Topline primary analysis of the safety and efficacy of weekly intravenous tividenofusp alfa in mucopolysaccharidosis type II: a phase 1/2 study

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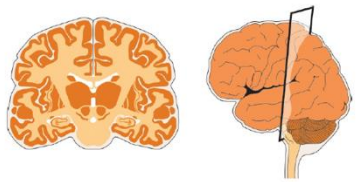
DEVELOPING A THERAPY FOR MPS II (HUNTER SYNDROME)

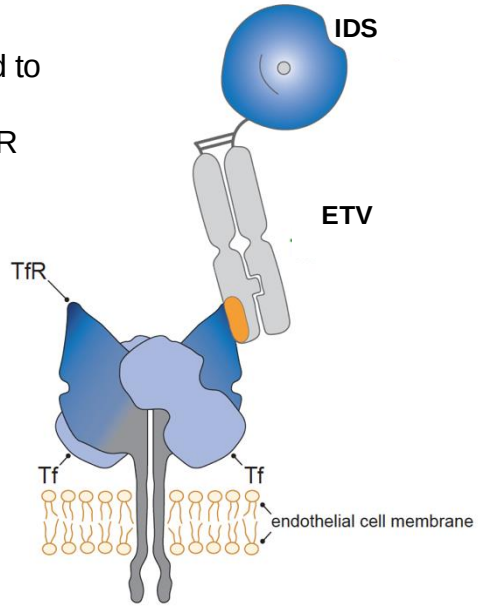
Tividenofusp alfa (DNL310)[1,2] is an investigational iduronate-2-sulfatase (IDS) fusion protein engineered to treat the brain and somatic manifestations of MPS II with a **single weekly IV infusion**

Tividenofusp alfa

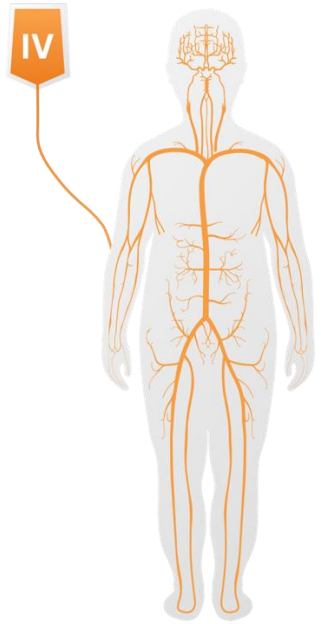
ETV technology is optimized to improve brain uptake of biotherapeutics using the TfR



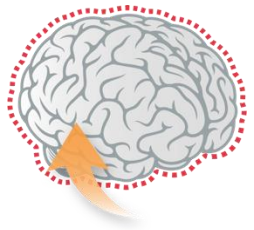
Capillary TfR expression in the brain facilitates widespread biodistribution of ETV and enzyme



Weekly IV infusion



Extensive tissue penetration



TfR is highly expressed at the blood–brain barrier. Design of the ETV is optimized to enable tividenofusp alfa to cross the blood–brain barrier[2–6]

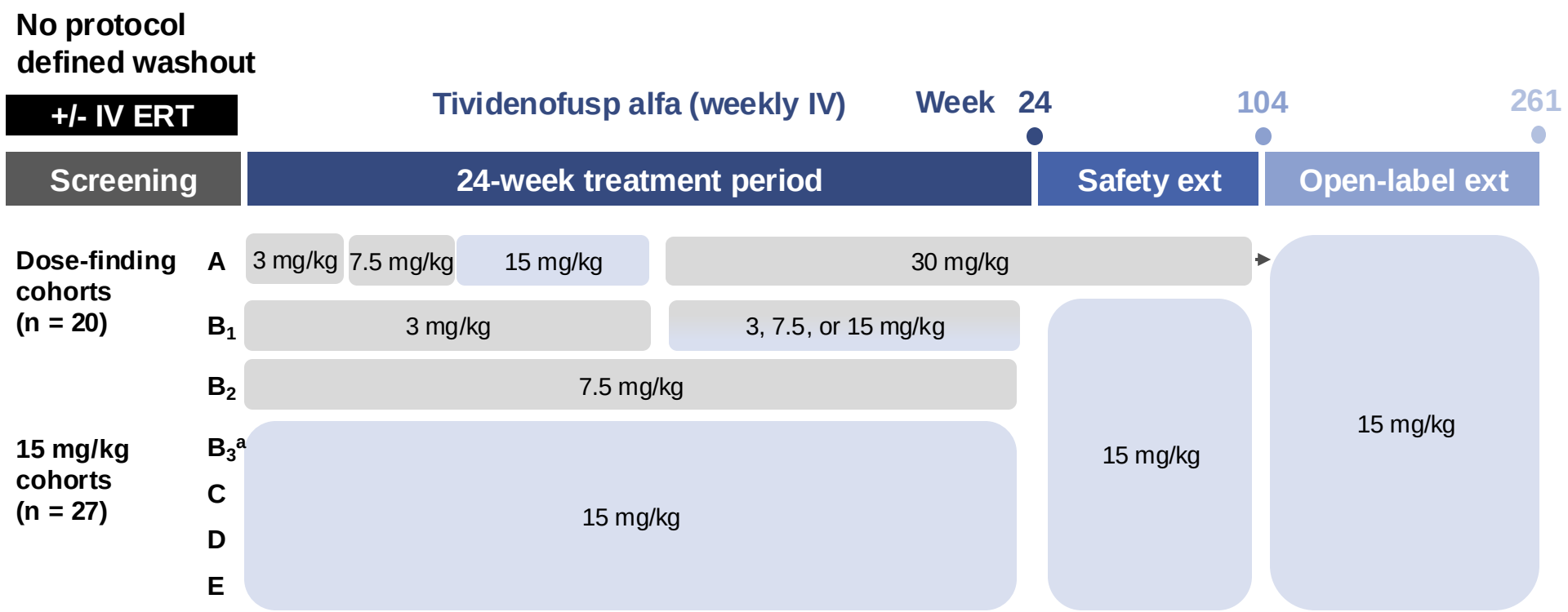
TfR may also facilitate IDS delivery into tissues such as bone, cartilage, and the heart[4,7]

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

1. Bhalla A et al. *Int J Mol Sci* 2020;21:5188; 2. Ullman JC *et al. Sci Transl Med* 2020;12:eaay1163; 3. Qian ZM *et al. Pharmacol Rev* 2002;54:561–87; 4. Arguello A *et al. JCI Insight* 2021;6:e145445;
5. Arguello A *et al. J Exp Med* 2022;219:e20211057; 6. Gammella E *et al. Metallomics* 2017;9:1367–75; 7. Carlevaro MF *et al. J Cell Biol* 1997;136:1375–84.
ETV, enzyme transport vehicle; IDS, iduronate-2-sulfatase; IV, intravenous; MPS II, mucopolysaccaridosis type 2; Tf, transferrin; TfR, Tf receptor.

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

- Study DNLI-E-0002 is a multicenter, open-label 24-week study with safety and open-label–extension periods (NCT04251026)
  - Primary Analysis of study objectives: all participants have completed 24-week treatment period
- 47 participants with MPS II aged ≤ 18 years (ERT-naive and treatment-experienced) were enrolled into five cohorts (A–E)
  - Differences in inclusion criteria between cohorts included age and phenotype
- Participants receiving SOC ERT at baseline switched to tividenofusp alfa without a washout period



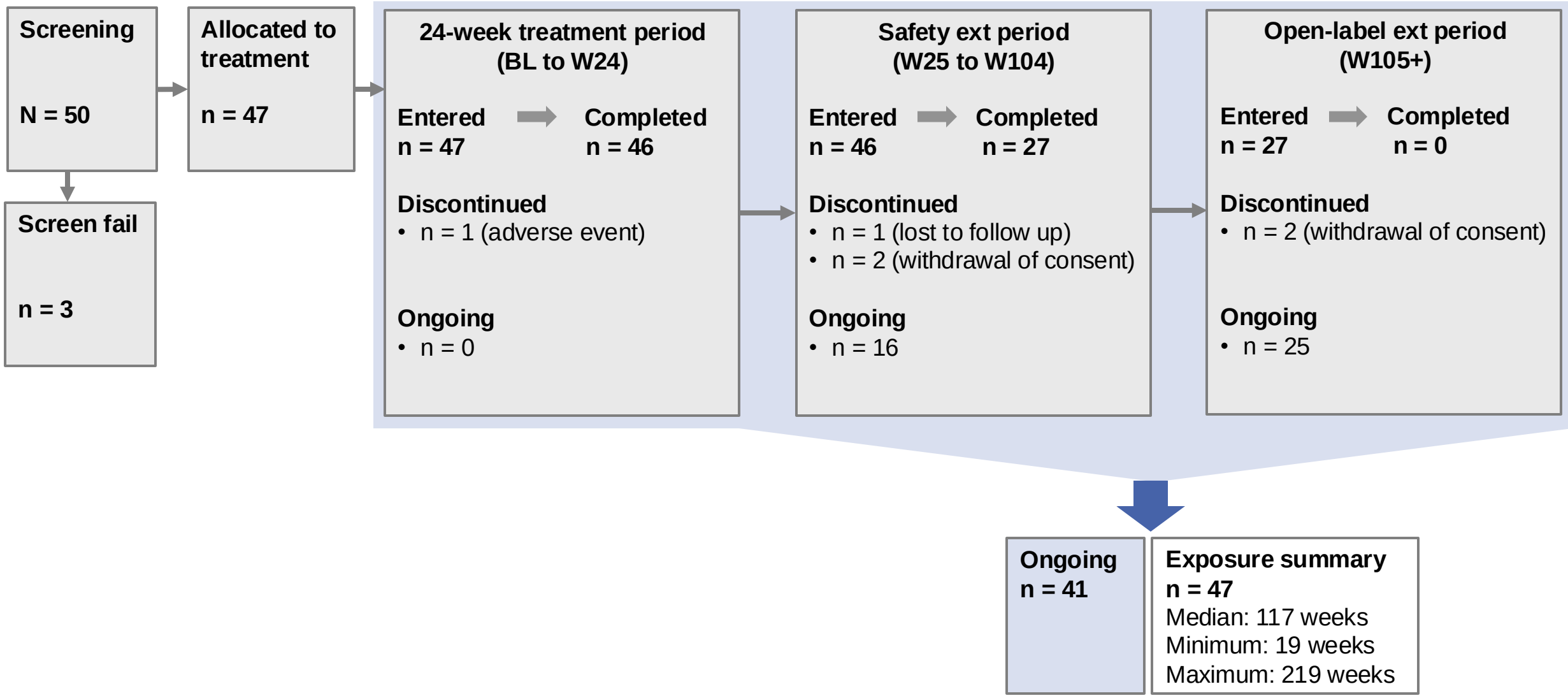
Primary endpoints
- Adverse events
- Infusion-related reactions
- Other indicators of safety and tolerability

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

Key exploratory endpoints
- Serum NfL
- CSF biomarkers
- Hearing thresholds
- Cognition (BSID, KABC)

[a]B_3 was part of the dose-finding cohorts. BSID, Bayley Scales of Infant Development; CSF, cerebrospinal fluid; ERT, enzyme replacement therapy; ext, extension; HS, heparan sulfate; IV, intravenous; KABC, Kaufman Assessment Battery for Children; MPS II, mucopolysaccharidosis type II; NfL, neurofilament light chain; SOC, standard of care.

PARTICIPANT ENROLLMENT AND DISPOSITION



Clinical cutoff date: October 9, 2024.
BL, baseline; ext, extension; W, week.

BASELINE CHARACTERISTICS

		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)

		All (cohorts A–E) n = 47
MPS II phenotype, n (%)	Neuronopathic	44 (93.6)
	Non-neuronopathic	3 (6.4)
DQ	Mean (SD)	55.1 (28.7)
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[b]	14 (29.8)
	HSCT/gene therapy[c]	4 (8.5)
Age at ERT (idursulfase IV) initiation, years	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)

Percentages were calculated based on the number of non-missing values. [a]ERT prior therapy group 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]One participant with idursulfase treatment < 4 months was considered under the ERT naive group. [c]Participants who received HSCT or gene therapy were included regardless of their prior ERT status. ADA, anti-drug antibody; DQ, developmental quotient; ERT, enzyme replacement therapy; HSCT, hematopoietic stem cell transplantation; IV, intravenous; max, maximum; min, minimum; MPS II, mucopolysaccharidosis type II; SD, standard deviation.

SAFETY OVERVIEW

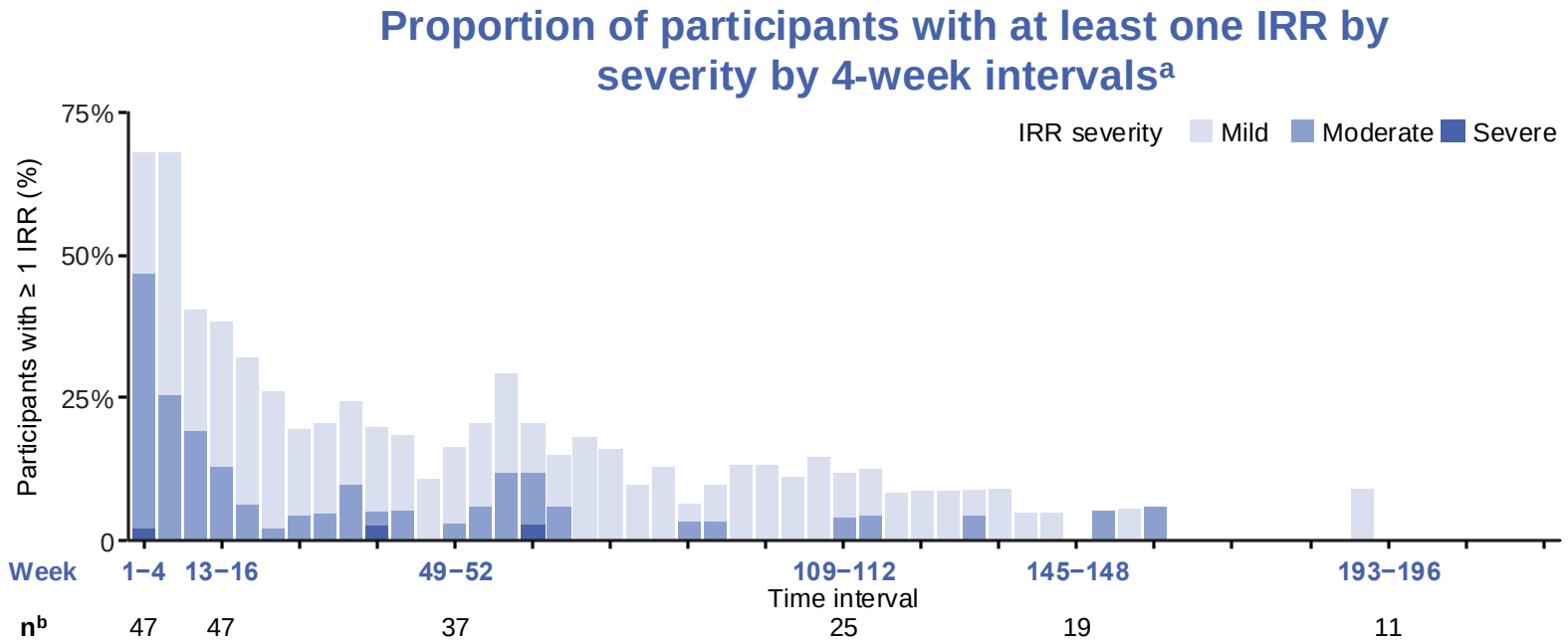
	24-week treatment period (BL to W24), n = 47	All periods (BL to W261), n = 47
TEAE,[a] n (%)	47 (100)	47 (100)
Mild	8 (17.0)	2 (4.3)
Moderate	35 (74.5)	32 (68.1)
Severe[b]	4 (8.5)	13 (27.7)
Serious TEAE, n (%)	6 (12.8)	18 (38.3)
Treatment-related serious TEAE	3 (6.4)	3 (6.4)
Fatal TEAE, n (%)	0	0
TEAE leading to discontinuation, n (%)	1 (2.1)	1 (2.1)

- Across all periods, most participants (72%) had TEAEs that were mild or moderate in severity
  - Only one participant (2.1%) discontinued due to a TEAE; discontinuation was in part due to a TEAE of IRR (and other adverse events considered not related to drug)
  - Three participants (6.4%) had serious TEAEs that were considered related to treatment
    - Two participants with IRRs (one mild, one severe);[c] both recovered and received subsequent doses
    - One participant with anemia (moderate CTCAE grade); participant remains stable with continued dosing
- In the 24-week treatment period (BL to W24), the most frequent TEAEs (> 20%) were IRRs,[c] anemia, vomiting, pyrexia, upper respiratory infection, and rash; the majority of these were mild to moderate in severity
  - Most IRRs were clinically manageable with standard pre-medications and/or adjustment of infusion time
  - Anemia-related adverse events generally improved over time

Tividenofusp alfa 15 mg/kg was generally well tolerated in pediatric study participants with MPS II

[a]TEAE by maximum severity. [b]Missing intensity was summarized as severe. [c]IRRs including allergic reactions and anaphylaxis.
BL, baseline; CTCAE, common terminology criteria for adverse events; IRR, infusion-related reaction; MPS II, mucopolysaccharidosis type 2; TEAE, treatment emergent adverse event; W, week.

INFUSION-RELATED REACTIONS

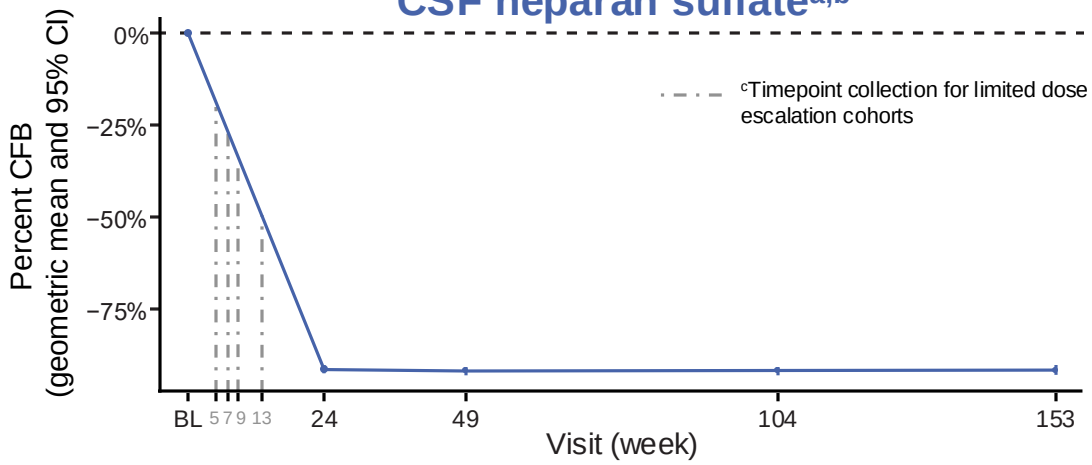


- Across all periods, 87.2% of participants experienced IRRs, of which most participants (92.7%) had IRRs that were mild or moderate
  - One participant (2.1%) discontinued the study in part due to a TEAE of IRR (and other adverse events considered not related to drug)
  - Two participants (4.3%), who remain in the study, experienced serious TEAEs owing to IRRs (previously reported in 2021) that resolved
    - One participant experienced a mild IRR and was hospitalized overnight for observation
    - One participant experienced a severe IRR at Weeks 3 and 4 that met Sampson criteria of anaphylaxis; IRRs were managed with pre-infusion medications, and dose and infusion rate reductions; participant subsequently dose escalated to 15 mg/kg
- IRR frequency in most participants decreased over time and was clinically manageable with standard pre-medications and/or adjustment of infusion time and frequency

[a]Proportions were calculated based on the number of participants who had an IRR/the number of participants exposed to tividenofusp alfa at any point during that time interval (maximum of one IRR per participant, per interval; the IRR with highest severity was included for each participant per time interval; ongoing IRRs were counted once in the interval of onset). [b]n refers to the number of participants dosed within a given time interval.
IRR, infusion-related reaction; TEAE, treatment emergent adverse effect.

CNS AND PERIPHERAL BIOMARKERS: HEPARAN SULFATE

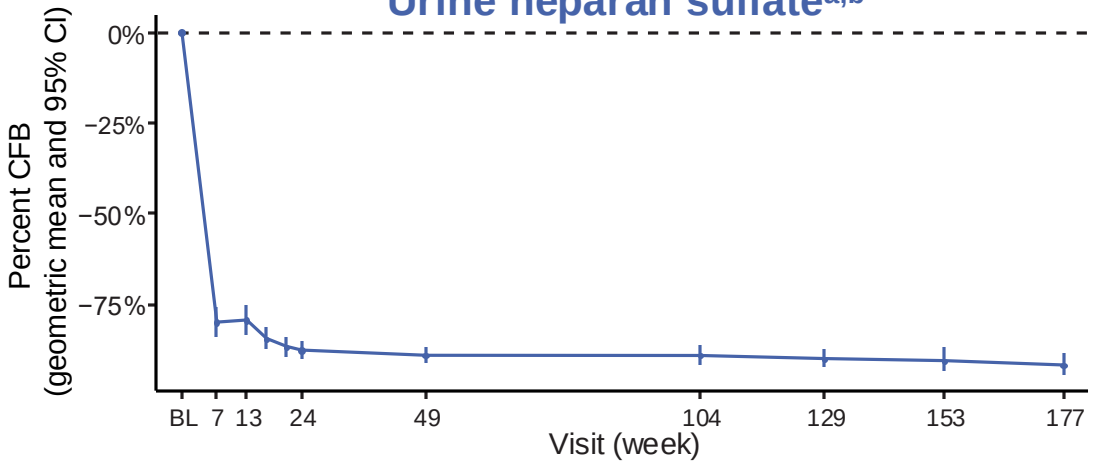
CSF heparan sulfate[a,b]



Summary of percent CFB and percentage below ULN

Visit	n	Geometric mean (95% CI) percent change	*P* value	% below ULN[d]
BL	47	-	-	0.0
W13 (A&B only)[c]	21	Range: –63.4%, –96.5%	-	81.0
W24[e]	**44**	**–91.4 (–92.2, –90.4)**	**< 0.0001**	**93.2**
W49	34	–91.8 (–92.6, –90.8)	< 0.0001	97.1
W104	25	–91.6 (–92.4, –90.7)	< 0.0001	96.0
W153	16	–91.5 (–92.5, –90.4)	< 0.0001	93.8
W201	3	Range: –93.1%, –84.3%	-	100.0

Urine heparan sulfate[a,b]



Summary of percent CFB and percentage below ULN

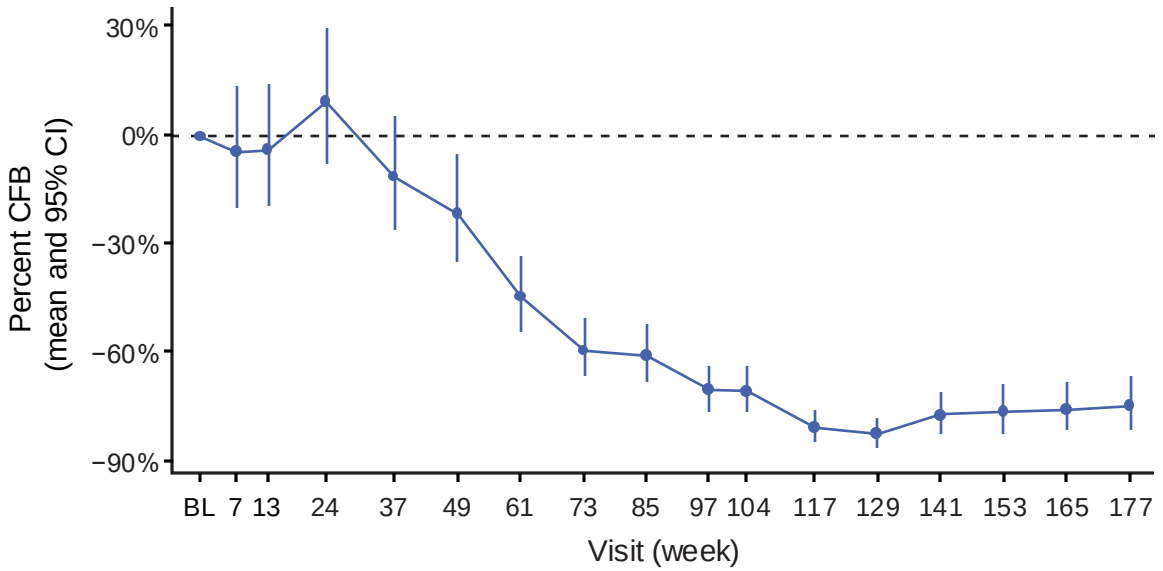
Visit	n	Geometric mean (95% CI) percent change	*P* value	% below ULN[d]
BL	47	-	-	0.0
W24[e]	**40**	**–87.9 (–90.1, –85.2)**	**< 0.0001**	**57.5**
W49	32	–89.4 (–91.5, –86.7)	< 0.0001	65.6
W104	22	–89.4 (–91.8, –86.3)	< 0.0001	72.7
W153	10	–90.8 (–93.6, –86.9)	< 0.0001	90.0
W201	3	Range: –95.2%, –82.1%	-	100.0

Tividenofusp alfa resulted in a substantial reduction from baseline in CSF and urine heparan sulfate levels by Week 24 with the majority of participants below the ULN; this effect was maintained through Week 153 of treatment

[a]Heparan sulfate was measured as a sum of the disaccharides D0A0, D0A6, D0S0, and D2S6 by mass spectrometry after enzymatic digestion. [b]Based on MMRM model with fixed effects for visit week, age group at tividenofusp alfa initiation, genotype, and baseline CSF or urine heparan sulfate (urine heparan sulfate was also adjusted for prior ERT status group); only protocol planned visits consistent across all cohorts and with ≥ 5 observations were included in the model. [c]CFB for timepoints with collection for limited dose escalation cohorts: W5 (cohort A only), range: –24.9%, –93.1%; W7 (cohort B only), range: –67.3, –92.7%; W9 (cohort A only), range –36.1%, –92.5%. [d]ULN ranges were determined as the 97.5th percentile using CSF samples from 67 non-affected pediatric individuals (median [min, max] age: 8.88 [0.06, 25.3] years) or urine samples from 149 non-affected pediatric individuals (median [min, max] age: 4.93 [0.05, 17.2] years). [e]Secondary endpoint. BL, baseline; CFB, change from baseline; CI, confidence interval; CNS, central nervous system; CSF, cerebrospinal fluid; MMRM, mixed model for repeated measures; ULN, upper limit of normal; W, week.

CNS BIOMARKERS: SERUM NFL

Serum NfL



Summary of percent CFB and percentage below ULN

Visit	n	Geometric mean (95% CI) percent change[a]	*P* value	% below ULN[b]
BL	47	-	-	19.1
W24	43	9.8 (–7.4, 30.3)	0.2786	23.3
W49	34	–21.1 (–34.6, –4.9)	0.0131	23.5
W104	24	–70.5 (–76.2, –63.3)	< 0.0001	79.2
W153	13	–76.1 (–82.0, –68.4)	< 0.0001	84.6

Robust reduction from baseline in serum NfL, a marker of neuronal damage, was observed with long-term dosing with the majority of participants below the ULN at Week 104

[a]Based on MMRM model with fixed effects for visit week, age group at tividenofusp alfa initiation, genotype, and baseline serum NfL. Only visits with ≥ 5 observations were included in the model. [b]Reference ranges from Schjorring *et al.* 2023[1] were used for serum NfL: if the participant was aged < 3 years at assessment, an upper limit of 16.6 ng/L was used; an upper limit of 13.9 ng/L was used otherwise.

1. Schjørring ME *et al. Scand J Clin Lab Invest* 2023;83:403–7.

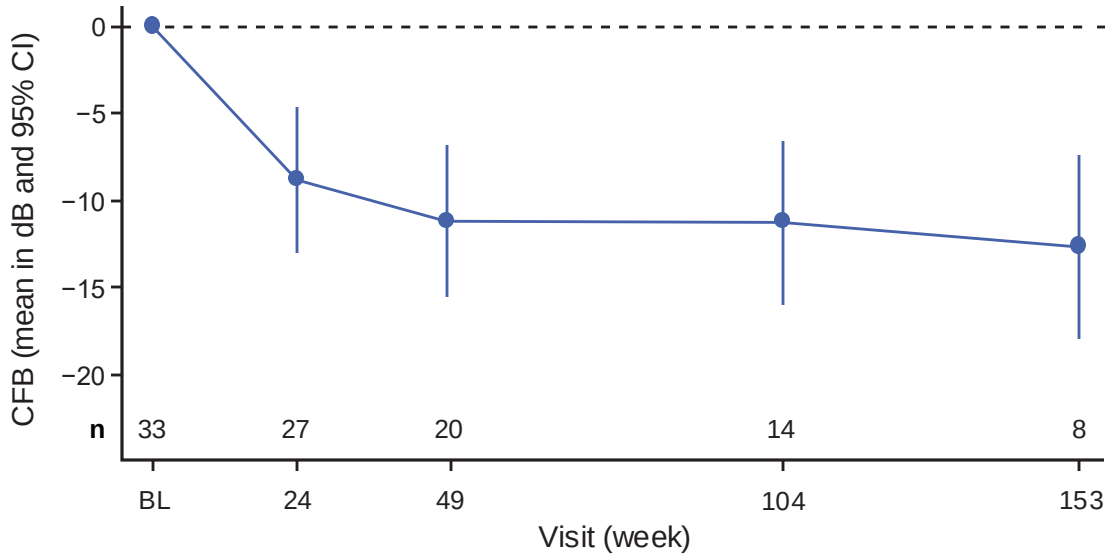
BL, baseline; CFB, change from baseline; CI, confidence interval; CNS, central nervous system; MMRM, mixed model for repeated measures; NfL, neurofilament light chain; ULN, upper limit of normal; W, week.

HEARING THRESHOLDS

Mean CFB in pure tone average[a] by ABR (eHL) and audiometry (HL)[b,c]

Visit	n	CFB in dB, mean (95% CI)[d]	*P* value
W24	27	–8.8 (–13.1, –4.5)	0.0002
W49	20	–11.1 (–15.6, –6.7)	< 0.0001
W104	14	–11.2 (–15.9, –6.5)	< 0.0001
W153	8	–12.6 (–17.9, –7.3)	< 0.0001

Pure tone average

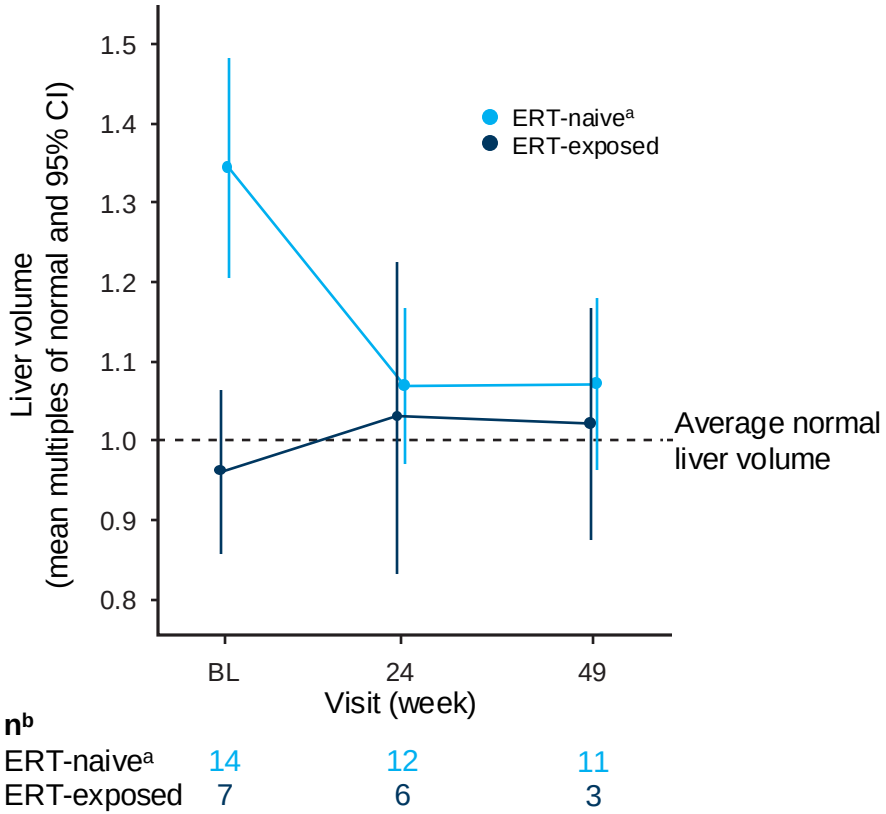


Mean hearing thresholds improved from baseline in all tested frequencies (500, 1000, 2000, 4000 Hz) and reductions were statistically significant from week 24 onward

[a]Pure tone average is defined as the average across the four tested frequencies (500, 1000, 2000, and 4000 Hz). Pure tone average is only calculated if the numeric values of all individual frequencies are available. [b]ABR (dB eHL) and any available standard hearing or behavioral audiometry test (in dB HL) are pooled. ABR is prioritized if more than one test is available within the same participant and analysis visit. [c]Exploratory endpoint. [d]Based on MMRM model with fixed effects for visit week, age group at tividenofusp alfa initiation, genotype, prior ERT status, and baseline eHL. ABR, auditory brainstem response; BL, baseline; CFB, change from baseline; CI, confidence interval; dB, decibels; eHL, estimated hearing level; ERT, enzyme replacement therapy; HL, hearing level; MMRM, mixed model for repeated measures; W, week.

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

Liver volume



Participants with liver volume below the ULN[c]

Population	Percent [proportion (n/N)][d] below the ULN[c] (defined as the 95% prediction interval of normal liver volume)		
	BL	W24[e]	W49[e]
ERT-naive[a]	64.3 (9/14)	100 (12/12)	100 (11/11)
ERT-exposed	100 (7/7)	100 (6/6)	100 (3/3)
All	76.2 (16/21)	100 (18/18)	100 (14/14)

All participants had liver volume below the ULN at Week 24 (18/18) and Week 49 (14/14), irrespective of prior ERT exposure

[a]One participant with idursulfase treatment < 4 months was considered under the ERT naive group. [b]Time points with data for ≤ 1 participant are not shown. [c]Values less than the upper bound of the 95% prediction interval for liver volume based on weight and height are defined as normal (Herden *et al.* 2013).[1] [d]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; exact 95% CI is the Clopper-Pearson confidence interval of the proportion. [e]Secondary endpoint. 1. Herden U *et al. Transpl Int* 2013;26:1217–24.
BL, baseline; CI, confidence interval; ERT, enzyme replacement therapy; MRI, magnetic resonance imaging; ULN, upper limit of normal; W, week.

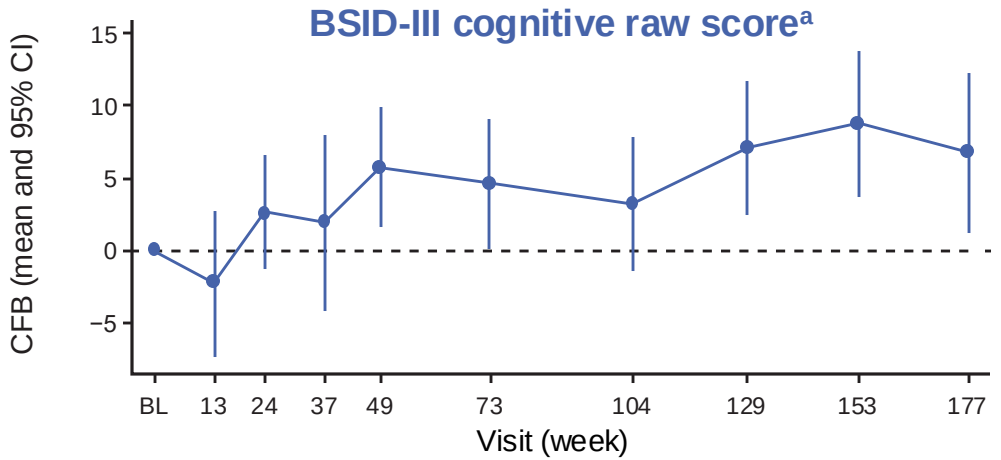
COGNITION AND ADAPTIVE BEHAVIOR

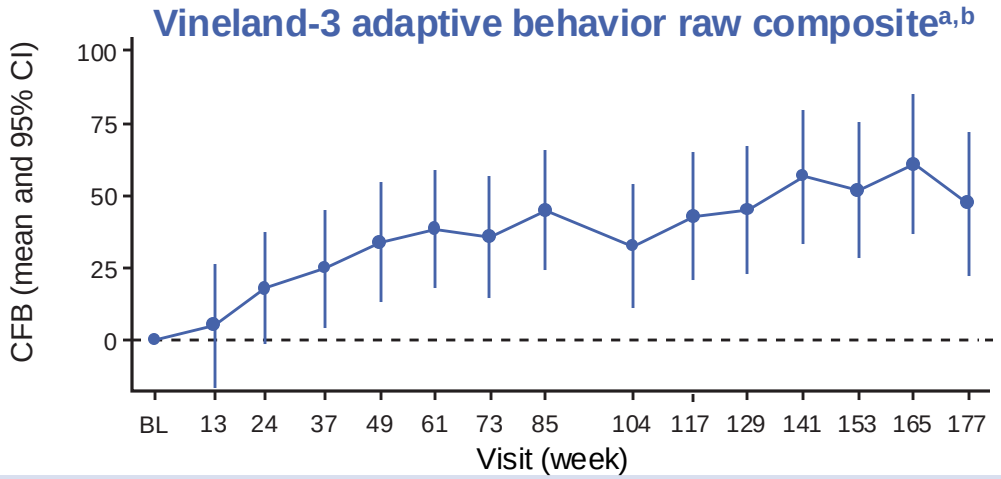
Mean CFB in BSID-III cognitive raw score[a]

Visit	n	Mean CFB (95% CI)	*P* value
BL	39	-	-
W24	33	2.6 (–1.3, 6.5)	0.1869
W49	26	5.7 (1.6, 9.8)	0.0078
W104	17	3.2 (–1.4, 7.9)	0.1725
W153	13	8.8 (3.7, 13.9)	0.0008

Mean CFB in Vineland-3 adaptive behavior raw composite[a,b]

Visit	n	Mean CFB (95% CI)	*P* value
BL	46	-	-
W24	44	18.2 (–1.2, 37.5)	0.0650
W49	33	33.8 (13.3, 54.2)	0.0015
W104	26	32.2 (10.7, 53.8)	0.0037
W153	18	51.8 (28.3, 75.4)	< 0.0001





Improvements from baseline in cognition and adaptive behavior were maintained throughout the follow-up period

[a]Based on MMRM model with fixed effects for visit week, age group at tividenofusp alfa initiation, genotype, and baseline BSID-IIII cognitive raw or Vineland-3 adaptive behavior raw composite score. Only visits with number of observation ≥ 5 were included in the statistical model. [b]Adaptive behavior raw composite is the derived sum of raw scores of eight subdomains (receptive, expressive, personal, interpersonal relationships, play and leisure, coping skills, fine motor, and gross motor). To evaluate change in adaptive behavior across both instruments, scores were converted from VABS-II to Vineland-3 using an errors-in-variables linear regression model adjusted by age. BL, baseline; BSID-III, Bayley Scales of Infant and Toddler Development, third edition; CFB, change from baseline; CI, confidence interval; MMRM, mixed model for repeated measures; VABS-II, Vineland Adaptive Behavior Scales, second edition; Vineland-3, Vineland Adaptive Behavior Scales, third edition; W, week.

CONCLUSIONS

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

- To normal or near-normal levels of CSF and urine heparan sulfate (LCMS/MS)
- To normal or near-normal levels of NfL, a well-established marker of neurodegeneration

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

- Normal liver volume after 24 weeks, irrespective of prior ERT exposure
- Hearing threshold improvement from baseline in all tested frequencies
- Skill gains relative to baseline in most participants on measures of adaptive behavior and cognition

Tividenofusp alfa was generally well tolerated in pediatric study participants with MPS II

- Most TEAEs, including IRRs, anemia, vomiting, pyrexia, respiratory infections, and rash, were mild or moderate
- Serious TEAEs (6.4%) were manageable, with participants recovering or continuing treatment
- One participant discontinued treatment owing to a moderate IRR and other non-drug-related adverse events

CNS, central nervous system; CSF, cerebrospinal fluid; ERT, enzyme replacement therapy; IRR, infusion-related reaction; LCMS/MS, liquid chromatography-tandem mass spectrometry; MPS II, mucopolysaccharidosis type II; NfL, neurofilament light chain; TEAE, treatment emergent adverse effect.

ACKNOWLEDGEMENTS

We give a special **thank you to the participants 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 data collection

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Thank you for your attention

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