PO-230

Neurofilament light chain (NfL) levels are associated with genotype and disease severity in mucopolysaccharidosis (MPS) type II

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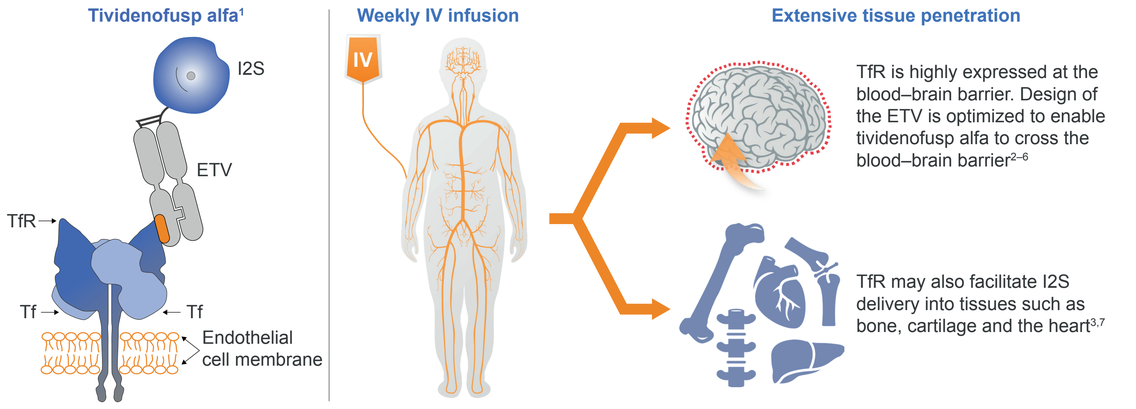
Background

- Mucopolysaccharidosis type II (MPS II; Hunter syndrome) is an X-linked recessive disease caused by a deficiency of iduronate-2-sulfatase (I2S) activity.[1]
- Deficient I2S activity leads to the accumulation of glycosaminoglycan substrates, particularly heparan sulfate (HS) and dermatan sulfate (DS), causing subsequent lysosome dysfunction in multiple organs and tissues, including the central nervous system (CNS).[1]
- MPS II presents with a wide range of symptoms; approximately two-thirds of patients have neuronopathic MPS II, characterized by progressive and debilitating neurocognitive deficits.[1]
- Neurofilament light chain (NfL), a marker of neuronal injury, is elevated in the cerebrospinal fluid (CSF) and serum of individuals with MPS II, and NfL can be used to monitor neurodegeneration.[1]
- Tividenofusp alfa (DNL310, ETV:IDS), a novel enzyme replacement therapy (ERT), is an investigational I2S fusion protein engineered to cross the blood–brain barrier and reach the CNS while maintaining or improving therapeutic benefit on somatic manifestations compared with standard of care (SOC; **Figure 1**).
- Using interim data from an ongoing phase 1/2 study of tividenofusp alfa (NCT04251026), we evaluated the effect of treatment with tividenofusp alfa on levels of NfL, a biomarker of neurodegeneration.

Figure 1. Structure and mechanism of action of tividenofusp alfa



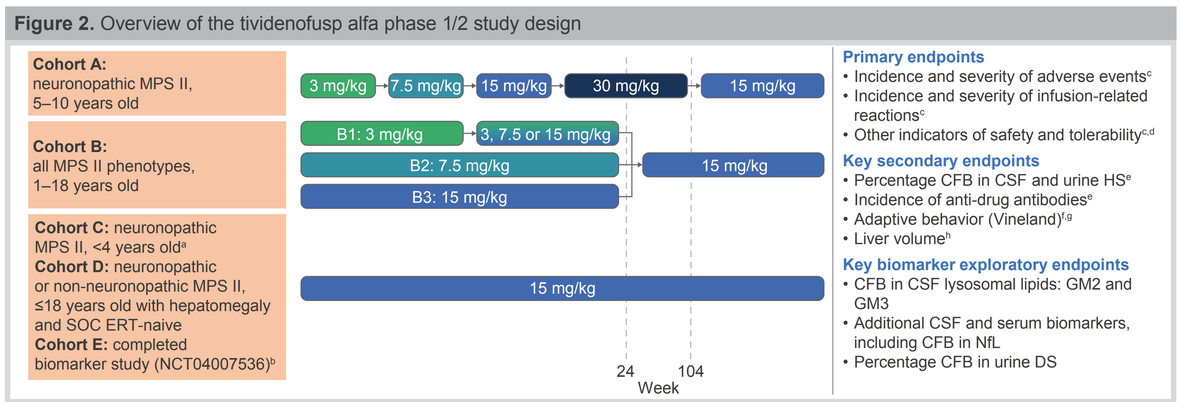
ETV, enzyme transport vehicle; I2S, iduronate-2-sulfatase; IV, intravenous; Tf, transferrin; TfR, transferrin receptor.

Methods

Study design

- NCT04251026 is an ongoing, open-label, 24-week, phase 1/2 study followed by an open-label extension in males with MPS II aged ≤18 years with either neuronopathic or non-neuronopathic disease (**Figure 2**).
- Participants were enrolled into 1 of 5 cohorts (A–E) of different patient inclusion criteria and/or tividenofusp alfa dose regimens (**Figure 2**).
- The safety population included all participants who received at least one dose of tividenofusp alfa (n=37). Serum NfL data were available for a subset of participants (n=27) as of September 1, 2023.
- Participants receiving SOC ERT at baseline were switched to tividenofusp alfa without a washout period.

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



[a]This cohort could include participants aged 4–18 years if they were a blood relative of a participant aged <4 years. [b]This cohort included participants who had completed at least 48 weeks in NCT04007536 and with neuronopathic MPS II (aged ≥6 years, or 1–18 years if they had a history of hematopoietic stem cell transplantation or gene therapy) or non-neuronopathic MPS II (aged <6 or ≥17 years). [c]Endpoint assessed at 24, 104 and 261 weeks. [d]CFB in urine total GAG concentrations and in concomitant medications. [e]Endpoint assessed at 24 weeks. [f]Endpoint assessed at 49 weeks. [g]CFB in the Vineland composite and subdomain scores. [h]Endpoint assessed at 24 and 49 weeks. CFB, change from baseline; CSF, cerebrospinal fluid; DS, dermatan sulfate; ERT, enzyme replacement therapy; GAG, glycosaminoglycan; GM, monosialic ganglioside; HS, heparan sulfate; MPS II, mucopolysaccharidosis type II; NfL, neurofilament light chain; SOC, standard of care.

Interim biomarker analyses

- HS levels (sum of D0A0, D0A6, D0S0 and D2S6) were quantified in CSF by liquid chromatography–mass spectrometry using reference and internal standards after enzymatic digestion.
- Serum NfL was measured using a validated single-molecule array ultrasensitive enzyme-linked immunosorbent assay.
- For change from baseline analyses for each biomarker, baseline was defined as the last result before the first dose of tividenofusp alfa. Unscheduled collections performed in lieu of a planned collection were treated as having occurred at the closest planned visit.

Results

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

Participants

- As of September 1, 2023, 37 participants (median age: 5.1 years; 91.9% with neuronopathic 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**).

Table 1. Baseline demographics and disease characteristics of participants

		Cohorts A–E (n=37)
Age	Category, n (%)	
	<4 years	10 (27.0)
	4–6 years	12 (32.4)
	>6 years	15 (40.5)
	Median (min–max), years	5.1 (1.8–12.6)
MPS II phenotype, n (%)	Neuronopathic	34 (91.9)
	Non-neuronopathic	3 (8.1)
Variant type, n (%)	Missense/synonymous	19 (51.4)
	Large deletions/rearrangement	5 (13.5)
	Other[a]	13 (35.1)
ERT status at enrollment	SOC ERT-naive,[b] n (%)	10 (27.0)
	SOC ERT-exposed, n (%)	27 (73.0)
	Duration of SOC ERT, median (min–max), years[c]	2.2 (0.4–11.2)
Race, n (%)	Asian	4 (10.8)
	Black or African American	1 (2.7)
	White	21 (56.8)
	Not reported, unknown or other	11 (29.7)
Ethnicity, n (%)	Hispanic or Latino	6 (16.2)
	Not Hispanic or Latino	29 (78.4)
	Not reported	2 (5.4)

Data are presented for the safety population. [a]Includes nonsense and splice site/intron. [b]Includes one participant who underwent allogeneic hematopoietic stem cell transplantation. [c]n=26. ERT, enzyme replacement therapy; max, maximum; min, minimum; MPS II, mucopolysaccharidosis type II; SOC, standard of care.

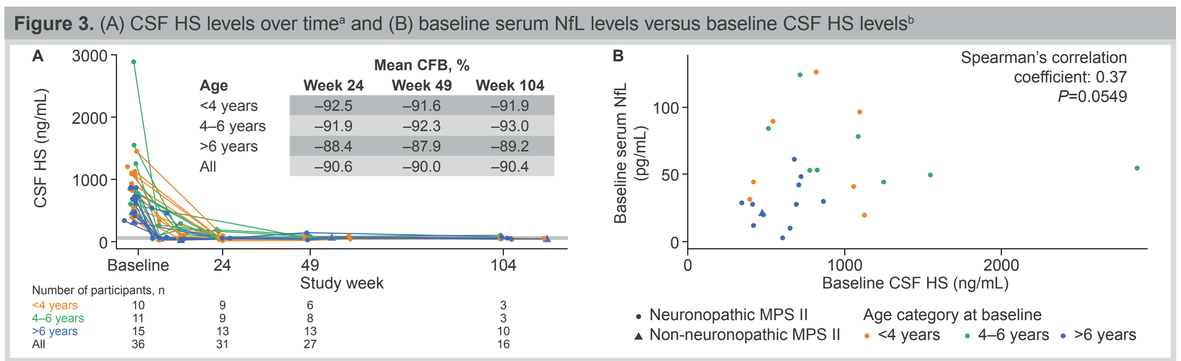
Change in CSF HS with tividenofusp alfa and correlation between baseline CSF HS and serum NfL

- A 90% reduction from baseline in CSF HS levels was observed as early as Week 24, at which point 27/31 participants had CSF HS values within the limits of normal. This reduction was sustained through Week 104 and was consistent across all age groups (**Figure 3A**).
- Baseline serum NfL levels tended to show a moderate positive correlation with baseline CSF HS levels (**Figure 3B**).

Change in serum NfL over time with tividenofusp alfa treatment

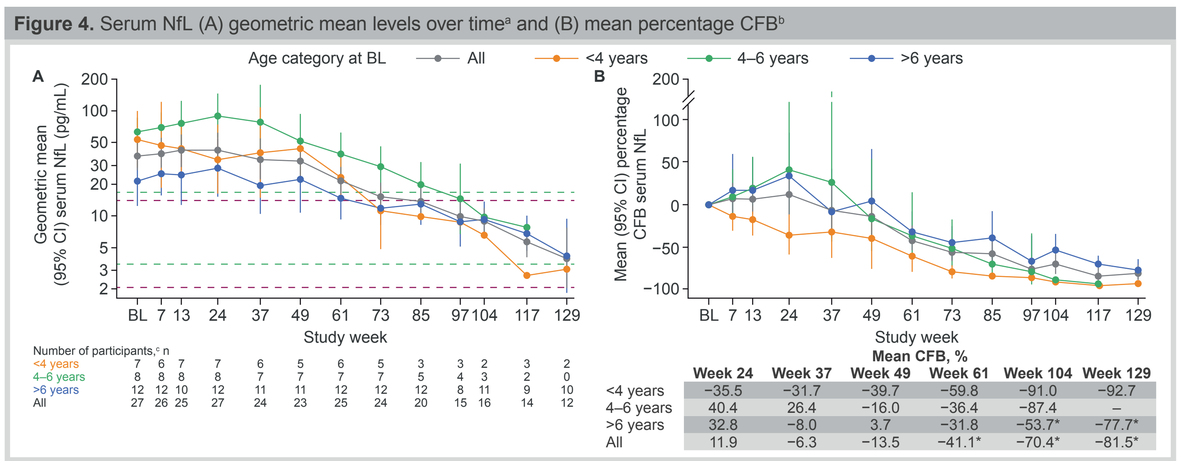
- Treatment with tividenofusp alfa showed a significant and sustained reduction from baseline in mean serum NfL levels from baseline, reaching a >80% reduction by Week 129 with all participants achieving levels below the upper limit of the normal range by Week 117 (**Figure 4A, B**).
  - Participants aged <4 years at treatment initiation exhibited a trend for more rapid reductions than other age groups, with a 36% reduction from baseline occurring as early as Week 24 (**Figure 4B**).

Figure 3. (A) CSF HS levels over time[a] and (B) baseline serum NfL levels versus baseline CSF HS levels[b]



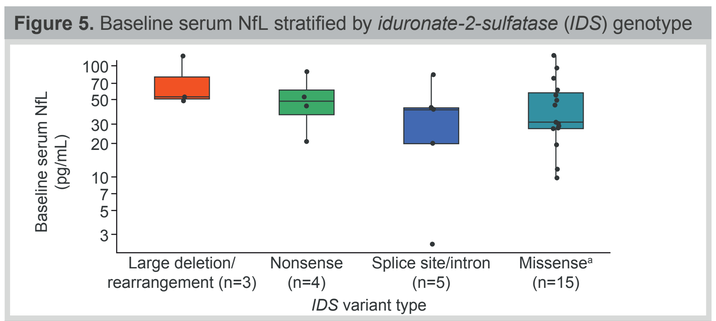
[a]Shaded gray area indicates the preliminary normal range of 39.1–92.5 ng/mL (10th to 90th percentiles) based on an analysis of CSF samples from 30 healthy adults (median [range] age: 52 [18–81] years). Total CSF GAG levels are similar in adults and children.[8] [b]Baseline serum NfL and CSF HS levels are available for 27 patients. CFB, change from baseline; CSF, cerebrospinal fluid; GAG, glycosaminoglycan; HS, heparan sulfate; MPS II, mucopolysaccharidosis type II; NfL, neurofilament light chain.

Figure 4. Serum NfL (A) geometric mean levels over time[a] and (B) mean percentage CFB[b]



*P<0.001. [a]Normal reference values for children aged <3 years are shown between the green dashed lines (3.5–16.6 pg/mL) and for children aged ≥3 years between the purple dashed lines (2.1–13.9 pg/mL).[9] [b]Aggregate summaries by time point were provided for analysis visits that are common across all cohorts. The Week 7 analysis visit included observations closest to the target day (i.e. Day 43) from Weeks 5, 7 or 9. Mean CFB was computed from the geometric mean ratio relative to BL. Corresponding 95% CI and P values were derived from the log ratio relative to BL. Percentage CFB was derived as 100^{x-1}, in which x denotes the mean ratio, upper and lower limits for the mean ratio. [c]Number of participants is the same in panels A and B. BL, baseline; CFB, change from baseline; CI, confidence interval; NfL, neurofilament light chain.

Figure 5. Baseline serum NfL stratified by *iduronate-2-sulfatase* (*IDS*) genotype



[a]Includes synonymous variants. *IDS*, iduronate-2-sulfatase gene; NfL, neurofilament light chain.

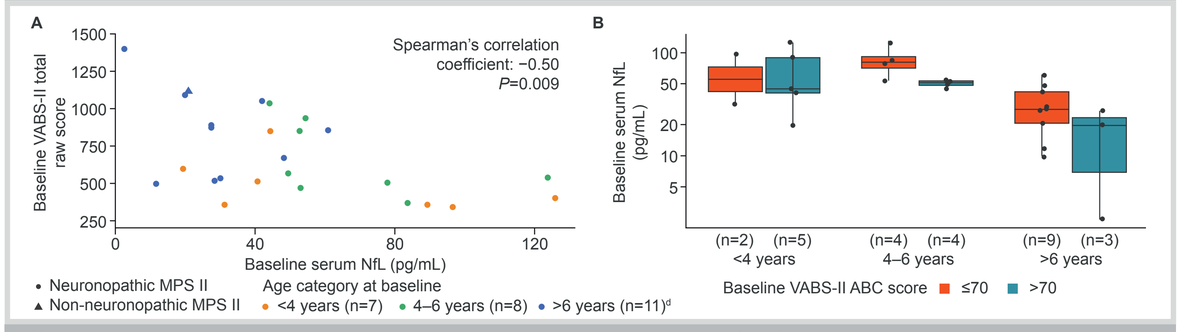
Baseline serum NfL and severity of MPS II variant type

- Median baseline serum NfL levels tended to be higher in participants with variants leading to a severe neuronopathic phenotype than in those with other variants (**Figure 5**).[10]

Baseline serum NfL and adaptive behavior and cognitive scores

- Higher baseline serum NfL levels were moderately correlated with lower baseline Vineland Adaptive Behavior Scales, second edition (VABS-II) total raw scores (**Figure 6A**).
- VABS-II adaptive behavior composite (ABC) standard scores account for age, so these data were stratified by age, as well as by ABC scores ≤70 (indicating significant impairment)[11] or >70.
  - Baseline median serum NfL levels were higher in participants with baseline ABC scores ≤70 versus >70 (**Figure 6B**).
- Higher baseline serum NfL levels were moderately correlated with lower baseline cognitive function, as measured by Bayley Scales of Infant and Toddler Development, third edition (BSID-III) cognitive raw scores (**Figure 7A**).
- This correlation was consistent when using BSID-III with Kaufman Assessment Battery for Children, second edition combined cognitive age-equivalent scores, allowing for cognitive scores above the BSID-III maximum age equivalence of 42 months (**Figure 7B**).
- All associations may be confounded by age because younger participants tended to have higher serum NfL levels and lower adaptive behavior and cognitive scores than older participants (**Figures 6 and 7**).

Figure 6. Baseline serum NfL and (A) baseline VABS-II total raw scores[a,b] and (B) baseline VABS-II ABC standard scores[c] stratified by baseline ABC score and age



[a]VABS-II total raw scores were the sum across all measured domains except written communication, domestic daily living and community daily living. [b]Six VABS-II total raw scores were converted from Vineland-3 scores by orthogonal regression. [c]Six VABS-II ABC scores were converted from Vineland-3 scores using a robust linear model adjusted by age. [d]Baseline ABC score not available for one participant. ABC, adaptive behavior composite; MPS II, mucopolysaccharidosis type II; NfL, neurofilament light chain; VABS-II, Vineland Adaptive Behavior Scales, second edition; Vineland-3, Vineland Adaptive Behavior Scales, third edition.

Figure 7. Baseline serum NfL levels versus baseline (A) BSID-III raw scores and (B) BSID-III/KABC-II combined age-equivalent scores

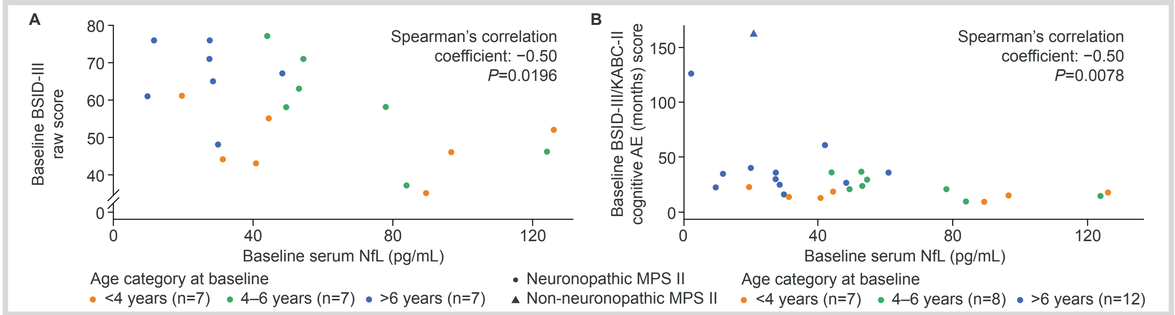


Figure 7A presents all available baseline BSID-III cognitive data and Figure 7B combines baseline BSID-III cognitive AEq or KABC-II AEq (average AEq from the triangle and hand movements subtests). If a patient had data on both BSID-III and KABC-II at baseline, the KABC-II AEq was prioritized for participants with a chronological age ≥36 months. AE, age-equivalent; AEq, age equivalence; BSID-III; Bayley Scales of Infant and Toddler Development, third edition; KABC-II, Kaufman Assessment Battery for Children, second edition; MPS II, mucopolysaccharidosis type II; NfL, neurofilament light chain.

Conclusions

- Serum NfL elevation in patients with MPS II appears to correlate with the severity of cognitive and behavioral impairments.
- A trend towards a moderate positive correlation between baseline serum NfL levels and baseline CSF HS level was observed.
- Tividenofusp alfa treatment significantly reduced serum NfL, a marker of neurodegeneration, with all participants achieving levels below the upper limit of the normal range by Week 117, suggesting a reduction of neuronal injury in participants with MPS II.
- These data support the potential of tividenofusp alfa to target the CNS manifestations of MPS II and for continued clinical development throughout this study and the ongoing COMPASS phase 2/3 trial (NCT05371613).

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DISCLOSURES

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