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Interim Analysis From a Phase 1/2 Study of Weekly Intravenous DNL310 (Brain-Penetrant Enzyme Replacement Therapy) in MPS II

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DISCLOSURES

- **Barbara Burton** has received consulting fees and/or honoraria from Agios, Alltrna, Aro, Biomarin, Chiesi, Horizon, JCR Pharma, Moderna, Orchard Therapeutics, Passage Bio, Sanofi, Takeda, and Ultragenyx and has conducted clinical trials funded by BioMarin, Denali Therapeutics, Homology Medicines, JCR Pharma, Sangamo, and Ultragenyx
- **Joseph Muenzer** has been a consultant and or/served on advisory boards for BioMarin, Takeda (Shire), Sanofi Genzyme, Regenxbio, Denali Therapeutics and JCR Pharmaceuticals. He is the principal investigator for a Phase I/II and Phase II/III intrathecal enzyme replacement clinical trials for MPS II, a Phase I/II gene-editing clinical trial for MPS II, a Phase I/II and a Phase II/III IV ERT clinical trial for MPS II and a phase I/II IV AAV gene therapy clinical trial for adults with MPS II
- **Paul Harmatz** has conducted research funded by Adrenas, Amicus Therapeutics, Ascendis, ASPA, Azafaros, BioMarin, Calcilytics, Denali Therapeutics, Homology, JCR, Orphazyme, QED, Regenxbio, Sangamo, and Takeda and has received consulting fees from Aeglea, Audentes, Capsida, Chiesi, Edigene, Grace Science, Inventiva Pharma, Novel Pharma, Orchard Therapeutics, Rallybio, Renoviron, and Saliogen
- **Deepa Rajan** is a PI on clinical trials funded by Denali Therapeutics, Regenxbio, JCR Pharma, Prevail Therapeutics, and Ultragenyx and has conducted research funded by the Scleroderma Foundation and Children's Neuroscience Institute, UPMC Children's Hospital of Pittsburgh
- **Simon Jones** is an investigator and/or consultant for Takeda (Shire), BioMarin, Alexion and Orchard Therapeutics, and is a SAB member and stockholder of Orchard Therapeutics.
- **JMP van den Hout** provides advices and participates in registries/clinical trials/provides lectures and participates in research via contracts between Erasmus MC University Medical Center and various industries (Denali Therapeutics, Takeda, Sanofi, Amicus Therapeutics, Spark Therapeutics, BioMarin) in the field of lysosomal storage, neuromuscular, and metabolic disorders
- **Steven Chessler, Natalie Engmann, Adam Scheller, Rupa Caprihan, Akhil Bhalla, Tony Hung, Jason Nachtigall, Imanol Zubizarreta, Cynthia Wong, Jeffrey Harris, Yuda Zhu, Peter Chin, Matthew Troyer, Carole Ho** and **Anna Bakardjiev** are full-time employees of Denali Therapeutics Inc., which has filed patent applications related to the subject matter

DISCLAIMER

DNL310 is an investigational drug and is not approved by any Health Authority.
All clinical candidates discussed are investigational drugs and are not approved by any Health Authority.

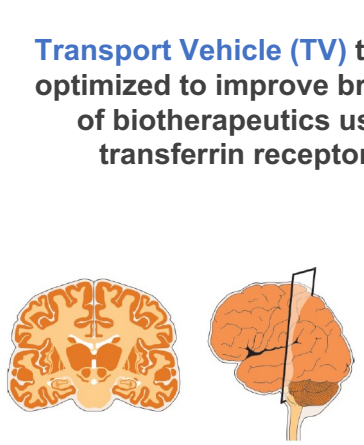
Funding provided by Denali Therapeutics Inc.

Developing a Therapy for MPS II (Hunter Syndrome)

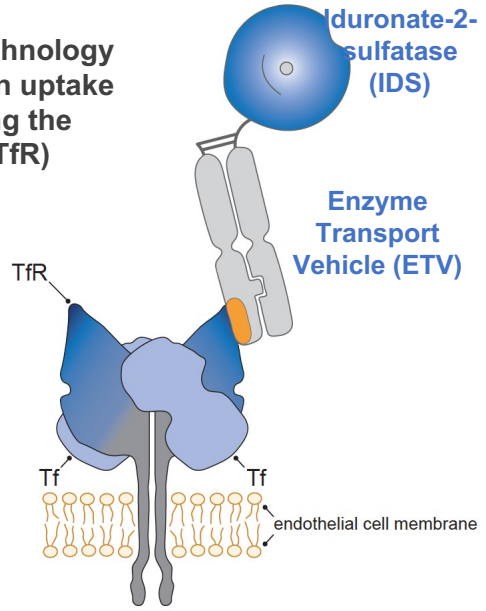
DNL310 (ETV:IDS) is an investigational iduronate-2-sulfatase (IDS) fusion protein engineered to treat both the brain and physical manifestations of mucopolysaccharidosis type II (MPS II) with a **single weekly IV infusion**

Enzyme Transport Vehicle (ETV)

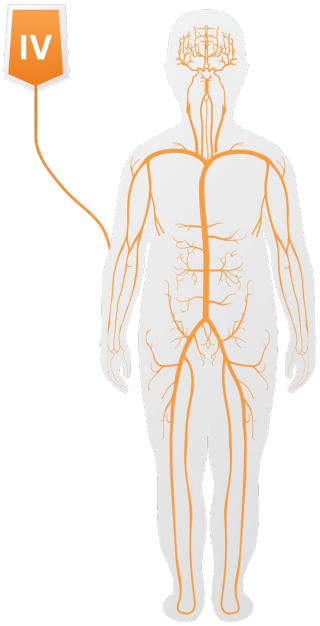
Transport Vehicle (TV) technology optimized to improve brain uptake of biotherapeutics using the transferrin receptor (TfR)



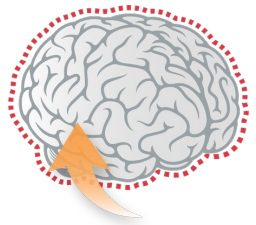
Capillary TfR expression in the brain facilitates widespread biodistribution of TV and enzyme



Administration by weekly IV infusion



Extensive tissue penetration



TfR is highly expressed at the blood-brain barrier. Design of the TV is optimized to enable DNL310 to cross the blood-brain barrier[1-6]

TfR may also facilitate IDS delivery into tissues such as bone, cartilage, and the heart[2,7-9]

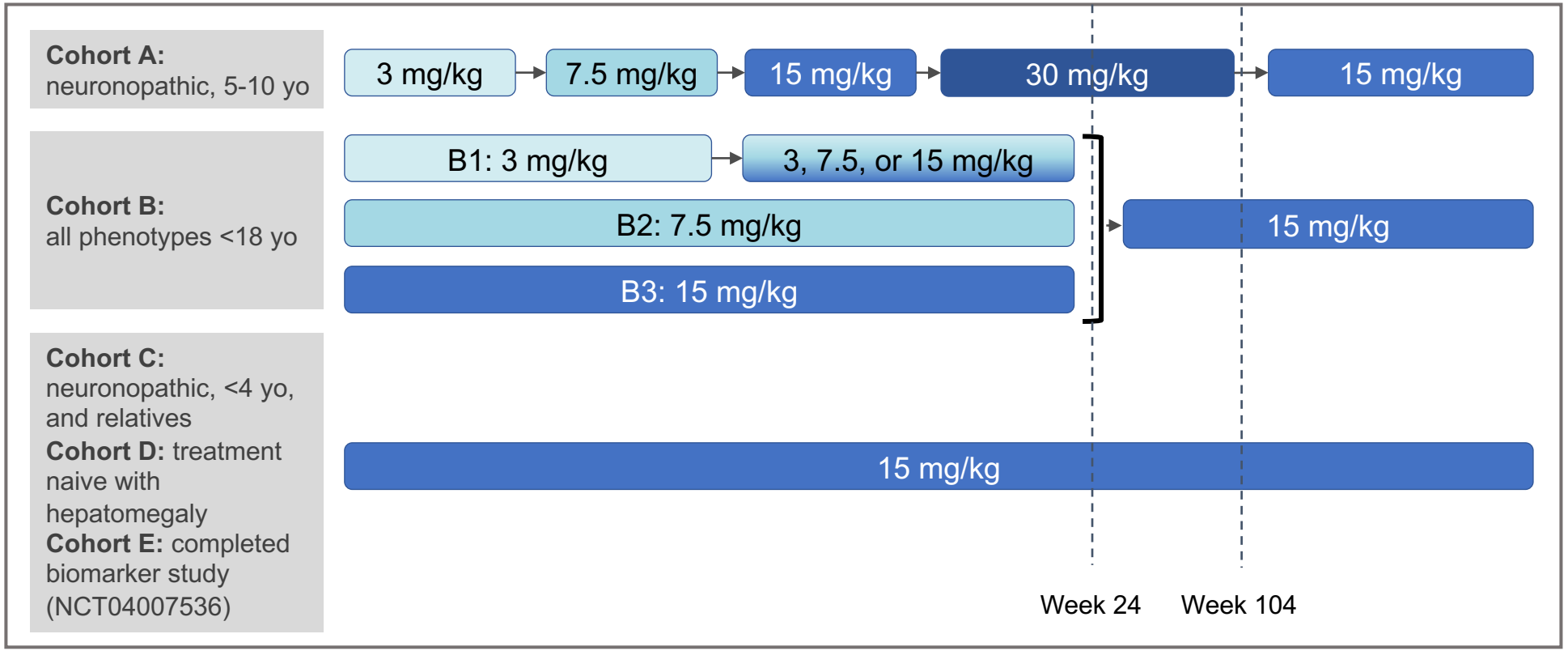
DNL310 has the potential to treat neuronopathic and physical manifestations of MPS II

IV, intravenous.

1. Jefferies WA, et al. *Nature*. 1984. 2. Qian ZM, et al. *Pharmacol Rev.* 2002. 3. Bakardjiev AI, et al. *Mol Genet Metab.* 2021. 4. Arguello A et al. *JCI Insight.* 2021. 5. Arguello A, et al. *J Exp Med*2022. 6. Ullman JC, et al. *Sci Transl Med.* 2020. 7. Wang S, et al. *Haematologica.* 2020.8. Gammella E, et al. *Metallomics.* 2017. 9. Carlevaro MF, et al. *J Cell Biol.* 1997.

DNL310 Phase 1/2 Study in Pediatric Patients With MPS II

- Open-label, 24-week study followed by an open-label extension (NCT04251026)
- Approximately 45 participants ≤18 years of age with MPS II are enrolling into 5 cohorts (A-E); treatment-naive and -experienced patients are eligible
- Differences between the cohorts include age, phenotype, and dose levels
- Participants receiving IDS at baseline switch to DNL310 without a washout period



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

Key secondary endpoints
- CSF and urine HS
- Anti-drug antibodies
- Adaptive behavior (Vineland)

Key exploratory endpoints
- CSF and serum biomarkers including neurofilament light chain (NfL)
- Cognition
- Urine DS
- Clinical outcomes of physical manifestations

CSF, cerebrospinal fluid; DS, dermatan sulfate; HS, heparan sulfate; IDS, iduronate-2-sulfatase; MPS II, mucopolysaccharidosis type II; yo, years old.

Interim Results: Patient Populations

		No. of participants at study week				Cut-off date
		1	24	49	104	
Safety population Participants from all cohorts who received ≥1 dose of DNL310		33	29	25	15	2Mar2023
Biomarker population Participants from all cohorts	CSF	29	28	24	11	
	Serum	27	27	23	13	
Clinical outcomes population Participants from cohorts A and B		23	22	20	4	1Sep2022

CSF, cerebral spinal fluid.

Baseline Demographics and Disease Characteristics

	Cohorts A-E (safety population) n=33	Cohorts A and B (clinical outcomes population) n=23
Age, median (range), years	5 (2-12)	6 (2-12)
Neuronopathic, n (%)	30 (91)	22 (96)
Non-neuronopathic, n (%)	3 (9)	1 (4)
Missense mutations, n (%)	17 (52)	13 (57)
Other mutations, n (%)	16 (48)	10 (43)
Pre-study enzyme replacement		
Participants with pre-study IDS, n (%)	25 (76)	23 (100)
Duration of IDS treatment; median (range), years	2.1 (0.4-11.2)	2.3 (0.4-11.2)
Pre-study treatment naive, n (%)	3 (9)	0
Participants per age group, n (%)		
<2 years	1 (3)	0
2 to <4 years	10 (30)	5 (22)
4 to <8 years	16 (49)	12 (52)
>8 years	6 (18)	6 (26)
Race, n (%)		
Asian	3 (9)	3 (13)
Black or African American	4 (12)	3 (13)
White	18 (55)	12 (52)
Race not reported, unknown, or other	8 (24)	5 (22)
Ethnicity, n (%)		
Hispanic or Latino	5 (15)	5 (22)
Not Hispanic or Latino or not reported/unknown	28 (85)	18 (78)

IDS, iduronate-2-sulfatase.

Interim Safety: Overview

Cumulative information, including previously reported[1,2]	

TEAEs	• All participants reported treatment-emergent adverse events (TEAEs), which were mostly mild or moderate
	• There were no dose-related safety findings
	• Infusion-related reactions (IRRs) were the most frequent TEAEs, IRR frequency declines over time (see next slide)
	• Adverse events of special interest (AESIs) were as follows:
	  • 20 participants experienced moderate IRRs, and 1 participant experienced severe IRRs
	  • 4 participants (all with mild baseline anemia or a history of anemia) had moderate anemia (3 resolved); dosing continued in all 4 cases; anemia is a known complication of lysosomal storage diseases such as MPS II[3]
	• One discontinuation related to TEAEs (including IRRs and other non–drug-related AEs) was observed in a participant with complex underlying disease; 3 other discontinuations due to social reasons (family circumstances, relocation)

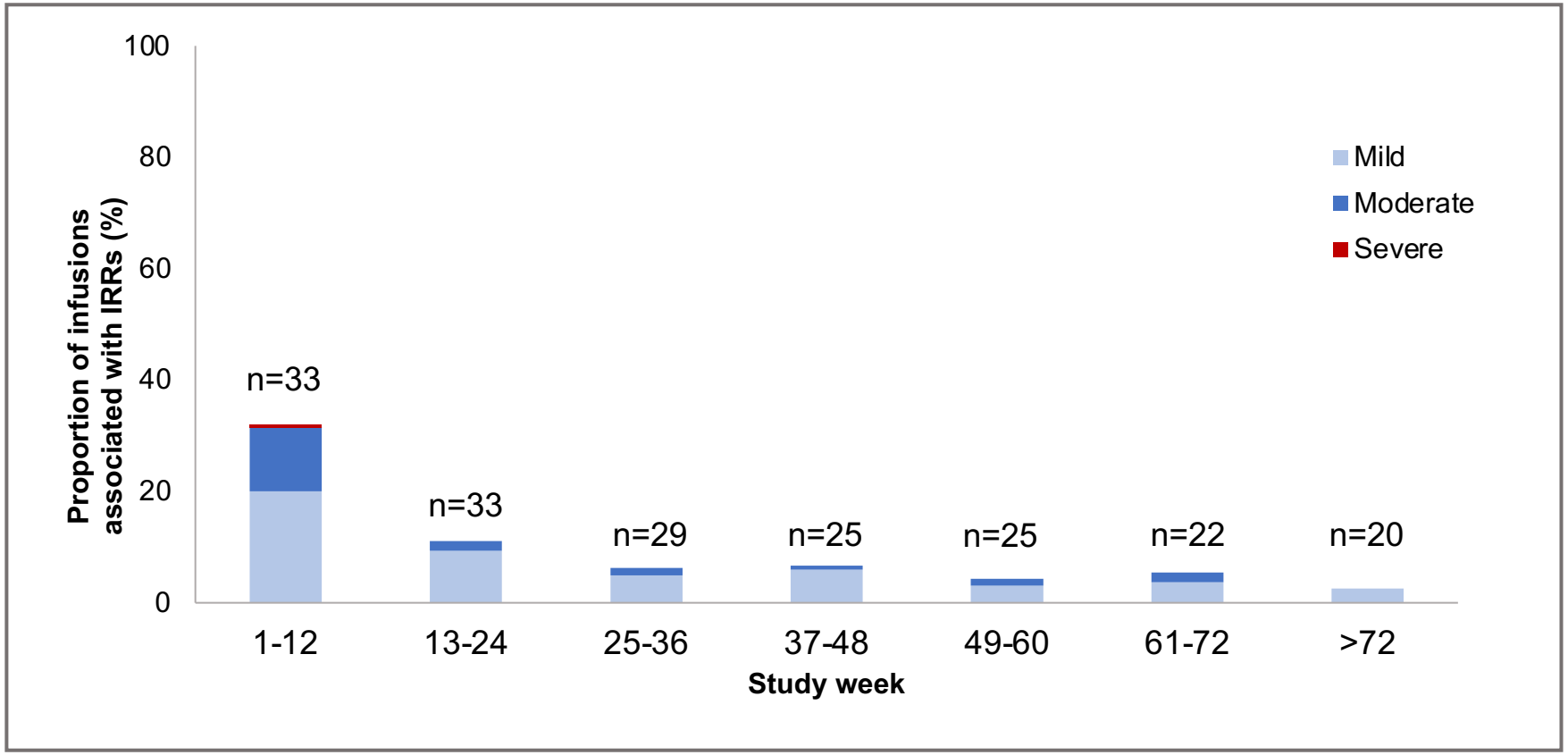
SAEs	• SAEs were reported in 10 participants; of these, 2 had IRRs, and 8 had SAEs that are largely known comorbidities of MPS II or childhood infections and are unrelated (per the investigators) to study drug or procedures (including constipation, upper respiratory tract infection, progressive cervical stenosis/thoracic syrinx, increased episodes of OSA, vomiting and diarrhea, viral parotitis, central line infection)
SAFETY LABS	• Prior to treatment, 15 participants had elevated total urine GAGs (colorimetric assay); all decreased after receiving DNL310 • No other significant trends in safety laboratory evaluations occurred post initiation of DNL310 treatment

Safety profile reflects median treatment duration of 91 weeks in 33 study participants; maximum treatment duration: 135 weeks
Independent Data Monitoring Committee recommended continuing study without modifications (May 2023)

DNL310 is generally well tolerated with a safety profile that continues to support development in MPSII

AE, adverse event; GAG, glycosaminoglycan; MPS II, mucopolysaccharidosis type II; OSA, obstructive sleep apnea; SAE, serious adverse event.
1.Bakardjiev AI, et al. WORLD 2021, 2022 and iMPS 2021. 2. Muenzer J, et al. SSIEM 2022 and WORLD 2023. 3. Stepien, et al. 2022 and 2023. Kaciulyte et al., 2023.

Safety: IRRs

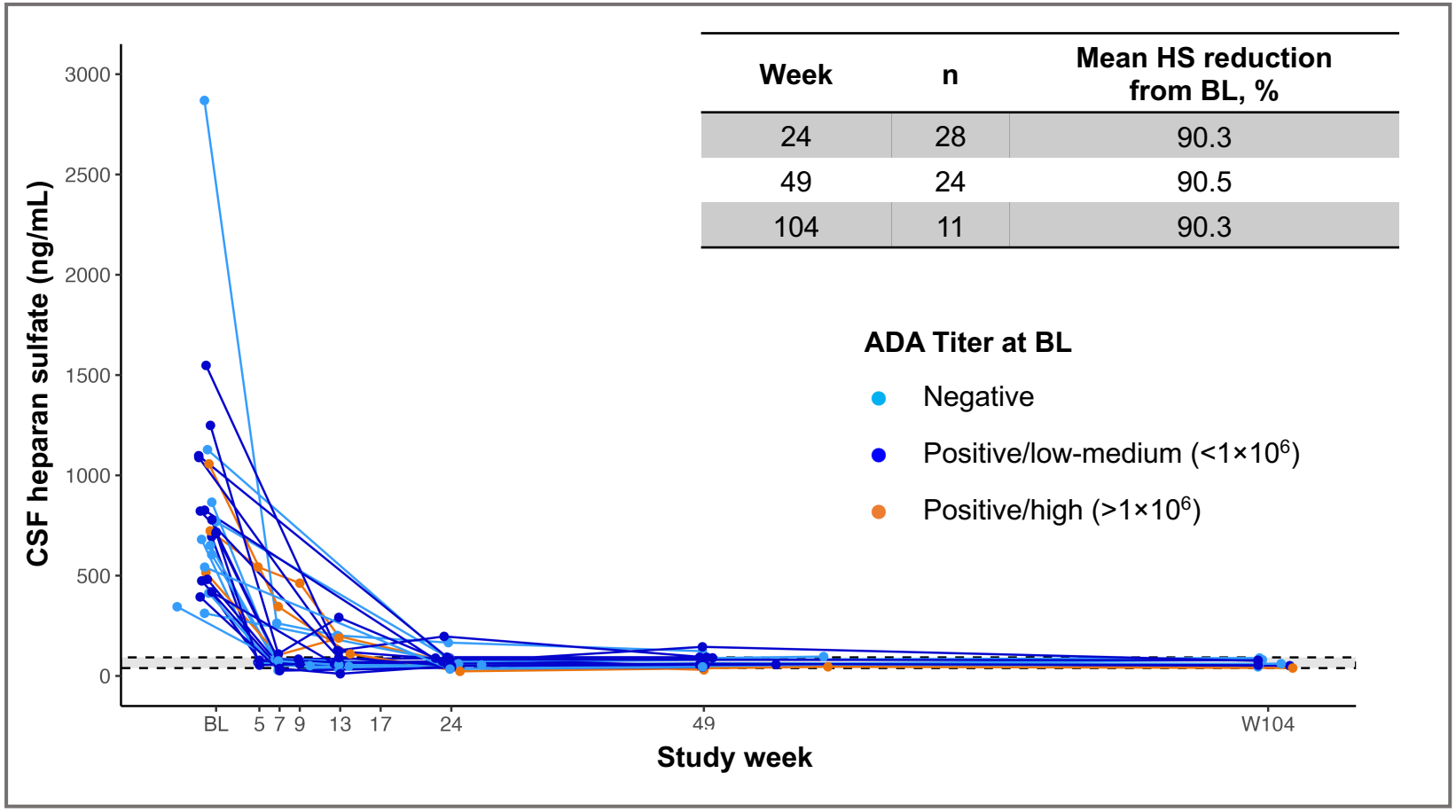


Total number of infusions during the study: 2471

Tolerance to DNL310 occurred with longer-term dosing

IRR, infusion-related reaction.

Biomarkers: CSF HS



Week	n	Mean HS reduction from BL, %
24	28	90.3
49	24	90.5
104	11	90.3

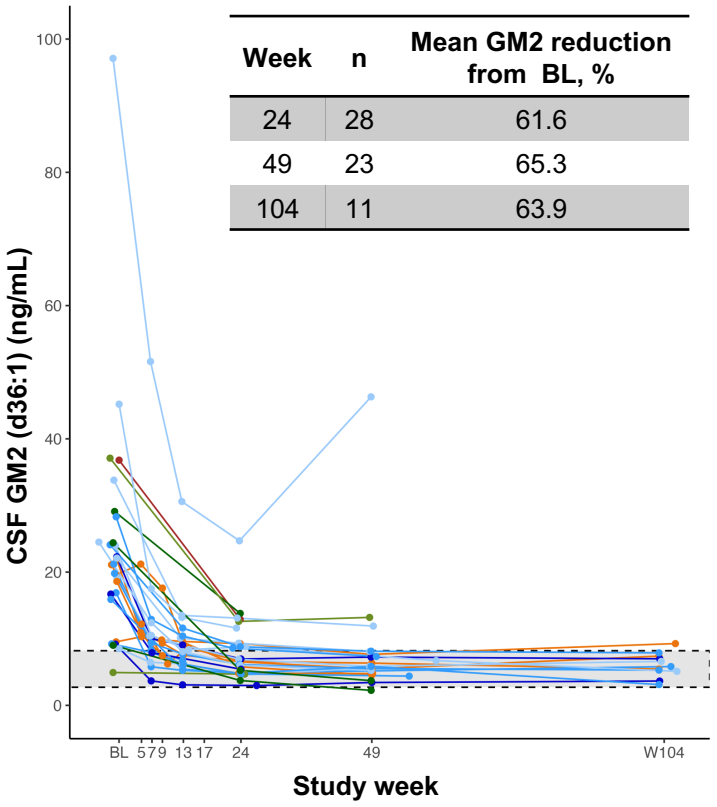
Achievement of normal levels of CSF HS,[a] sustained over time, including in those with high pre-existing ADA

ADA, anti-drug antibody; BL, baseline; CSF, cerebral spinal fluid; HS, heparan sulfate.
[a]Preliminary normal range (10th and 90th percentile) determined using 30 healthy adult CSF samples (age range, 18-81 years; median, 52 years). Total CSF GAG levels were similar in adults and children (Hendriksz et al. 2015). Normal range for CSF HS, 39.1-92.51 ng/mL. HS was measured as a sum of the disaccharides D0A0, D0A6, D0S0, D2S6.

Biomarkers: CSF Lysosomal Lipids

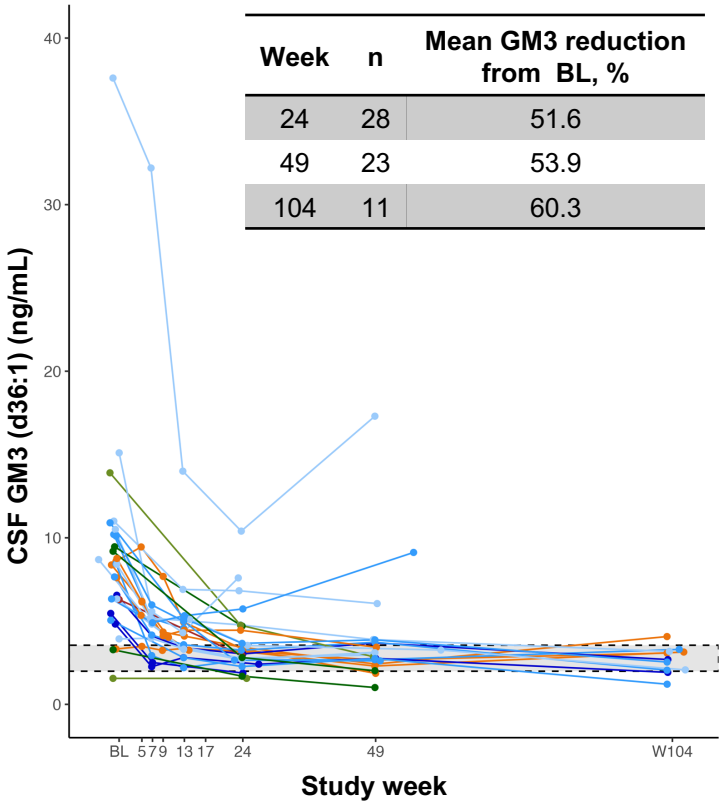
GM2[a]

Week	n	Mean GM2 reduction from BL, %
24	28	61.6
49	23	65.3
104	11	63.9



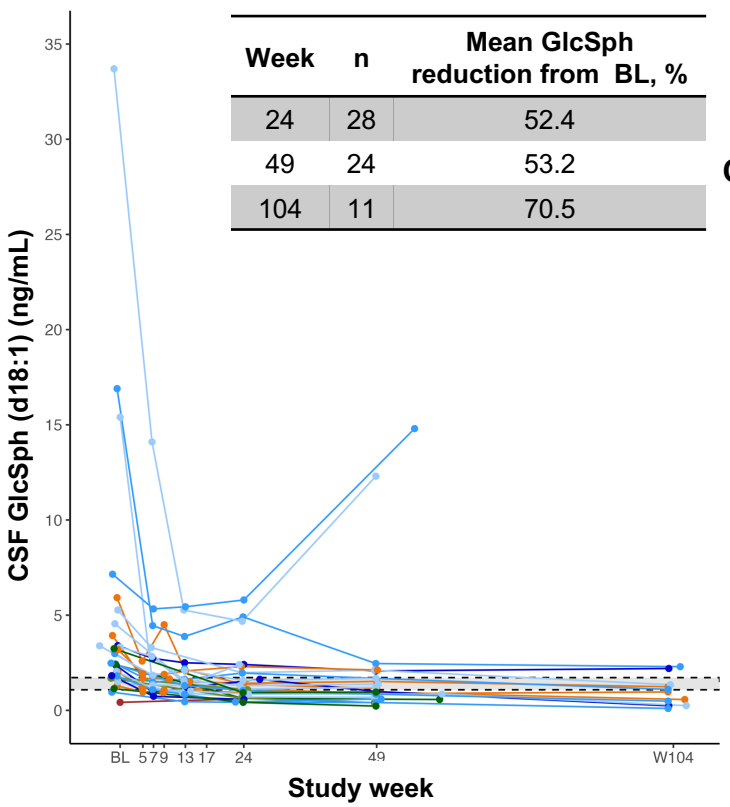
GM3[a]

Week	n	Mean GM3 reduction from BL, %
24	28	51.6
49	23	53.9
104	11	60.3



GlcSph[a]

Week	n	Mean GlcSph reduction from BL, %
24	28	52.4
49	24	53.2
104	11	70.5

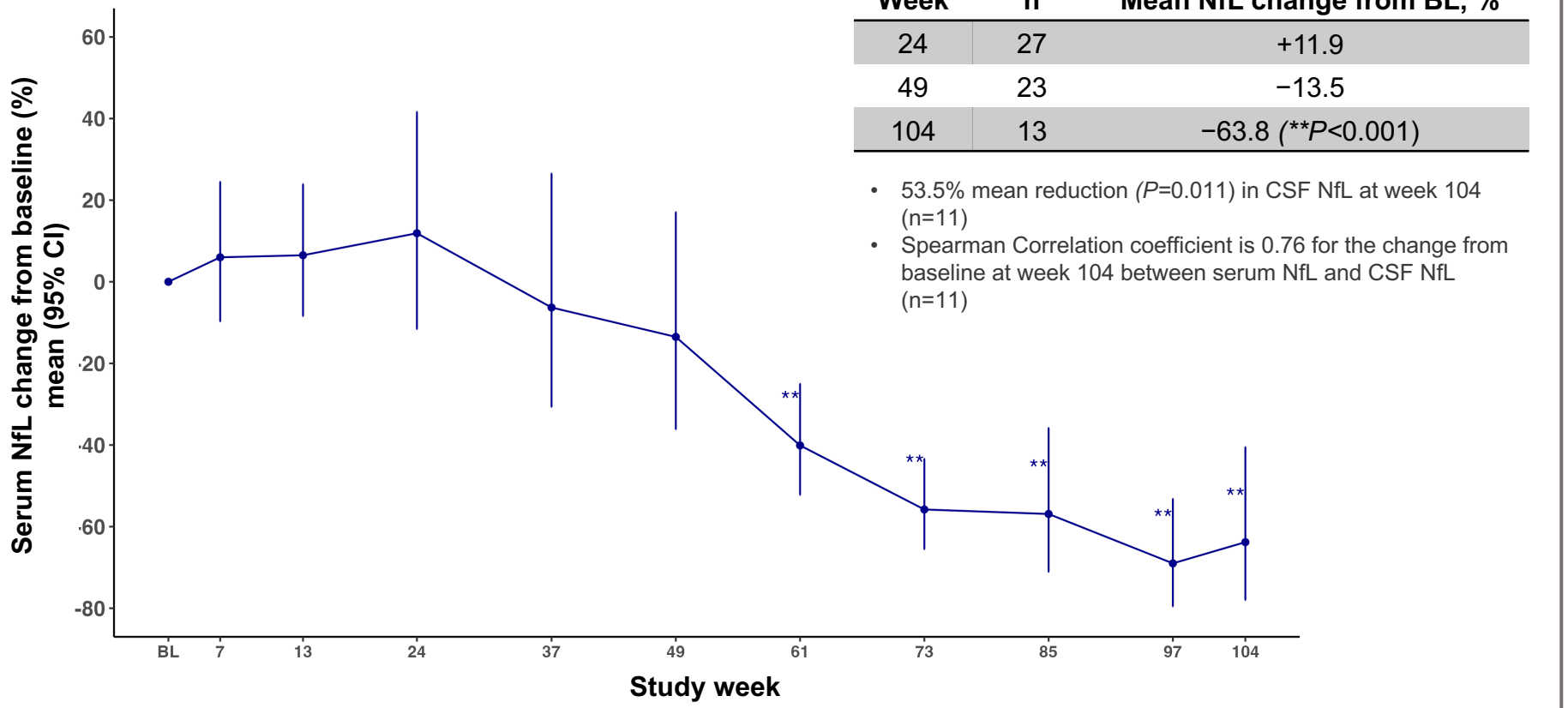


Cohort	Dose (mg/kg)
A	3-30
B1	3-15
B2	7.5-15
B3	15
C	15
D	15
E	15

Sustained normal levels of CSF lysosomal lipids in most participants are consistent with improved lysosomal function

BL, baseline; CSF, cerebral spinal fluid; GlcSph, glucosylsphingosine; GM, ganglioside.
[a]Preliminary GM3 normal range (10th and 90th %ile gray dashed lines) determined using 17 healthy adult CSF samples (age range 22-50 years, median 27 years; ng/mL): 1.99-3.55; Preliminary normal range (10th and 90th %ile gray dashed lines) determined using 18 healthy adult CSF samples (age range 19-52 years, median 24.5 years); GM2 (ng/mL): 2.72-8.2. GlcSph (ng/mL): 1.08-1.72.

Biomarkers: Serum Neurofilament (NfL)



Week	n	Mean NfL change from BL, %
24	27	+11.9
49	23	−13.5
104	13	−63.8 (**P<0.001)

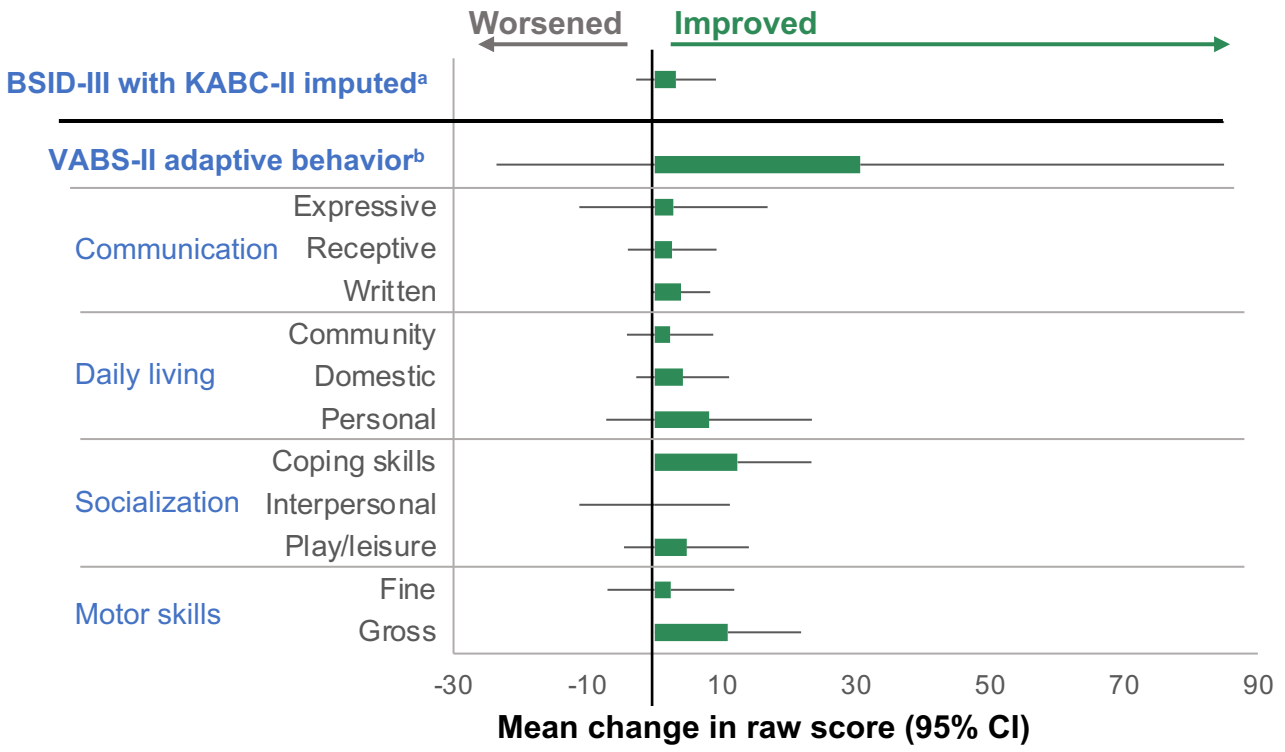
- 53.5% mean reduction (P=0.011) in CSF NfL at week 104 (n=11)
- Spearman Correlation coefficient is 0.76 for the change from baseline at week 104 between serum NfL and CSF NfL (n=11)

Robust reduction in serum NfL, a marker of neuronal damage, significant after 61 weeks and reaching a 64% reduction after two years of dosing with DNL310

**P<0.001.
BL, baseline; CSF, cerebral spinal fluid; NfL, neurofilament light chain.
Aggregate summaries by time point are provided for analysis visits that are common across all cohorts. The Week 7 analysis visit includes observations closest to the target day (i.e. Day 43) from weeks 5, 7, or 9. Mean change from baseline are computed from the geometric mean ratio relative to baseline. Corresponding 95% CI and P values are derived from the log ratio relative to baseline. Percent change from baseline are derived as 100(exp(x)-1); where x denotes the mean ratio, upper and lower limit for the mean ratio.

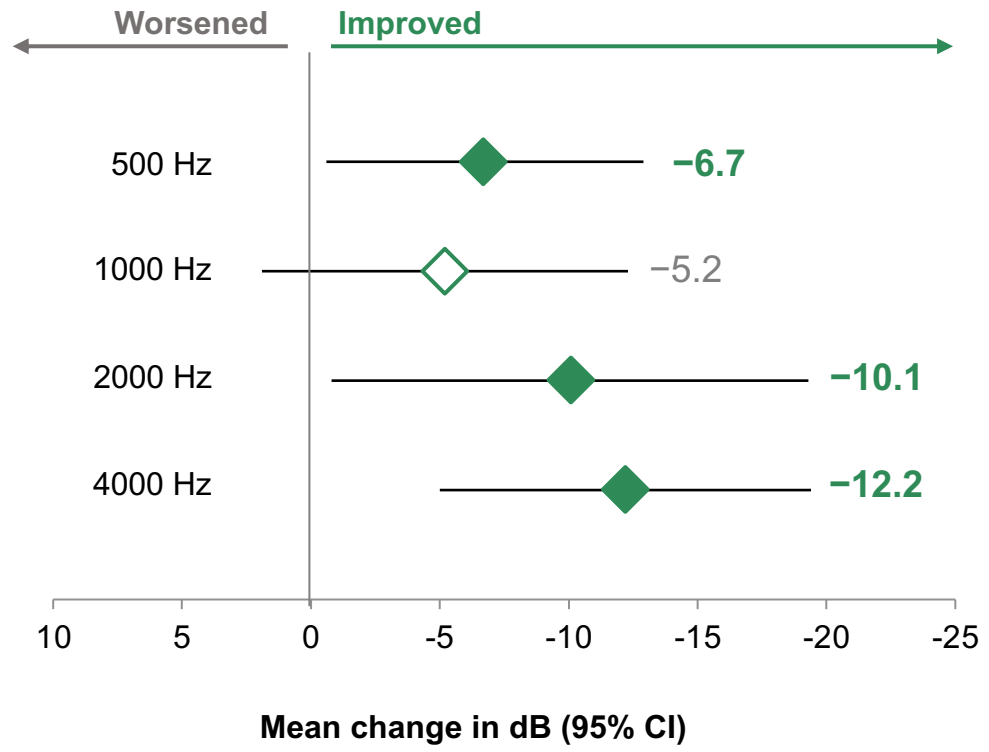
Clinical Outcomes at Week 49

BSID-III and VABS-II Raw score mean change from BL



(n=16)

ABR thresholds mean change from BL[c]



(n=18 to 20 participants, varies by frequency)

Improvements in mean cognitive BSID-III and VABS-II raw scores, and ABR thresholds at week 49 of DNL310 treatment suggest positive effects on cognition, adaptive behavior, and hearing

ABR, auditory brainstem response; BL, baseline; BSID-III; Bayley Scales of Infant and Toddler Development III; KABC, Kaufman Assessment Battery for Children; VABS-II, Vineland Adaptive Behavior Scales II.
[a]Imputed values are taking a value of 91. Participants with imputed values at W49 and Baseline are not considered in the mean change as both values are 91 leading to an undesired change values of 0. [b]Data from 4 participants either unavailable (n=1) or only VABS-3 collected (n=3) at Week 49. The Total Adaptive Behavior raw score derives from all Communication, Daily Living, and Socialization subdomains except for Communication-Written, Daily Living-Domestic, and Daily Living-Community. [c]Results are based on air conduction tests. Least squares mean (95% CI), adjusted for age at ERT initiation.

Summary of Interim Results

Clinical safety	• Safety profile is based on 33 participants with MPS II with a median treatment duration of 91 weeks, and supports continued development in MPS II • IRRs accounted for the most frequent TEAEs and decreased in frequency and severity with continued dosing
Biomarkers	• Rapid normalization or near normalization of CSF HS was observed in all participants, sustained at weeks 49 and 104 • Normalization of CSF HS was observed even in participants with high preexisting ADA • Normalization of CSF lysosomal lipids in most participants consistent with improved lysosomal function • Robust reduction of 64% in serum NfL, a marker of neurodegeneration, with long-term dosing
Clinical outcomes	• Interim clinical outcomes data suggest positive change in adaptive behavior and cognition with DNL310 treatment • ABR data suggest that DNL310 treatment improves auditory function

DNL310 is an investigational, intravenously administered, Enzyme Transport Vehicle (ETV)-enabled, iduronate-2-sulfatase (IDS) replacement therapy designed to cross the BBB and address the behavioral, cognitive and physical manifestations of MPS II

A potentially registrational phase 2/3 study with sites in North America, South America, and Europe is enrolling (NCT05371613)

ABR, auditory brainstem response; ADA, anti-drug antibody; CSF, cerebral spinal fluid; HS, heparan sulfate; IRR, infusion-related reaction; MPS II, mucopolysaccharidosis type II; NfL, neurofilament light chain; TEAE; treatment-emergent adverse event.

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