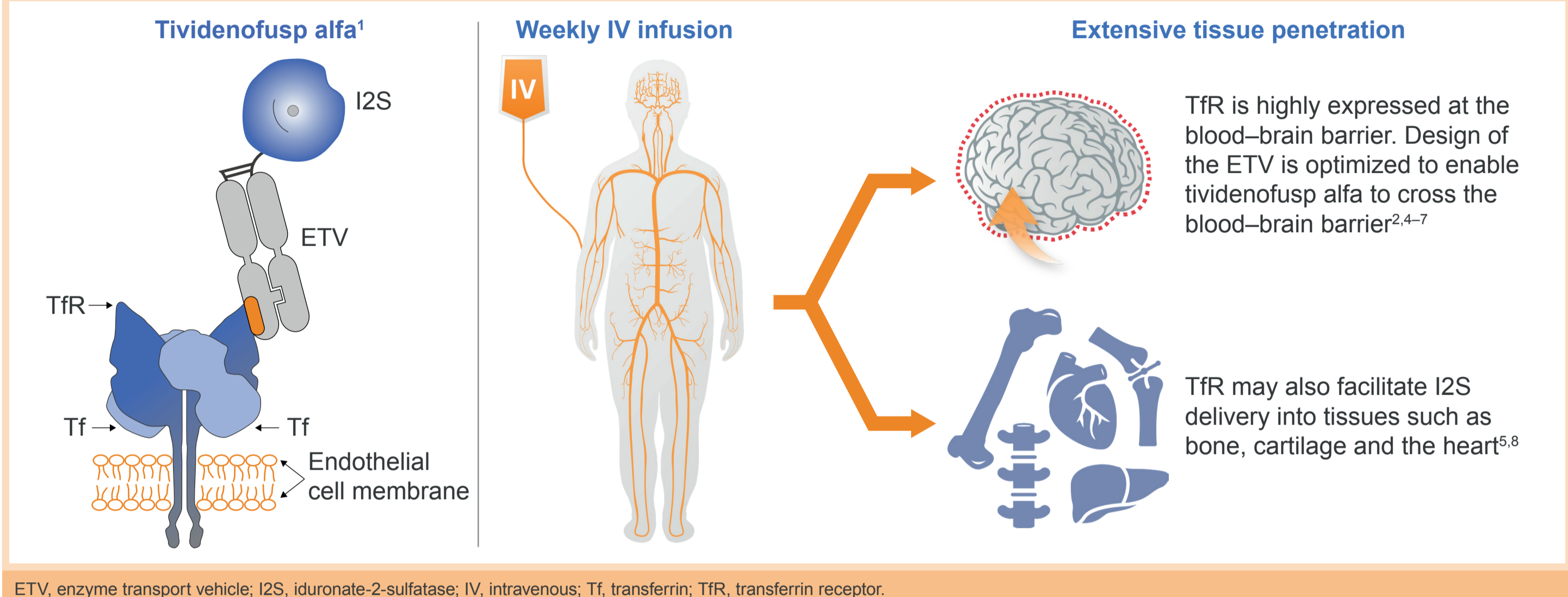
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Background

- Mucopolysaccharidosis type II (MPS II; Hunter syndrome) is a rare, X-linked, genetic disease caused by insufficient or absent activity of the lysosomal enzyme, iduronate-2-sulfatase (I2S).¹
- Deficient I2S activity leads to the accumulation of glycosaminoglycans, particularly heparan sulfate (HS) and dermatan sulfate (DS).^{1,2}
- Disease manifestations include both somatic and neurocognitive signs and symptoms; however, standard of care (SOC) enzyme replacement therapy (ERT) does not address the neurocognitive symptoms of MPS II because SOC ERT does not cross the blood-brain barrier.^{1,3}
- Tvidenofusp alfa (DNL310, ETV:IDS), a novel ERT, is an investigational I2S fusion protein engineered to cross the blood-brain barrier and reach the central nervous system (CNS) while maintaining or improving therapeutic benefit on somatic manifestations compared with SOC (Figure 1).
- Here, we evaluate the safety and efficacy of tvidenofusp alfa to treat CNS and somatic manifestations of MPS II using interim data from an ongoing phase 1/2 study (NCT04251026).

Figure 1. Structure and mechanism of action of tvidenofusp alfa

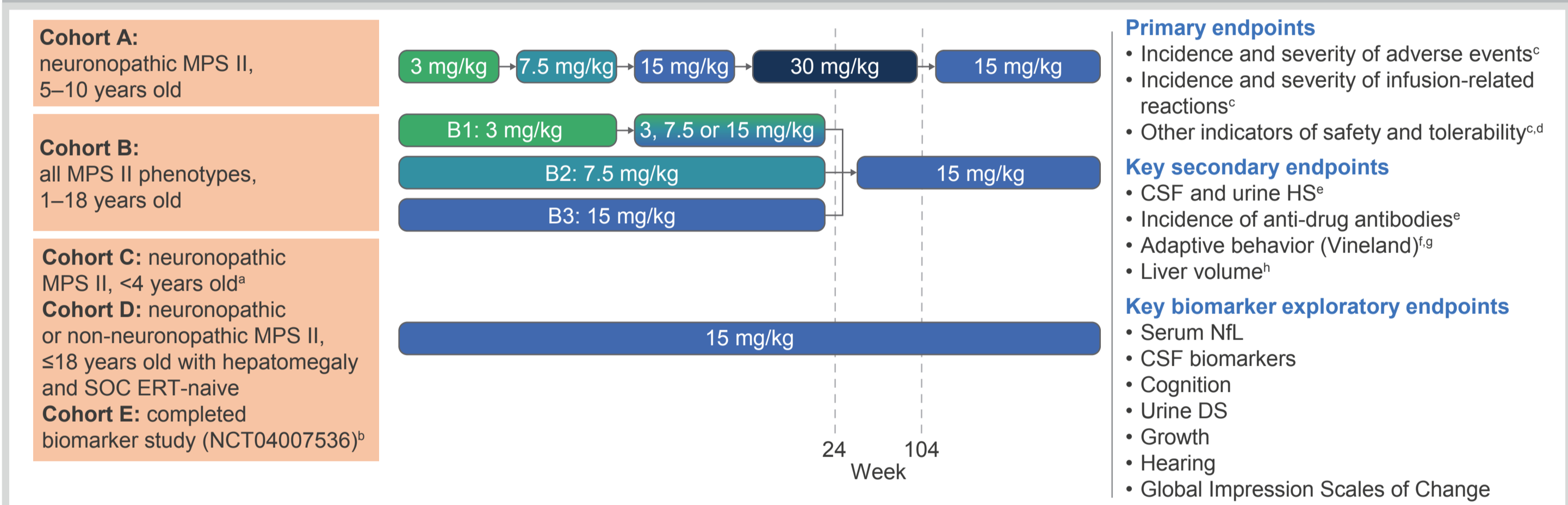


Methods

Study design

- NCT04251026 is an ongoing open-label, 24-week, phase 1/2 study followed by an open-label extension (Figure 2).
- Male individuals with MPS II aged ≤18 years were eligible.
- Participants were enrolled into 1 of 5 cohorts (A–E) based on variables, including age, MPS II phenotype and tvidenofusp alfa dose levels (Figure 2).
- Participants receiving SOC ERT at baseline were switched to tvidenofusp alfa without a washout period.

Figure 2. Overview of the tvidenofusp alfa phase 1/2 study design



^aThis cohort could include participants aged 4–16 years if they were a blood relative of a participant aged <4 years. ^bThis cohort included participants who had completed at least 48 weeks in NCT04007536 and with neuropathic MPS II (aged ≥8 years, or 1–18 years if they had a history of hematopoietic stem cell transplantation or gene therapy) or non-neuropathic MPS II (aged <6 or ≥17 years). ^cEndpoint assessed at 24, 104 and 261 weeks. ^dCFB in urine total GAG concentrations and in concomitant medications. ^eEndpoint assessed at 24 weeks. ^fEndpoint assessed at 49 weeks. ^gCFB in the Vineland composite and subdomain scores. ^hEndpoint assessed at 24 and 49 weeks. CFB, change from baseline; CSF, cerebrospinal fluid; DS, dermatan sulfate; ERT, enzyme replacement therapy; GAG, glycosaminoglycan; HS, heparan sulfate; MPS II, mucopolysaccharidosis type II; NFL, neurofilament light chain; SOC, standard of care.

Study assessments

- Safety outcomes were assessed in the safety population (all participants who received at least one dose of tvidenofusp alfa).
- For biomarker analyses, mean percentage change from baseline is reported for cerebrospinal fluid (CSF) HS, urine HS and DS, and serum neurofilament light chain (NFL), with baseline defined as the last result before the first dose of tvidenofusp alfa. Unscheduled collections performed in lieu of a planned collection were treated as having occurred at the closest planned visit.
- The following clinical outcomes were assessed: Vineland Adaptive Behavior Scales, second edition (VABS-II) and third edition (Vineland-3) scores; Bayley Scale of Infant Development, third edition (BSID-III) scores; Kaufman Assessment Battery for Children, second edition (KABC-II) scores; auditory brain stem response (ABR); height and weight over time; liver volume assessed by MRI over time.

Results

- All data are presented as of the September 1, 2023 interim data cutoff.

Participants

- For full baseline demographics and disease characteristic data, see Poster PO-230 or scan the QR code for Supplemental Table 1.
- As of September 1, 2023, 37 participants (median age: 5.1 years; 91.9% with neuropathic MPS II) were included in the safety population (cohort A, n=5; cohort B, n=18; cohort C, n=5; cohort D, n=6; cohort E, n=3; Table 1).
- Treatment is ongoing in 32/37 participants; five participants discontinued the study (withdrawal by parent or guardian [n=3], adverse event [n=1] or lost to follow-up [n=1]).
- Median duration of exposure of participants to study treatment was 100.0 weeks.

Table 1. Select baseline demographics and disease characteristics of participants

Age	Category, n (%)	Cohorts A–E (n=37)	
		n	(%)
MPS II phenotype, n (%)	<4 years	10	(27.0)
	4–6 years	12	(32.4)
	>6 years	15	(40.5)
MPS II phenotype, n (%)	Median (min–max), years	5.1	(1.8–12.6)
	Neuropathic	34	(91.9)
ERT status at enrollment	Non-neuropathic	3	(8.1)
	SOC ERT-naïve, n (%) ^a	10	(27.0)
	SOC ERT-exposed, n (%)	27	(73.0)

Data are presented for the safety population. ^aIncludes one participant who underwent allogeneic hematopoietic stem cell transplantation. ERT, enzyme replacement therapy; max, maximum; min, minimum; MPS II, mucopolysaccharidosis type II; SOC, standard of care.

Safety outcomes

- Tvidenofusp alfa was generally well tolerated. Treatment-emergent adverse events (TEAEs) were reported in 37 participants (100%) in the safety population; however, the highest severity of TEAE experienced was mostly mild or moderate (n=31 [83.8%]).

Biomarkers

- For full biomarker data, see Poster PO-230 or scan the QR code for Supplemental Figures 1–3.
- Treatment with tvidenofusp alfa resulted in a 90% reduction from baseline in CSF HS levels, observed as early as Week 24. At this point, 27/31 participants (87.1%) had CSF HS values within the limits of normal. This reduction was sustained through Week 104 and was observed across all age groups (Supplemental Figure 1).
- Urine HS showed a >80% mean percent reduction from baseline at Week 24 and this effect was sustained through Week 129; consistent results were observed in urine DS levels (for all patients, $P<0.0001$; Supplemental Figure 2). Total urinary GAGs (as measured by colorimetric assay) showed 2/37 participants (5.4%) were within the normal range at baseline, and after treatment with tvidenofusp alfa the proportion increased to 20/26 participants (76.9%) at Week 24 and was sustained through Week 129, with 10/12 participants (83.3%) within normal range.
- Treatment with tvidenofusp alfa showed a significant and sustained reduction from baseline in mean serum NFL levels from baseline, which reached significance at Week 61 and had a >80% reduction by Week 129. All participants were below the upper limit of the normal range by Week 129 (please see Poster PO-230 Figure 4A).
- This suggests a robust and sustained improvement in neuronal health across all age groups (Supplemental Figure 3).

Tvidenofusp alfa (DNL310) is an investigational drug and has not been approved by any health authority. Denali Therapeutics Inc. All rights reserved 2024.
Presented at the Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM), September 3–6, 2024, Porto, Portugal.

Clinical

Neurocognitive and behavioral outcomes

- VABS-II total raw score continued to increase from baseline through Week 104 (Figure 3A).
- Cognitive function, as measured by BSID-III raw score, showed continued stabilization in the 12 participants with 104 weeks of follow-up (Figure 3B).
 - In these 12 participants, improvement was observed at both Week 49 (mean change=+2.7) and Week 104 (mean change=+3.2).
 - Notably, 5/6 patients assessed with KABC-II at baseline stabilized or improved on KABC-II at Week 104 and are represented in Figure 3A but not in Figure 3B.

ABR thresholds

- ABR thresholds showed evidence of improvement in hearing from baseline to Week 24, with statistically significant improvement observed at the higher frequencies (1000, 2000, 4000 Hz) at Week 104 (Figure 4).
- Change from baseline in average ABR threshold by ear showed that most participants either had improved or unchanged hearing at the last time point (n=30; Figure 4B).
- Consistent results were obtained when assessing the pure tone average (defined as the average of 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz) in the subset of participants with all four frequencies at baseline and the last follow-up (n=20; data not shown).

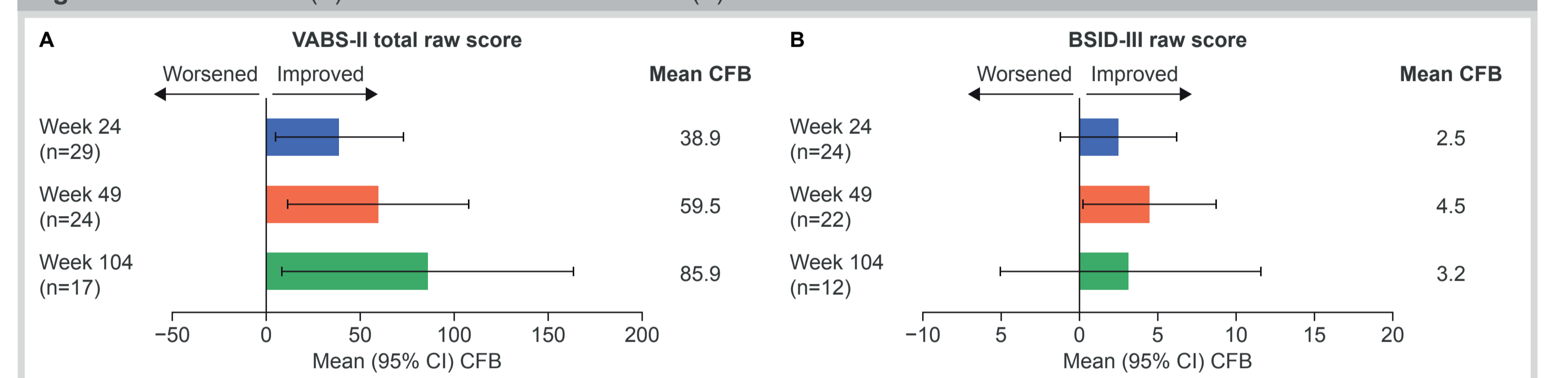
Growth

- When plotted on growth curves, height and weight tended to follow a consistent percentile for age throughout the study period (Supplemental Figure 4A, B).
 - Height and weight were above the 50th percentile for healthy males in most participants across all study time points.
- Participants tended to have stable height and weight Z-scores, suggesting that the growth velocity was in line with an age-matched normative sample (Supplemental Figure 4C, D).

Liver volume

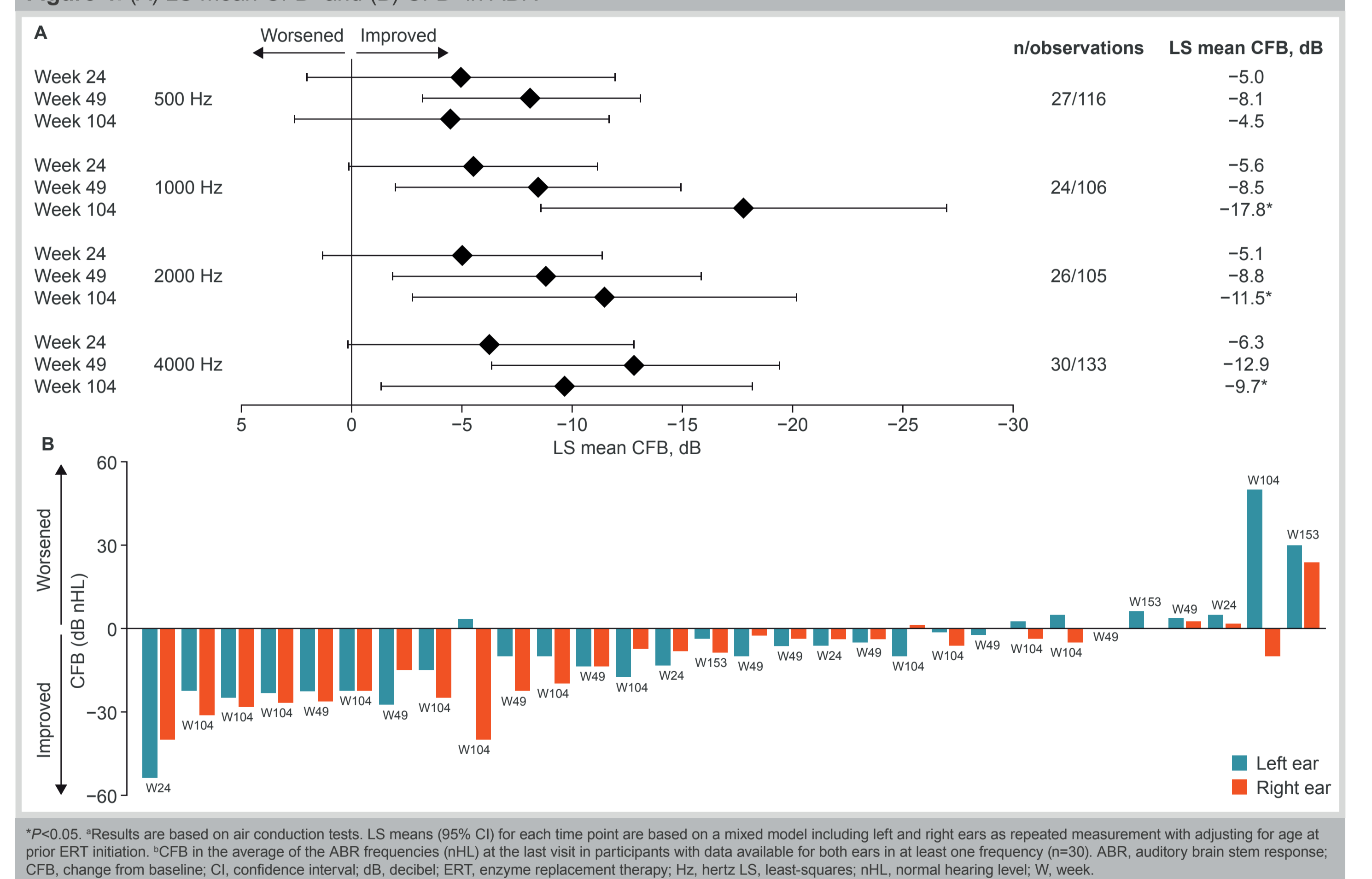
- For liver volume assessed by MRI, 3/7 participants (42.9%) had values within the normal range at baseline, compared with all 6/6 participants at Week 24 and 11/11 participants at Week 49.

Figure 3. Mean CFB in (A) VABS-II total raw score^a and (B) BSID-III raw score^b



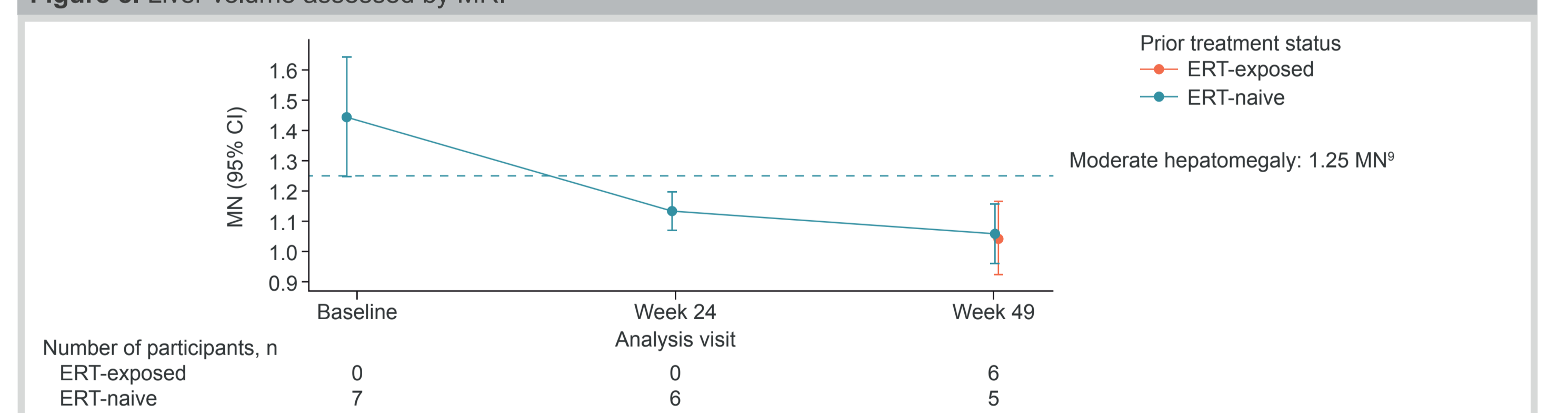
^aVABS-II total raw scores were the sum across all measured domains except written communication, domestic daily living and community daily living. Vineland-3 total adaptive behavior scores were converted to VABS-II using orthogonal regression in eight participants at Week 24, nine participants at Week 49 and one participant at Week 104. For participants who transitioned from BSID-III to KABC-II during follow-up, a BSID-III score of 91 was imputed in this analysis. Imputed values were used in three participants at Week 24, four participants at Week 49 and two participants at Week 104. Participants who had a baseline KABC-II value but no baseline BSID-III value were excluded because such an imputation would lead to an uninformative change value of 0. BSID-III, Bayley Scales of Infant and Toddler Development, third edition; CFB, change from baseline; CI, confidence interval; KABC-II, Kaufman Assessment Battery for Children, second edition; VABS-II, Vineland Adaptive Behavior Scales, second edition; Vineland-3, Vineland Adaptive Behavior Scales, third edition.

Figure 4. (A) LS mean CFB^a and (B) CFB^b in ABR



^a $P<0.05$. ^bResults are based on air conduction tests. LS means (95% CI) for each time point are based on a mixed model including left and right ears as repeated measurement with adjusting for age at prior ERT initiation. ^cCFB in the average of the ABR frequencies (nHL) at the last visit in participants with data available for both ears in at least one frequency (n=30). ABR, auditory brain stem response; CFB, change from baseline; CI, confidence interval; dB, decibel; ERT, enzyme replacement therapy; Hz, hertz; LS, least-squares; nHL, normal hearing level; W, week.

Figure 5. Liver volume assessed by MRI



Most ERT-exposed participants (n=23–24; n varies by time point) underwent abdominal ultrasound (not shown), whereas most ERT-naïve participants (n=5–7; n varies by time point) underwent abdominal MRI at baseline, Week 24 and Week 49. CI, confidence interval; ERT, enzyme replacement therapy; MN, multiples of normal; MRI, magnetic resonance imaging.

Conclusions

- Interim data of >2 years of tvidenofusp alfa treatment from the ongoing phase 1/2 study show normalization of the key biomarkers of CSF HS, urine HS and DS, and serum NFL.
- These data also show continued CNS and somatic effects in adaptive behavior and cognitive scores, as well as growth outcomes.
- Tvidenofusp alfa is generally well tolerated, with a safety profile that continues to support development as a treatment for MPS II. A registration-enabling phase 2/3 study (COMPASS; NCT05371613) is enrolling, with sites in Europe and North and South America.

ACKNOWLEDGMENTS

We give a special thank you to the patients and families who generously contributed through their participation. We also thank our collaborators and the Denali Therapeutics team for the conduct of the study and the collection of data.

DISCLOSURES

This poster was sponsored by Denali Therapeutics Inc. Medical writing support was provided by Ishmam Nawar MSc of Oxford PharmaGenesis Ltd, UK and was funded by Denali Therapeutics Inc. **BKB** has received consulting fees and/or honoraria from Agios Pharmaceuticals, Ailtra, Aro Biotherapeutics, BioMarin Pharmaceutical, Chiesi, Horizon Therapeutics, JCR Pharmaceuticals, Mazze Therapeutics, Moderna, Orchard Therapeutics, Passage Bio, Sanofi, Spur Therapeutics (formerly Freeline), Takeda and Ultragenyx; and has conducted clinical trials funded by BioMarin Pharmaceutical, Denali Therapeutics, Homology Medicines, JCR Pharmaceuticals, Sangamo Therapeutics and Ultragenyx. **JM** has served as a consultant and/or on advisory boards for BioMarin Pharmaceutical, Denali Therapeutics, JCR Pharmaceuticals, REGENXBIO, Sanofi Genzyme and Takeda (formerly Shire), and is the principal investigator for phase 1/2 and phase 2/3 intrathecal enzyme replacement clinical trials for MPS II, a phase 1/2 gene editing clinical trial for MPS II, and phase 1/2 and phase 2/3 IV ERT clinical trials for MPS II. **PH** has conducted research funded by Adrenas Therapeutics, Amicus Therapeutics, Ascendis Pharma, ASPA Therapeutics, Azafaros, BioMarin Pharmaceutical, Calylix Therapeutics, Denali Therapeutics, Homology Medicines, JCR Pharmaceuticals, Orphazyme, Preval Therapeutics, QED Therapeutics, REGENXBIO, Sangamo Therapeutics and Takeda, and has received consulting fees from Aeglea BioTherapeutics, Audentes Therapeutics, Capsida Biotherapeutics, Chiesi, Edigene Biotechnology, Grace Science, Inventiva Pharma, Neurogene, Novel Pharma, Orchard Therapeutics, Rallybio, Renoviron and SatisGen Therapeutics. **DR** is a principal investigator on clinical trials funded by Denali Therapeutics, Preval Therapeutics, REGENXBIO, Takeda and Ultragenyx; and has conducted research funded by the Scleroderma Foundation and the Children's Neuroscience Institute, UPMC Children's Hospital of Pittsburgh. **SAJ** is an investigator and/or consultant for Alexion Pharmaceuticals, BioMarin Pharmaceutical, Orchard Therapeutics and Takeda (formerly Shire), and is a scientific advisory board member and stockholder of Orchard Therapeutics. **JMPvdH** has acted as a consultant, lecturer and investigator for registries and clinical trials, and has participated in research via contracts between Erasmus University Medical Center and Amicus Therapeutics, BioMarin Pharmaceutical, Denali Therapeutics, Sanofi, Spark Therapeutics and Takeda. **JJM** has served as a consultant for BioMarin Pharmaceutical, Denali Therapeutics, Sanofi Genzyme, Takeda and Ultragenyx. **KM**, **MDT**, **NJE**, **RC**, **AB**, **IZ**, **AW**, **PC** and **CH** are full-time employees of Denali Therapeutics Inc., which has filed patent applications related to the subject matter. **AIB** is a former employee of Denali Therapeutics Inc.

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