Phase 1/2 Study of Intravenous Tividenofusp Alfa for Mucopolysaccharidosis Type II

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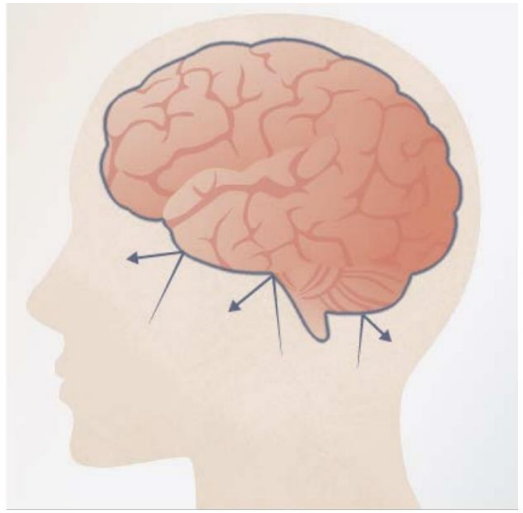
DEVELOPING A THERAPY FOR MPS II (HUNTER SYNDROME)

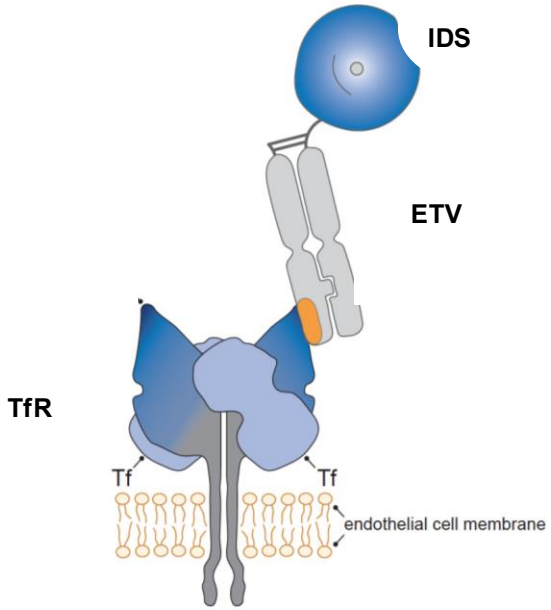
Tividenofusp alfa (DNL310) is an investigational IDS fusion protein engineered for CNS and peripheral delivery to address cognitive, behavioral, and somatic disease control in MPS II with a **weekly IV infusion**[1–3]

THE BBB CHALLENGE



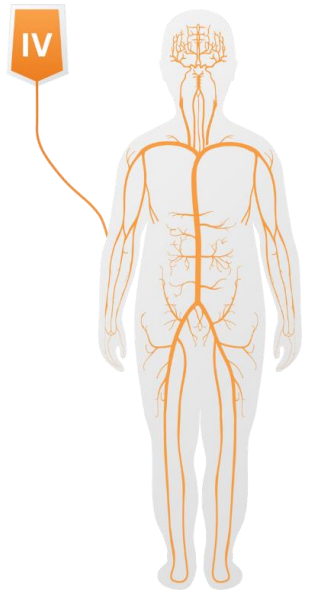
- The BBB is a major obstacle for brain delivery of enzymes

ETV™



- ETV is designed to use the TfR to cross the BBB and enhance delivery of biotherapeutics into the brain
- The TfR is the body's mechanism for iron transport from blood into brain and is highly expressed at the BBB

IV ADMINISTRATION AND BROAD BIODISTRIBUTION



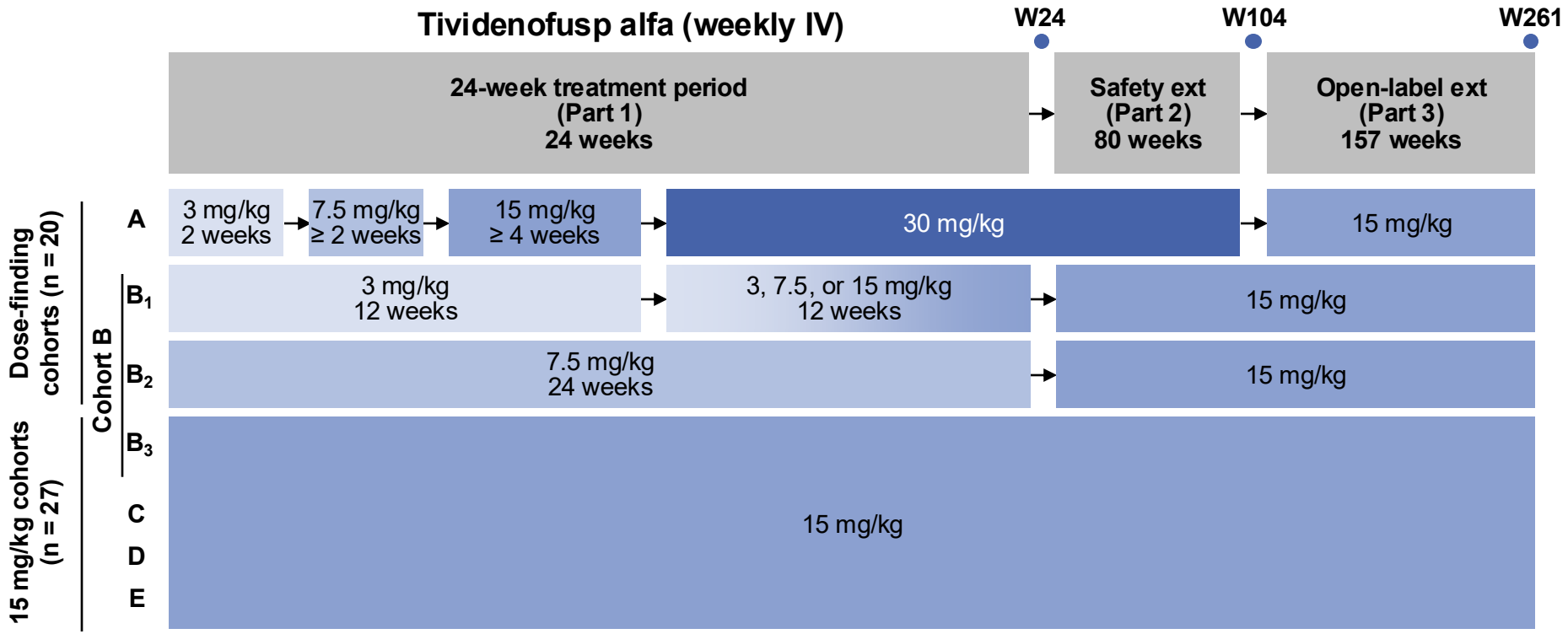
- Design of the ETV is optimized to enable DNL310 to cross the BBB and may also facilitate uptake into peripheral tissues

Tividenofusp alfa has the potential to treat neuronopathic and somatic manifestations of MPS II

1. Muenzer *et al. N Engl J Med* 2026;394:39–50; 2. Bhalla A *et al. Int J Mol Sci* 2020;21:5188; 3. Ullman JC *et al. Sci Transl Med* 2020;12:eaay1163. BBB, blood–brain barrier; CNS, central nervous system; ETV, Enzyme TransportVehicle™; IDS, iduronate-2-sulfatase; IV, intravenous; MPS II, mucopolysaccharidosis type 2; Tf, transferrin; TfR, Tf receptor.

TIVIDENOFUSP ALFA PHASE 1/2 STUDY IN PEDIATRIC PARTICIPANTS WITH MPS II

- Study DNLI-E-0002 is an international, open-label, 24-week study with safety and open-label extension periods (NCT04251026)
  - Data are presented from the clinical cutoff date of March 28, 2025 (when the last participant completed the Week 49 visit)
- 47 male participants with MPS II aged ≤ 18 years (ERT-naive and treatment-experienced) were enrolled into five cohorts (A–E) that differed in inclusion criteria for characteristics such as participant age and MPS II phenotype
- Participants receiving SOC IV ERT at baseline switched to tividenofusp alfa without a washout period



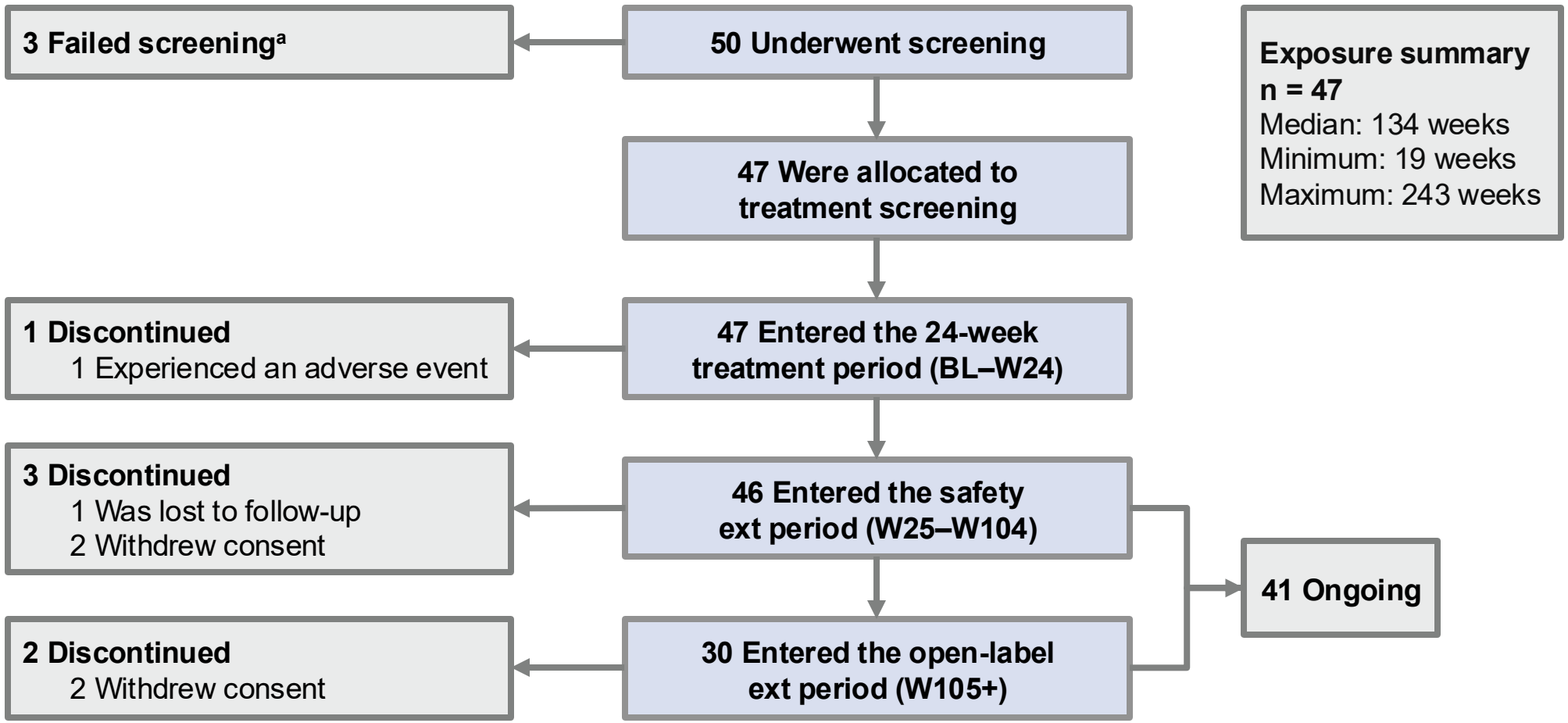
Primary endpoints
- Adverse events
- IRRs
- Other indicators of safety and tolerability

Key secondary endpoints
- CSF HS
- Urine HS
- Adaptive behavior (Vineland)
- Liver volume

Key exploratory endpoints
- Serum NfL
- CSF biomarkers
- Hearing threshold
- Cognition (BSID-III, KABC-II)

Figure adapted from *New Engl J Med*, Muenzer J *et al.*, An Intravenous Brain-Penetrant Enzyme Therapy for Mucopolysaccharidosis II, Vol. 394, pp. 39–50. Copyright © 2026 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. BSID-III, Bayley Scales of Infant Development, Third edition; CSF, cerebrospinal fluid; ERT, enzyme replacement therapy; ext, extension; HS, heparan sulfate; IRR, infusion-related reaction; KABC-II, Kaufman Assessment Battery for Children, Second Edition; NfL, neurofilament light chain; SOC, standard of care; W, week.

PARTICIPANT ENROLLMENT AND DISPOSITION



[a]Three participants were excluded due to withdrawal of consent, missing/not available DQ at screening, and lack of preexisting liver enlargement. BL, baseline; DQ, developmental quotient.

BASELINE CHARACTERISTICS

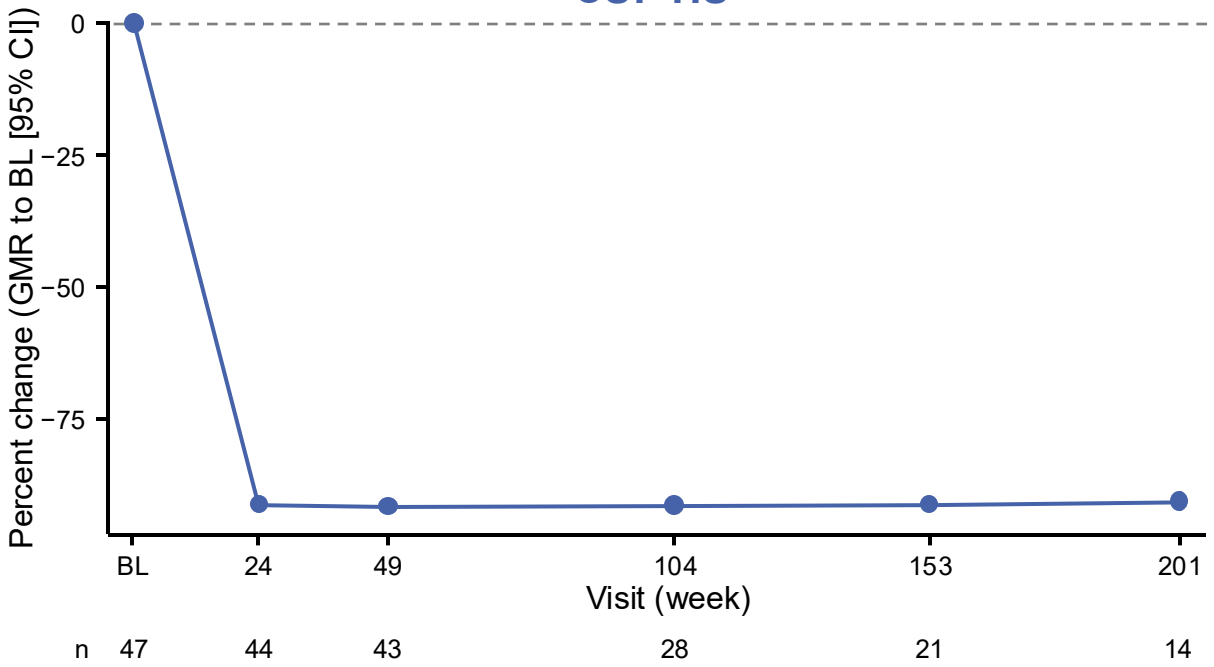
Characteristic		All (cohorts A–E) n = 47
Age, years	Mean (SD)	5.5 (3.1)
	Median (min, max)	5.0 (0.3, 12.6)
Age group, n (%)	< 4 years	14 (29.8)
	≥ 4 years	33 (70.2)
Sex, n (%)	Male	47 (100)
	Female	0
Race, n (%)	Asian	4 (8.5)
	Black/African American	4 (8.5)
	White	27 (57.4)
	Other	1 (2.1)
	More than one race	3 (6.4)
	Not reported/unknown	8 (17.0)
Ethnicity, n (%)	Hispanic/Latino	7 (14.9)
	Not Hispanic/Latino	38 (80.9)
	Not reported	2 (4.3)

Characteristic		All (cohorts A–E) n = 47
MPS II phenotype, n (%)	Neuronopathic	44 (93.6)
	Non-neuronopathic	3 (6.4)
DQ (n = 46)	Mean (SD)	55.1 (28.7)
Genetic variant type, n (%)	Missense/synonymous	22 (46.8)
	Large deletion/ rearrangement/stop/ frameshift shift/splice	25 (53.2)
Prior therapy group, n (%)	ERT (idursulfase IV)[a]	29 (61.7)
	ERT-naive	14 (29.8)
	HSCT/gene therapy[b]	4 (8.5)
Age at ERT (idursulfase IV) initiation, years (n = 33)	Mean (SD)	3.0 (2.0)
	Median (min, max)	3.1 (0.3, 10.1)
Duration on prior ERT (idursulfase IV), months	Mean (SD)	38.4 (32.3)
	Median (min, max)	25.6 (1.0, 134.5)
ADA status, n (%)	Positive	24 (51.1)
	Negative	23 (48.9)

Data previously reported in *New Engl J Med*, Muenzer J *et al*., An Intravenous Brain-Penetrant Enzyme Therapy for Mucopolysaccharidosis II, Vol. 394, pp. 39–50. Copyright © 2026 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Percentages were based on the number of nonmissing values. [a]Includes participants who were on a stable idursulfase IV treatment for 4 months prior to tividenofusp alfa initiation and had not received HSCT or gene therapy. [b]Participants who underwent HSCT or gene therapy all also received idursulfase IV prior to these treatments. ADA, anti-drug antibody; HSCT, hematopoietic stem cell transplantation; max, maximum; min, minimum; SD, standard deviation.

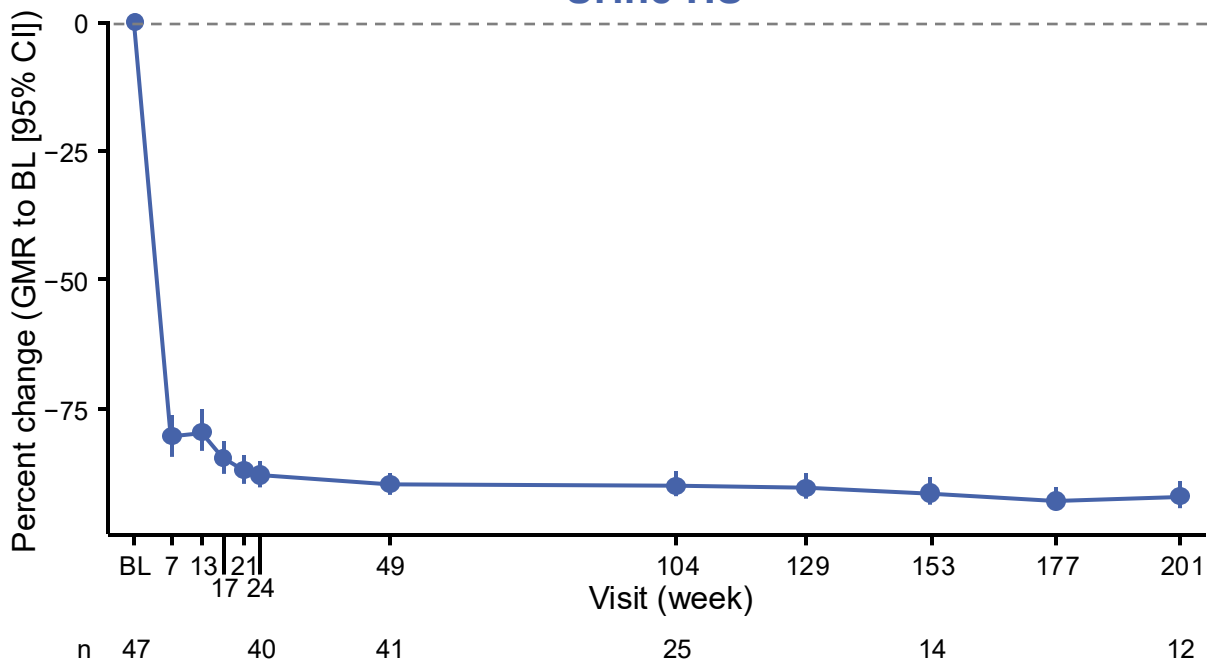
CNS AND PERIPHERAL BIOMARKERS: CSF AND URINE HS

CSF HS



Participants below ULN (n/N), %					
0	93.2	97.7	96.4	95.2	92.9

Urine HS

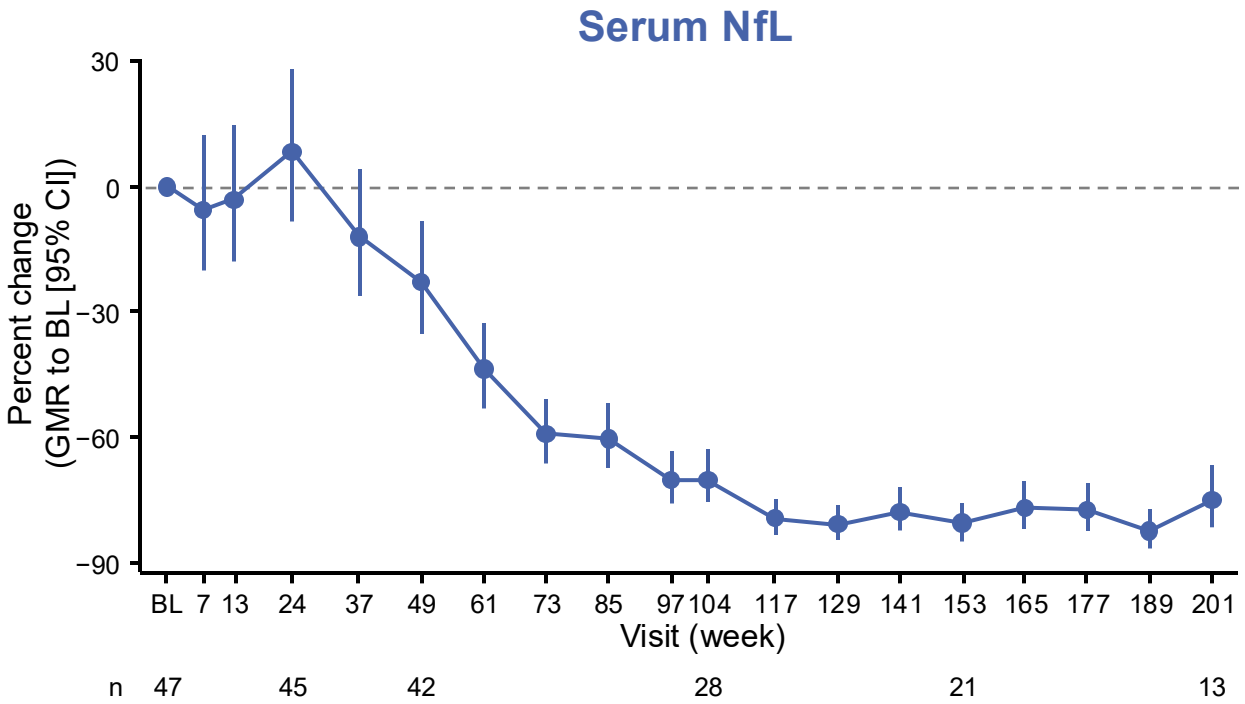


Participants below ULN (n/N), %					
0	57.5	61.0	68.0	78.6	83.3

Substantial reductions and normalization of CSF and urine HS were achieved with tividenofusp alfa treatment, and these reductions were maintained long-term

Full methodologies for biomarker assays and statistical analyses are published in Muenzer *et al. N Engl J Med* 2026;394:39–50. ULN ranges were determined as the 97.5th percentile using CSF samples from 67 pediatric individuals without MPS II (median [min, max] age: 8.88 [0.06, 25.3] years) or urine samples from 149 pediatric individuals without MPS II (median [min, max] age: 4.93 [0.05, 17.2] years). CI, confidence interval; GMR, geometric mean ratio; ULN, upper limit of normal.

CNS BIOMARKERS: SERUM NfL



Participants below ULN (n/N), %					
19.1	24.4	26.2	75.0	85.7	61.5

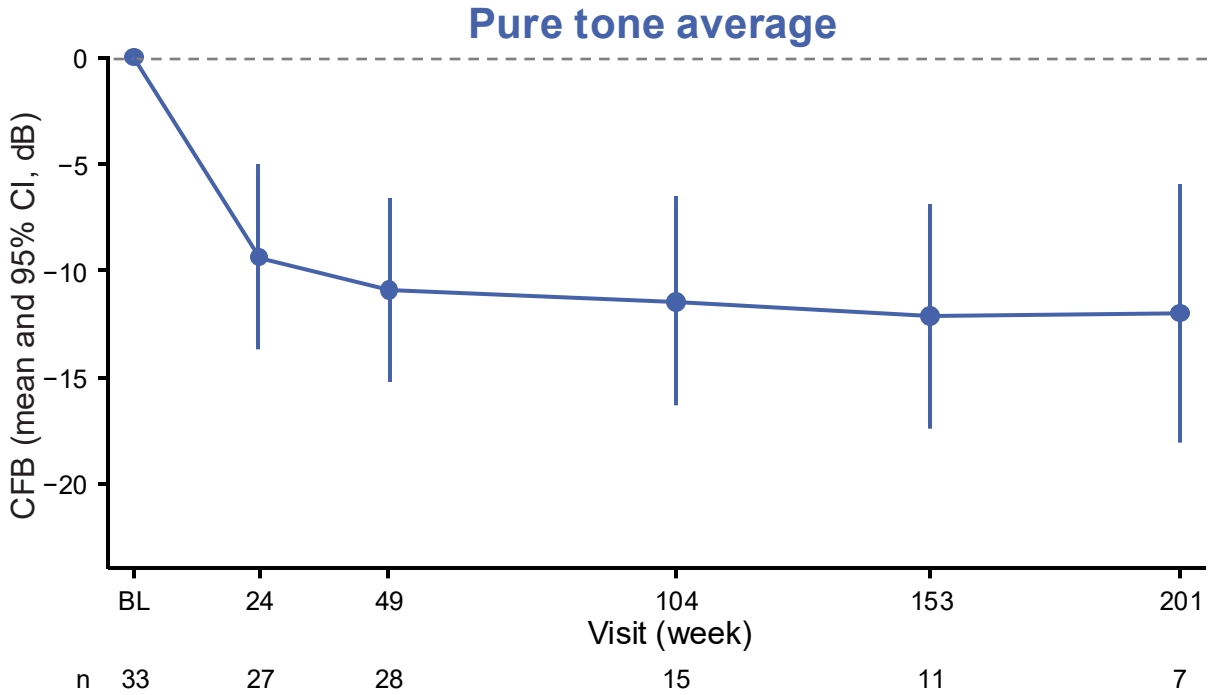
Substantial reduction in serum NfL, a marker of neuronal damage, was achieved with tividenofusp alfa treatment, with normalization in most participants by Week 104

Full methodologies for biomarker assays and statistical analyses are published in Muenzer *et al*. *N Engl J Med* 2026;394:39–50. ULN ranges from Schjørring *et al*. 2023 were used for serum NfL;[1] if the participant was aged < 3 years at that visit, an upper limit of 16.6 ng/L was used, else an upper limit of 13.9 ng/L was used. 1. Schjørring ME *et al*. *Scand J Clin Lab Invest* 2023;83:403–7.

HEARING THRESHOLD

Mean CFB in pure tone average by ABR (eHL) and audiometry (HL)

Visit	n	CFB in dB, adjusted mean (95% CI)	*P* value
W24	27	−9.4 (−13.7, −5.0)	< 0.0001
W49	28	−10.9 (−15.2, −6.6)	< 0.0001
W104	15	−11.4 (−16.3, −6.5)	< 0.0001
W153	11	−12.1 (−17.4, −6.8)	< 0.0001
W201	7	−12.0 (−18.0, −5.9)	0.0002

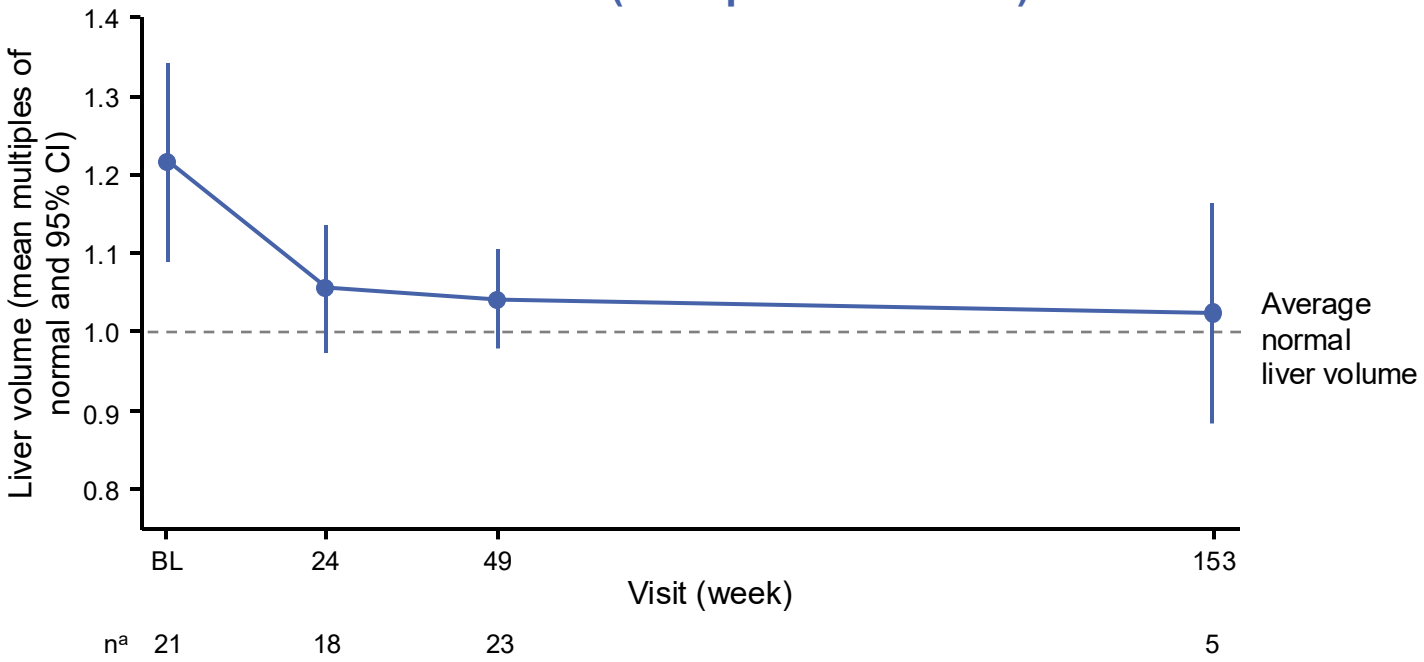


Hearing threshold as assessed by pure tone average (across 500, 1000, 2000, and 4000 Hz) decreased, reflecting improved hearing from baseline

Full methodologies for hearing assessments and statistical analyses are published in Muenzer *et al. N Engl J Med* 2026;394:39–50. Pure tone average is defined as the average across the four tested frequencies (500, 1000, 2000, and 4000 Hz) and was calculated only if numeric values for all individual frequencies were available. ABR, auditory brainstem response; CFB, change from baseline; dB, decibels; eHL, estimated hearing level; HL, hearing level; Hz, Hertz.

LIVER VOLUME: MRI (COHORTS C, D, AND E)

Liver volume (multiples of normal)



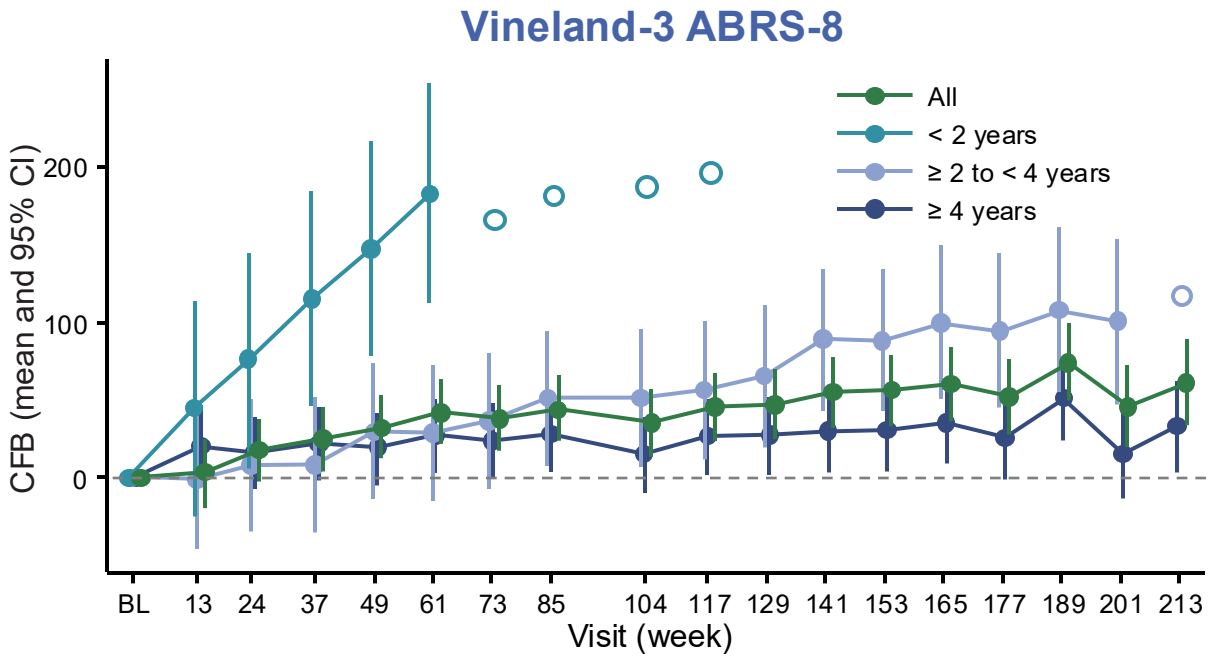
Liver volume (proportion below ULN)[b]

Population	Percent [proportion (n/N)][c] below the ULN[b]			
	BL	W24	W49	W153
All	76.2 (16/21)	100 (18/18)	100 (23/23)	100 (5/5)

All participants had normal liver volume at Weeks 24, 49, and 153

[a]Participants recruited early for whom ultrasound was used at baseline were switched to MRI at later visits; as a result, n at baseline does not match the n at later time points. [b]Values less than the upper bound of the 95% prediction interval for liver volume based on weight and height are defined as normal.[1] [c]n is the number of participants with normal liver volume at that visit; N is the number of participants with available liver MRI volume value at that visit; proportion = n/N. 1. Herden U *et al. Transpl Int* 2013;26:1217–24. MRI, magnetic resonance imaging.

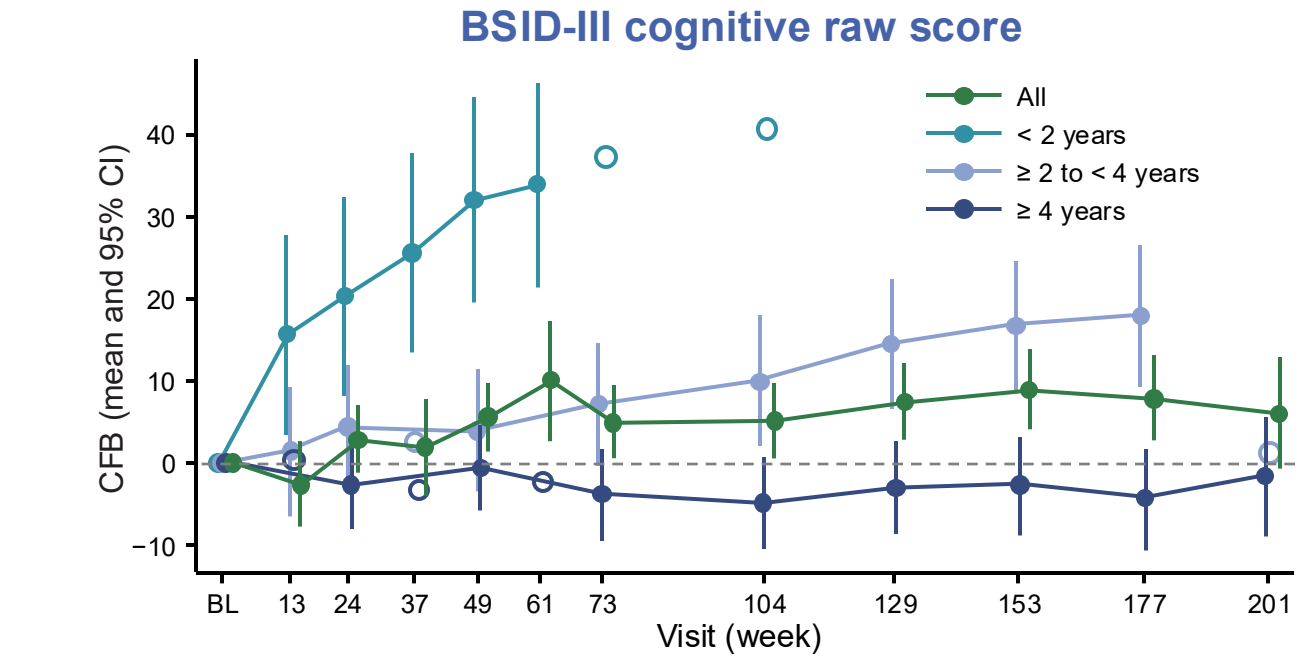
ADAPTIVE BEHAVIOR



Improvement from baseline in adaptive behavior scores was observed in the younger age groups; stabilization was observed in the ≥ 4 years age group

Full methodologies for assessments of cognitive outcomes and adaptive behavior and statistical analyses are published in Muenzer *et al. N Engl J Med* 2026;394:39–50. ABRS-8 is derived sum of raw scores of eight subdomains (receptive, expressive, personal, interpersonal relationships, play and leisure, coping skills, fine motor, and gross motor). Hollow points indicate visits for which data for less than three participants are available. ABRS-8, eight-subdomain Adaptive Behavior Raw Score composite; Vineland-3, Vineland Adaptive Behavior Scales, Third Edition.

COGNITION



n	39	13	33	9	31	5	23	20	19	16	13	6
< 2 years	5	5	5	5	4	4	2	1				
≥ 2 to < 4 years	9	6	8	2	8		8	6	6	6	4	1
≥ 4 years	25	2	20	2	19	1	13	13	13	10	9	5

Improvement from baseline in cognitive scores was observed in the younger age groups; stabilization was observed in the ≥ 4 years age group

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SAFETY OVERVIEW

- Long-term exposure (median ~2.5 years) demonstrated a stable safety profile with no new safety signals since the primary analysis (October 9, 2024)[1]
- All participants experienced at least one TEAE; the maximum severity was moderate in 75% of participants
- In total, 21 participants (45%) had at least one serious TEAE
  - Of these participants, three experienced serious TEAEs considered related to treatment (two had IRRs and one had anemia; previously reported; all continued to receive tividenofusp alfa in the study)
- One participant (2.1%) discontinued treatment due to a TEAE

Most frequently reported TEAEs

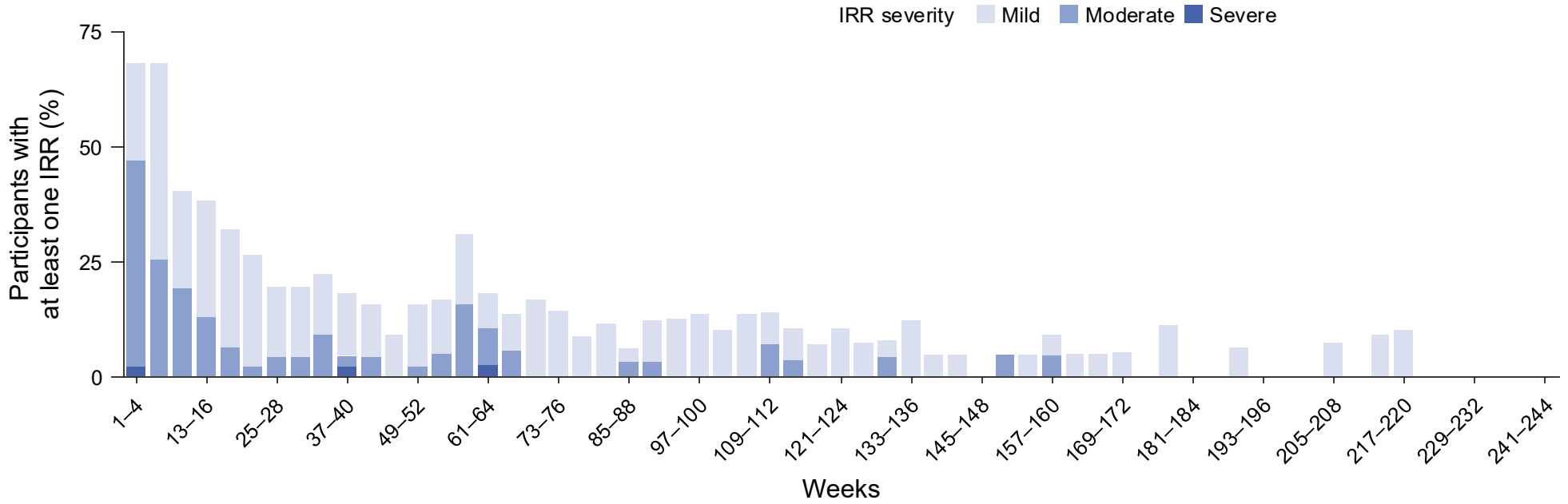
Preferred term	All cohorts (n = 47) n (%) of participants
IRR	41 (87%)
Upper respiratory tract infection	32 (68%)
Pyrexia	28 (60%)
Cough	23 (49%)
Anemia	20 (43%)
Diarrhea	20 (43%)
Rash	20 (43%)
Vomiting	20 (43%)
COVID-19	18 (38%)
Rhinorrhea	18 (38%)
Nasal congestion	17 (36%)

Tividenofusp alfa 15 mg/kg had a manageable safety profile in pediatric participants with MPS II

1. Muenzer *et al. N Engl J Med* 2026;394:39–50. TEAE, treatment emergent adverse event.

IRRs

Proportion of participants with at least one IRR during each 4-week interval, categorized by severity[a]



- In total, 41 participants (87%) had at least one IRR; among the 47 total participants, the maximum severity was moderate in 55.3% of participants
- IRRs were clinically manageable with standard premedications, slowing the infusion rate, and/or reducing the dose level

IRRs, a known risk of ERTs, were the most common adverse event, decreasing in incidence and severity over time

[a]Proportions were number of participants who had an IRR/number of participants exposed to tividenofusp alfa at any point during that time interval (maximum of one IRR (IRR with highest severity) per participant, per interval.

CONCLUSIONS

Treatment with tividenofusp alfa led to substantial reductions from baseline in CNS and peripheral biomarkers of disease

- The majority of participants achieved normalization of CSF and urine HS, and serum NfL
- Reduction and normalization in CNS and peripheral biomarkers was maintained through Week 201

While receiving tividenofusp alfa treatment, CNS and peripheral clinical outcomes showed:

- Improvement from baseline in mean hearing threshold, as assessed by pure tone average
- Normal liver volume at 24, 49, and 153 weeks
- Improvement or stabilization relative to baseline on measures of adaptive behavior and cognition

Tividenofusp alfa demonstrated a stable long-term safety profile with no new safety signals since the primary analysis

- All study participants experienced TEAEs, with IRRs being the most common
- For most participants, the maximum severity for TEAEs was moderate
- Incidence and severity of IRRs decreased, and tolerability improved over time

ACKNOWLEDGMENTS

We would like to give a special **thank you to the participants and families** who generously contributed through their participation in this study sponsored by Denali Therapeutics Inc.

We also thank the study principal investigators, collaborators, and the Denali Therapeutics team for the conduct of the study and data collection

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COMPASS, a Phase 2/3, multicenter, double-blind, randomized efficacy and safety study of tividenofusp alfa vs idursulfase in MPS II, is ongoing (NCT05371613)

Thank you for your attention

Tividenofusp alfa (DNL310) is an investigational drug and has not been approved by any Health Authority