Robust Reduction in Neurofilament Light (NfL) with DNL310 (ETV:IDS) Treatment in MPS II (Hunter Syndrome)

June 20, 2023

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AGENDA

TOPIC	SPEAKER
Introduction	Ryan Watts, PhD Chief Executive Officer
Robust Reduction in Neurofilament Light (NfL) with DNL310 (ETV:IDS) Treatment in MPS II (Hunter Syndrome)	Carole Ho, MD Chief Medical Officer and Head of Development
Closing Remarks	Ryan Watts, PhD Chief Executive Officer
Q&A	Ryan Watts, PhD Chief Executive Officer Carole Ho, MD Chief Medical Officer and Head of Development Alex Schuth, MD Chief Operating & Financial Officer

Introduction

Ryan Watts, PhD, Chief Executive Officer

OUR PURPOSE: DEFEAT DEGENERATION

RARE NEURODEGENERATIVE DISEASES	AMYOTROPHIC LATERAL SCLEROSIS	PARKINSON'S	ALZHEIMER'S
Orphan	15,000+ (US)	1,000,000+ (US)	6,000,000+ (US)

Significant unmet medical need with few disease-modifying medicines

OUR DEVELOPMENT PORTFOLIO

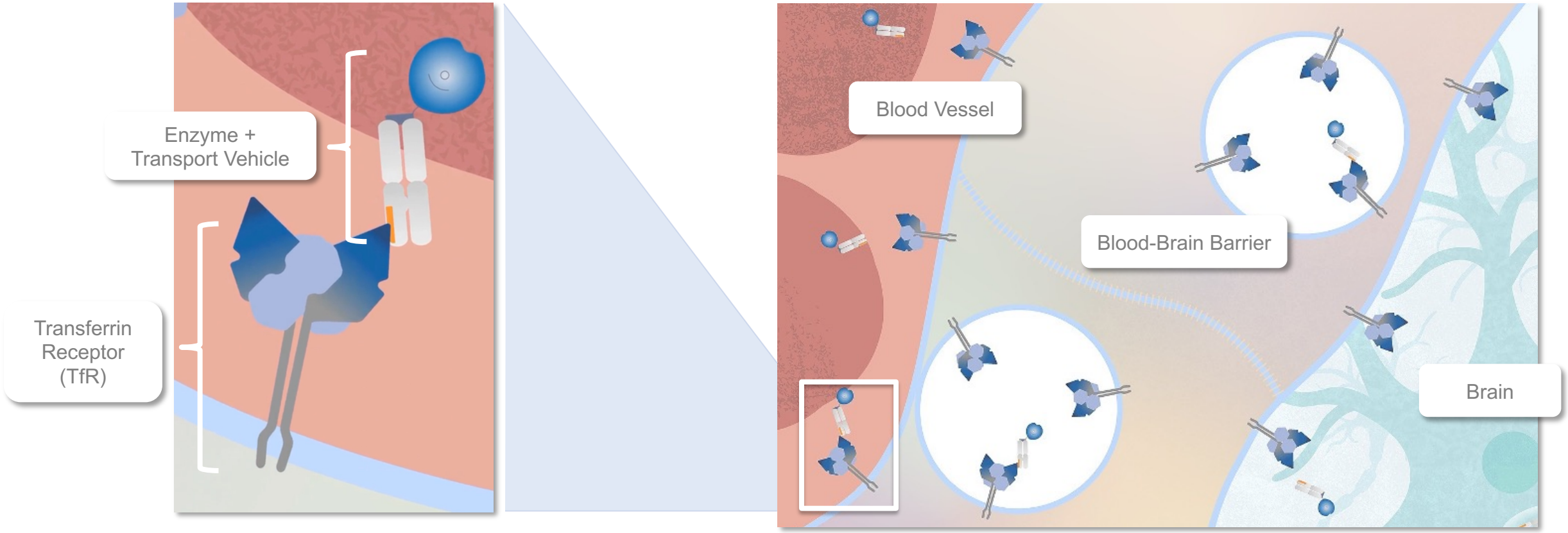
MODALITY	TARGET	BIOLOGY	DRUG CANDIDATE*	DISEASE INDICATION	DEVELOPMENT STAGE	PARTNER
LARGE MOLECULE (TV-ENABLED)	Iduronate-2-Sulfatase	Lysosomal Function	**DNL310** (ETV:IDS)	MPS II (Hunter)	IND-Enabling / Early / Mid / Late	
	PGRN	Lysosomal Function	**TAK-594/DNL593** (PTV:PGRN)	Frontotemporal Dementia-Granulin (FTD-GRN)	IND-Enabling / Early / Mid / Late	Takeda
	TREM2	Glial Biology	**TAK-920/DNL919** (ATV:TREM2)	Alzheimer's	IND-Enabling / Early / Mid / Late	Takeda
	Sulfamidase	Lysosomal Function	**DNL126** (ETV:SGSH)	MPS IIIA (Sanfilippo)	IND-Enabling / Early / Mid / Late	
	Alpha-L-iduronidase	Lysosomal Function	**DNL622** (ETV:IDUA)	MPS I (Hurler)	IND-Enabling / Early / Mid / Late	
	Multiple	Multiple	**OTV:Multiple**	Multiple	IND-Enabling / Early / Mid / Late	
SMALL MOLECULE	LRRK2	Lysosomal Function	**BIIB122/DNL151** (LRRK2 inhibitor)	Parkinson's disease	IND-Enabling / Early / Mid / Late	Biogen
	RIPK1 (CNS)	Glial Biology	**SAR443820/DNL788** (RIPK1 inhibitor)	Amyotrophic Lateral Sclerosis (ALS) Multiple Sclerosis (MS)	IND-Enabling / Early / Mid / Late	sanofi
	RIPK1 (Peripheral)	Other	**SAR443122/DNL758** (RIPK1 inhibitor)	Cutaneous Lupus Erythematosus (CLE) Ulcerative Colitis (UC)	IND-Enabling / Early / Mid / Late	sanofi
	eIF2B	Cellular Homeostasis	**DNL343** (eIF2B activator)	Amyotrophic Lateral Sclerosis (ALS)	IND-Enabling / Early / Mid / Late	

Biotherapeutics **Small Molecules** 50/50 US Commercial Royalty *Investigational – not approved for treatment

Broad, diverse, and differentiated portfolio, including multiple TV-enabled and small molecule programs in discovery

ADDRESSING THE CHALLENGE OF DELIVERING THERAPY TO THE BRAIN

The Transport Vehicle (TV) is engineered to deliver efficacious concentrations of biotherapeutics (large molecules) to brain cells via receptor mediated transcytosis

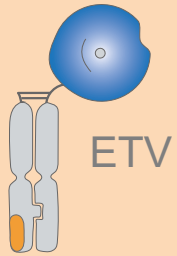


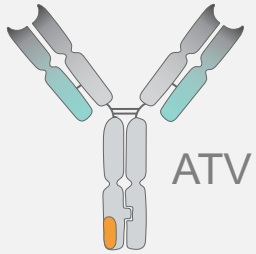
https://www.denalitherapeutics.com/patients

FURTHER VALIDATION OF TRANSPORT VEHICLE PLATFORM POTENTIAL

Enzyme Transport Vehicle

Deliver **enzymes** to the brain to replace deficient or missing enzyme activity



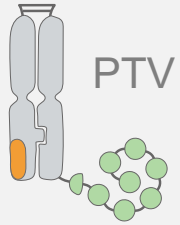


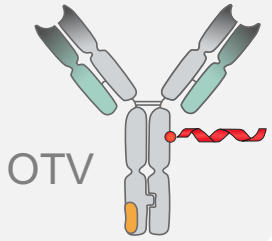
Antibody Transport Vehicle

Deliver **antibodies** in bivalent or bispecific format to the brain

Protein Transport Vehicle

Deliver **proteins** to the brain to replace deficient or missing protein





Oligonucleotide Transport Vehicle

Deliver **oligonucleotides** to the brain and modify gene expression

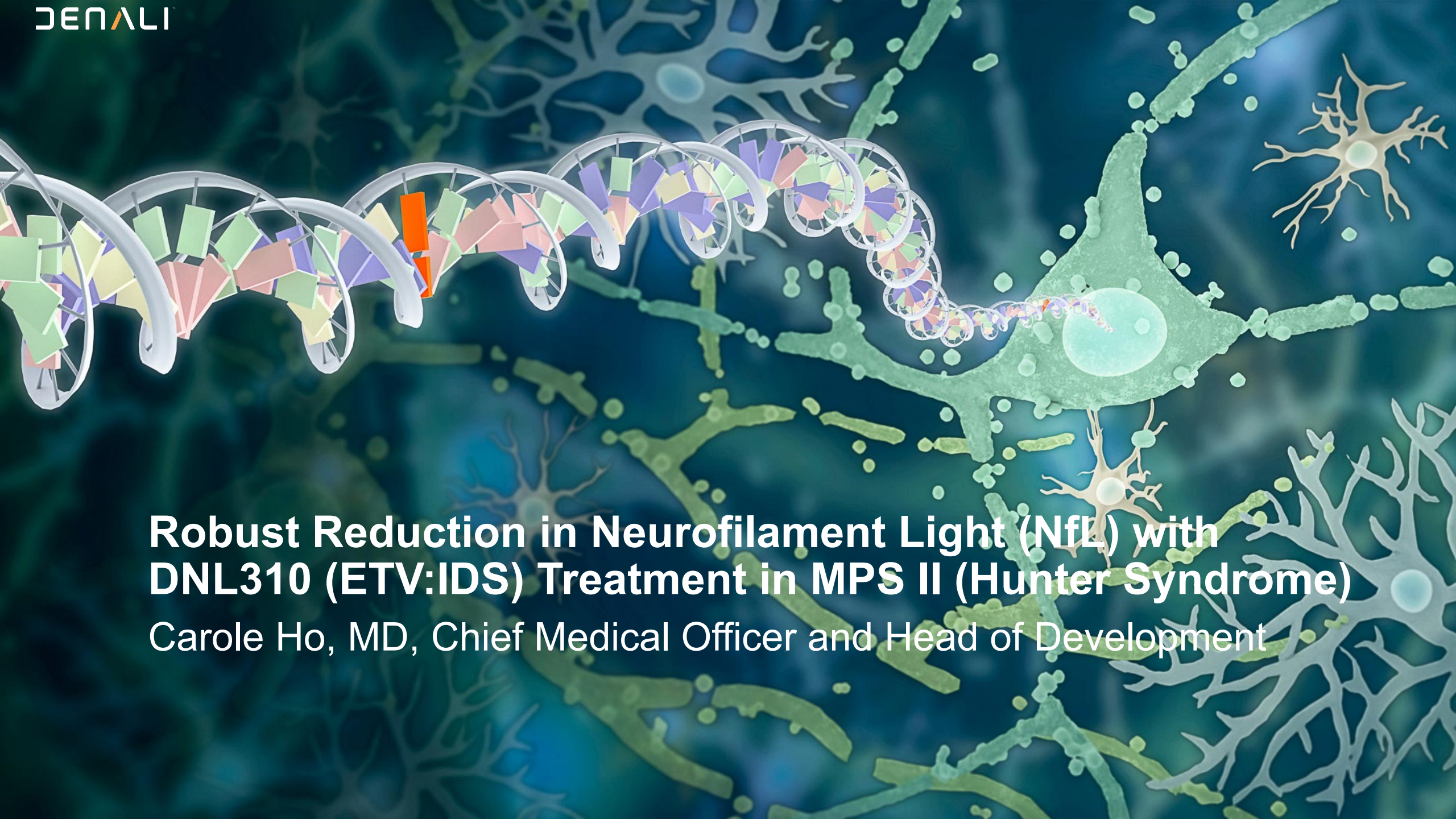
Each TV modality is a platform opportunity

TODAY'S NEWS

- Interim results demonstrate average reduction of 64% ($p < 0.001$) from baseline in serum NfL after 2 years of dosing with DNL310 in Phase 1/2 study

- FDA has recommended assessment of NfL, a marker of neuroaxonal damage, as a possible biomarker in MPS II

- Additional interim data from the DNL310 Phase 1/2 study will be presented at the SSIEM symposium in August



Robust Reduction in Neurofilament Light (NfL) with DNL310 (ETV:IDS) Treatment in MPS II (Hunter Syndrome)

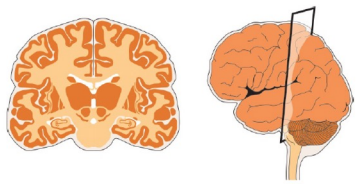
Carole Ho, MD, Chief Medical Officer and Head of Development

DEVELOPING A THERAPY FOR MPS II (HUNTER SYNDROME)

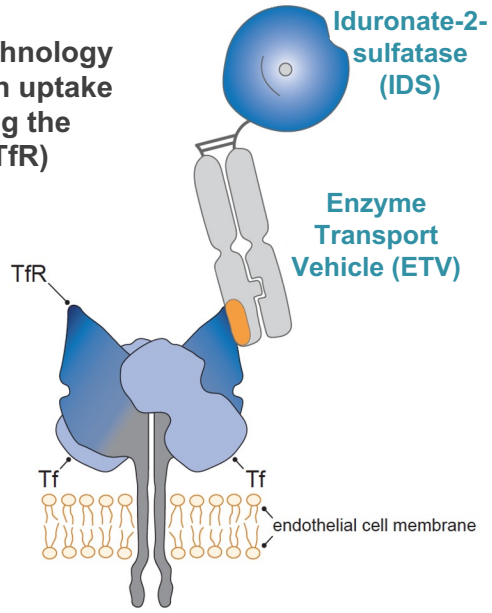
DNL310 (ETV:IDS) is an investigational iduronate-2-sulfatase (IDS) fusion protein engineered to treat both the brain and physical manifestations of mucopolysaccharidosis type II (MPS II) with a single weekly IV infusion

Enzyme Transport Vehicle (ETV)

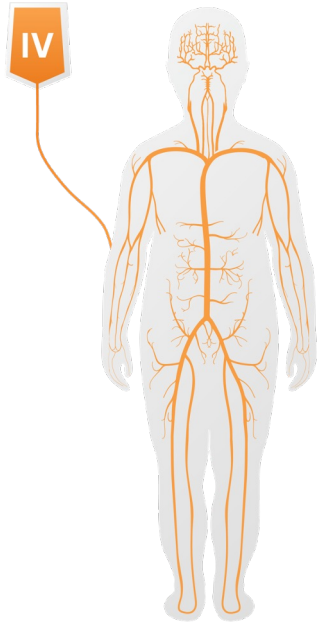
Transport Vehicle (TV) technology optimized to improve brain uptake of biotherapeutics using the transferrin receptor (TfR)



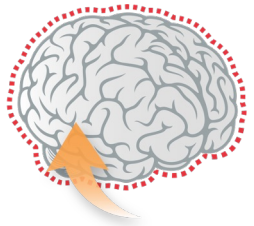
Capillary TfR expression in the brain facilitates widespread biodistribution of TV and enzyme



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 THERAPEUTIC HYPOTHESIS AND DEVELOPMENT STRATEGY

Replace IDS in periphery and brain

Restore Cellular Health (Improve Lysosomal Function and Neuronal Health)

Improve Clinical Outcomes

Biochemical Correction

Reduction / normalization HS / GAGs

Cellular Correction

Reduction / normalization GM2 / GM3 / lysosomal lipids

Neuronal Correction

Reduce abnormal levels of Neurofilament-light (NfL)

Patient Impact

- VABS (adaptive behavior)
- BSID (cognition)
- ABR (hearing)
- Other somatic endpoints

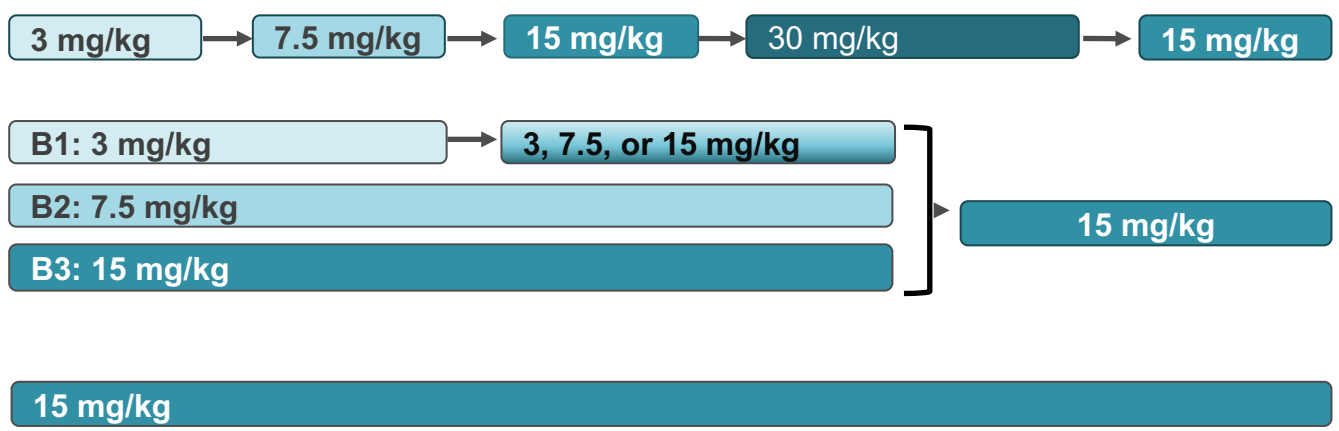
DNL310 Phase 1/2 interim data suggest biochemical correction leads to restoration of cellular and neuronal health, potentially driving improved clinical outcomes

IDS: iduronate-2-sulfatase; GAGs: glycosaminoglycans; VABS: Vineland Adaptive Behavior Scales; BSID: Bayley Scales of Infant and Toddler Development; ABR: auditory brainstem response

DNL310 PHASE 1/2 STUDY DESIGN AND INTERIM ANALYSIS POPULATION

- Open-label, 24-week study followed by an open-label extension (NCT04251026)
- Approximately 45 participants ≤18 years of age with MPS II
- Participants receiving IDS at baseline switch to DNL310 without a washout period

COHORTS



BSID, Bayley Scales of Infant Development; CSF, cerebrospinal fluid; DS, dermatan sulfate; HS, heparan sulfate; IDS, iduronate-2-sulfatase; KABC, Kaufman Assessment Battery for Children; MPS II, mucopolysaccharidosis type II; yo, years old.

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
- Additional CSF and serum biomarkers
- Urine DS
- Clinical outcomes, including cognition (BSID/KABC)

Clinical cutoff date (CCOD) of March 2, 2023 for NfL analysis
Data Monitoring Committee (DMC) on May 31, 2023 - recommended continue study without modification

	No. of Participants at Study Week		
	24	**49**	**104**
NfL analysis population participants with available plasma samples	27	23	13

CLINICAL PHENOTYPE OF MPS AND GAG ACCUMULATION

TYPE	NAME	ENZYME DEFICIENCY	GAG
MPS I	Hurler / Scheie	α-L-iduronidase	**HS,** DS
MPS II	Hunter	Iduronate-2-sulfatase	**HS**, DS
MPS IIIA	Sanfilippo A	Heparan sulfamidase	**HS**
MPS IIIB	Sanfilippo B	N-acetyl-α-D-glucosaminidase	**HS**
MPS IIIC	Sanfilippo C	Acetyl-CoA:α-glucosaminidase	**HS**
MPS IIID	Sanfilippo D	N-acetylglucosamine-6-sulfatase	**HS**
MPS IVA	Morquio A	N-acetylgalactosamine-6-sulfatase	KS, CS
MPS VI	Maroteaux-Lamy	N-acetylgalactosamine-4-sulfatase	DS, CS
MPS VII	Sly	β-Glucuronidase	**HS**, DS, CS
MPS IX	Natowicz	Hyaluronidase	HA

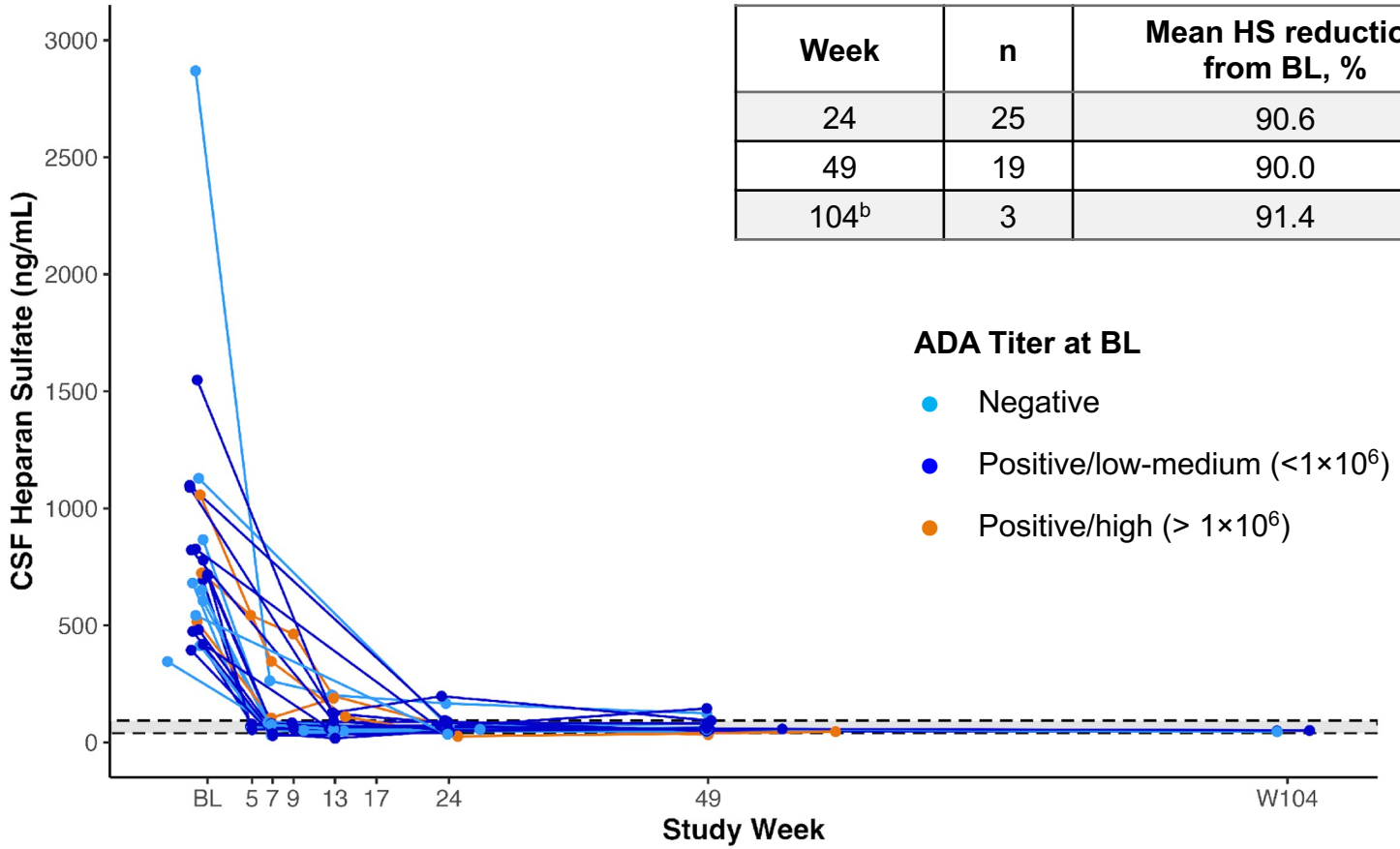
CNS involvement

GAG= glycosaminoglycan
HS= heparan sulfate
DS= dermatan sulfate
CS= chondroitin sulfate
KS= keratin sulfate
HA= hyaluronic acid

Heparan sulfate is associated with MPS disorders with CNS involvement

Kobayashi et al., Journal of Human Genetics 2019

BIOMARKERS: CSF HS[a]



Week	n	Mean HS reduction from BL, %
24	25	90.6
49	19	90.0
104[b]	3	91.4

Rapid and sustained normalization of CSF HS achieved with DNL310 treatment

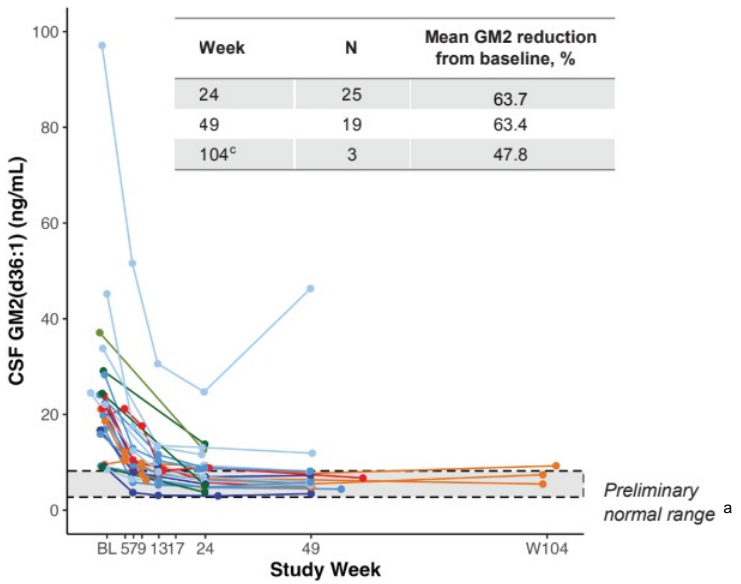
ADA, anti-drug antibodies. [a]Preliminary normal range (10th and 90th percentile) determined using 30 healthy adult CSF samples (age range, 18-81 years; median, 52 years). Total CSF GAG levels were similar in adults and children (Hendriksz et al. 2015). Normal range for CSF HS, 39.1-92.51 ng/mL. HS was measured as a sum of the disaccharides D0A0, D0A6, D0S0, D2S6. [b]Data for 1 week 104 time point was collected post clinical cutoff date.

Source: Muenzer, J et al. 2023 WORLD*Symposium*™

BIOMARKERS OF LYSOSOMAL FUNCTION

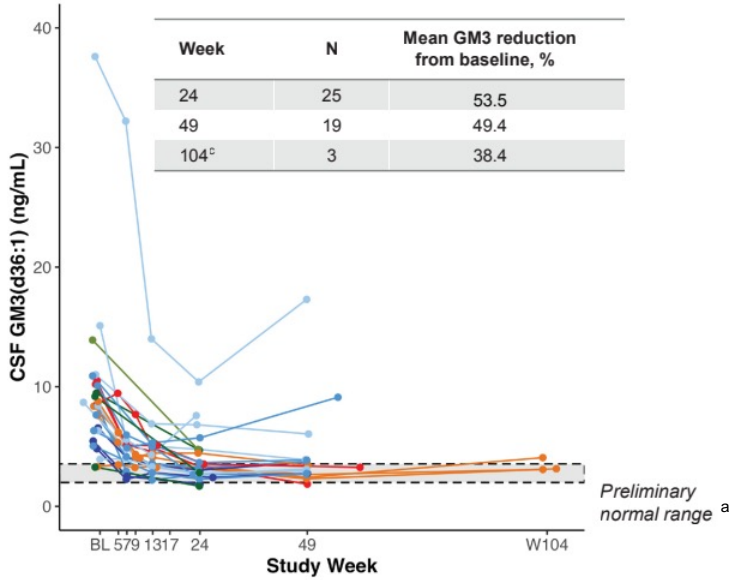
GM2

Week	N	Mean GM2 reduction from baseline, %
24	25	63.7
49	19	63.4
104[c]	3	47.8



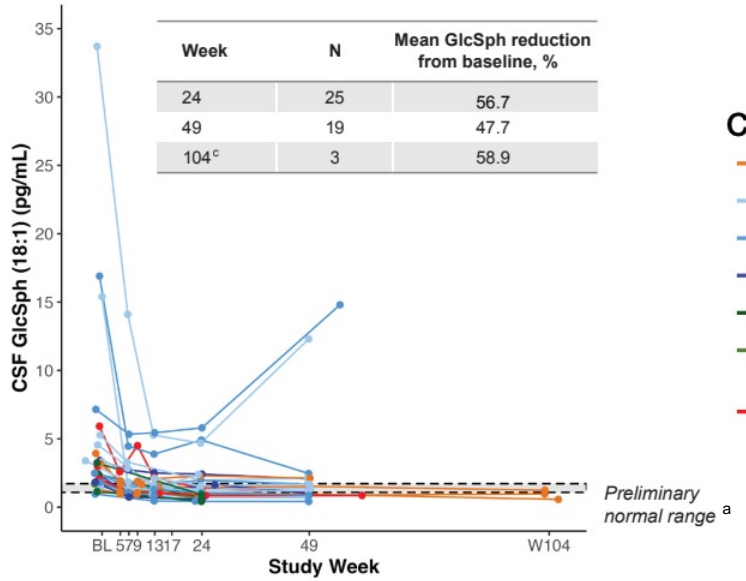
GM3

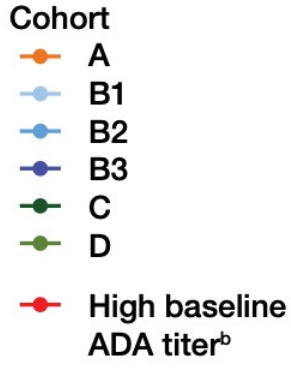
Week	N	Mean GM3 reduction from baseline, %
24	25	53.5
49	19	49.4
104[c]	3	38.4



GlcSph

Week	N	Mean GlcSph reduction from baseline, %
24	25	56.7
49	19	47.7
104[c]	3	58.9

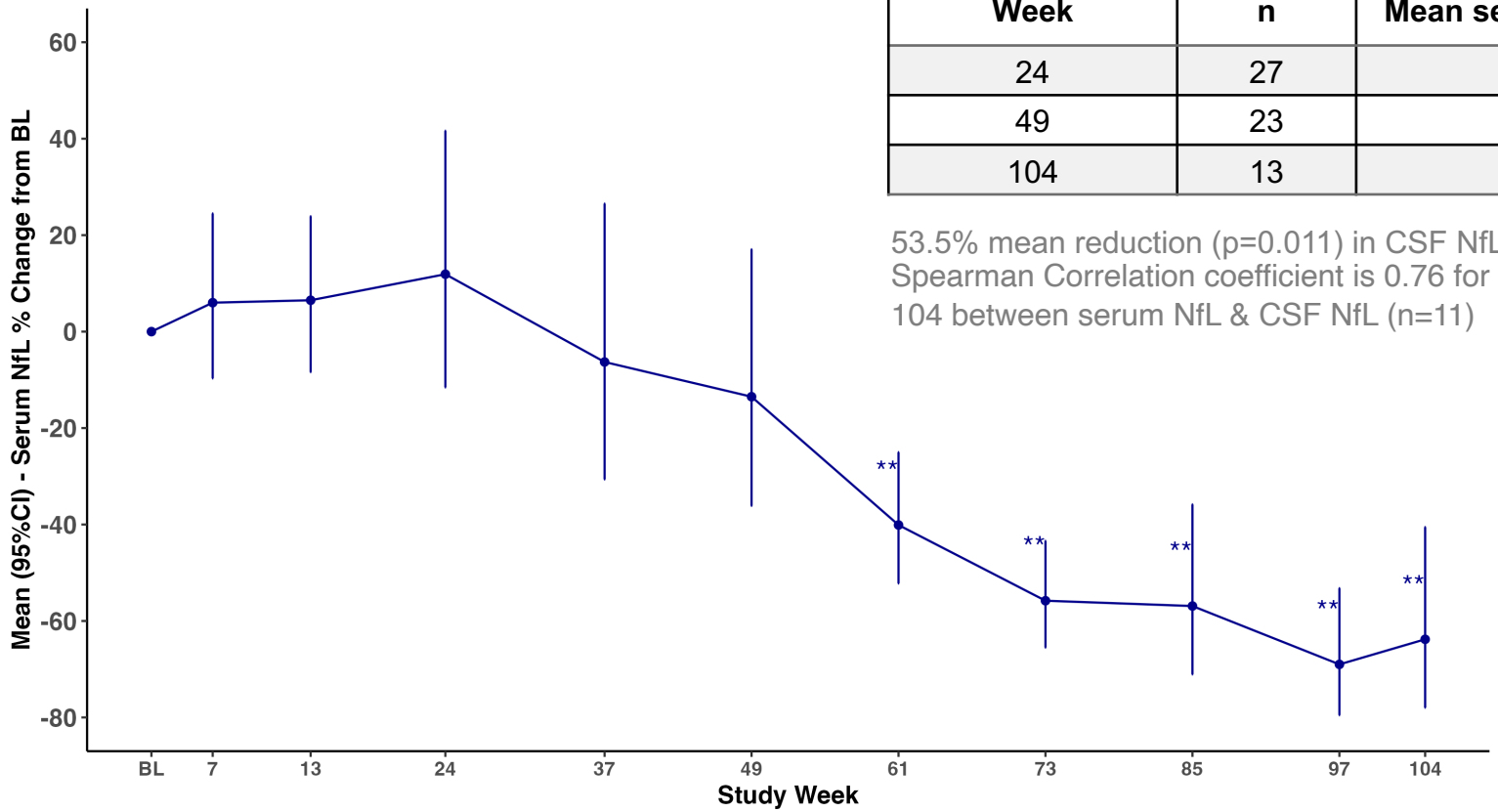




ADA, anti-drug antibody; BL, baseline; CSF, cerebrospinal fluid; GM, ganglioside; GlcSph, glucosylsphingosine; W, week. [a]Preliminary GM3 normal range (gray dashed lines indicate 10th and 90th percentiles) determined using CSF samples from 17 healthy adults (age range, 22-50 years; median 27 years): 1.99 to 3.55 ng/mL. Preliminary GM2 and GlcSph normal ranges (gray dashed lines indicate 10th and 90th percentiles) were determined using CSF samples from 18 healthy adults (age range, 19-52 years; median, 24.5 years): GM3, 1.99 to 3.55 ng/mL; GM2, 2.72 to 8.2 ng/mL; GlcSph, 1.08 to 1.72 pg/mL. [b]High titer was defined as participants with pre-existing ADA titers to IDS of >1:106 ; The 3 participants with high pre-existing ADA titers are from Cohorts A, B1, and B2. [c]At week 104, 1 sample was collected after the clinical cutoff date.

Near or complete normalization of lysosomal biomarkers was observed in most participants, and the effect was sustained

DNL310: SERUM NfL IN PH1/2 PARTICIPANTS



Week	n	Mean serum 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 & CSF NfL (n=11)

**p<0.001
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.

Robust reduction of 64% in serum NfL after two years of dosing with DNL310

NEUROFILAMENT (NfL): A MARKER OF NEUROAXONAL DAMAGE

Indication	NfL elevation disease vs. non-disease control	Therapeutic	NfL reduction on treatment	FDA approval
CLN2[a]	~50-fold (plasma)	cerliponase alfa	~85% (plasma @ 3 yrs)	✓
SMA Type 1[b]	~30-fold (CSF)	nusinersen	75% (CSF @ ~ Wk 12)	✓
SOD1 ALS[c,d]	~4-fold (serum)	tofersen	55% (plasma @ Wk 28)	✓ Accelerated approval
RRMS[e,f]	~2-3-fold (plasma)	ocrelizumab interferon beta-1a fingolimod	44% (serum @ Wk 96) 31% (serum @ Wk 96) 43% (plasma@ Wk 52)	✓
PPMS[e]	~2-3-fold (plasma)	ocrelizumab	19% (plasma @ Wk 120)	✓
MPS II[g] (neuronopathic)	**~5-fold (serum)**	**DNL310 (ETV:IDS)**	**64% (serum @ Wk 104)**	

a. Ru Y, et al. "Neurofilament light is a treatment-responsive biomarker in CLN2 disease." *Ann Clin Transl Neurol*. 2019 Dec;6(12):2437-2447.
b. Olsson B, et al. "NFL is a marker of treatment response in children with SMA treated with nusinersen." *J Neurol* 2019 Sep;266(9):2129-2136.
c. Halbgebauer, S et al. "Comparison of CSF and serum neurofilament light and heavy chain as differential diagnostic biomarkers for ALS" Neurodegeneration 2022; 93, 68-74
d. Tofersen Prescribing Information
e. 2020 8TH Joint ACTRIMS-ECTRIMS, Ocrelizumab Treatment Induces a Sustained Blood NfL Reduction in Patients with PPMS and RMS, P0125
f. Kuhlke, et al. "Blood neurofilament light chain as a biomarker of MS disease activity and treatment response." Neurology 2019 Mar 5; 92(10): e1007–e1015
g. Bhalla A, et al. "Characterization of Fluid Biomarkers Reveals Lysosome Dysfunction and Neurodegeneration in Neuronopathic MPS II Patients." Int. J. Mol. Sci. 2020, 21, 5188

DNL310 (ETV:IDS): SUMMARY OF CLINICAL ASSESSMENTS IN PHASE 1/2 STUDY

VABS-II Raw Score Mean Change From Baseline

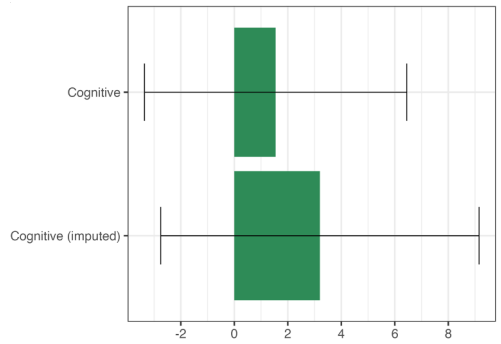
Week 49

(n=16; Data from 4 participants either unavailable (n=1) or only VABS-3 collected (n=3) at week 49)

BSD-III Raw Score Mean Change From Baseline

BSID Cognitive Raw Score
(age equivalent <=42 months, n=11)

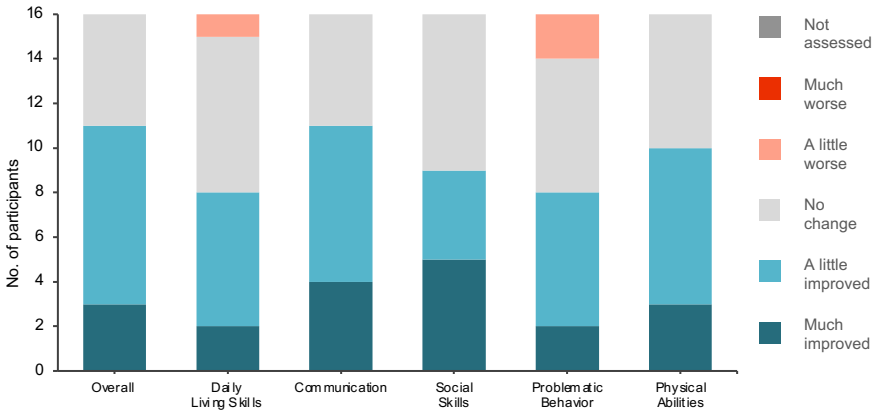
BSID Cognitive Raw Score (with imputation of KABC)[a]
(n=15)



[a]Imputed KABC scores used maximum BSID score of 91. Participants with imputed values at both BL and week 49 (n=3) were not included in the mean change (would be uninformative); 2 participants expected to have data did not complete either cognitive assessment at Week 49

Clinician Assessed Global Impression of Change (CGI-C)

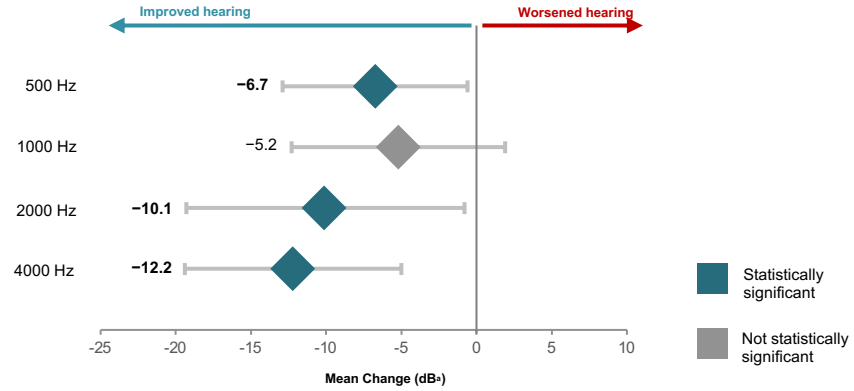
Week 49



(n=16; CGI-C version 3; graph does not include 4 subjects assessed using version 2)

Change in Hearing Assessed by Auditory Brainstem Response (ABR)

Week 49



(n=18 to 23 participants; varies by frequency)

Open label data suggest improvement or stabilization of clinical symptoms including improvement in hearing

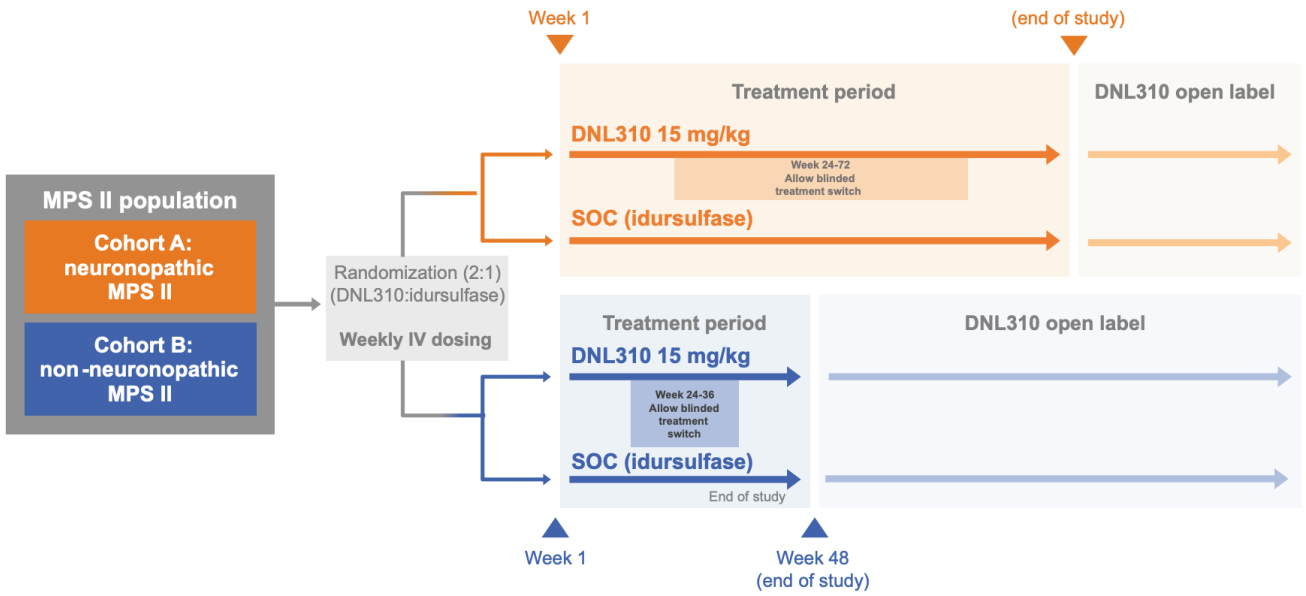
DNL310 PHASE 2/3 STUDY DESIGN IN PEDIATRIC MPS II PATIENTS

DNLI-E-0007 STUDY OVERVIEW (NCT05371613)

Study Design	**Double-Blind, Randomized Study of DNL310 vs Idursulfase in children with neuronopathic (96-week study) or non-neuronopathic (48-week study) MPS II followed by OLE** • DNL310 is administered by weekly IV infusion • n= 54 patients in 2 cohorts
Key Eligibility	• Cohort A (n=33): neuronopathic patients aged ≥2 to <6 years • Cohort B (n=21): non-neuronopathic patients aged ≥6 to <17 years • Receiving approved IDS for >4 months • IDS-treated patients will be switched to DNL310 without a washout period

Key Endpoints	**Key Efficacy Endpoints**
	• Effect of DNL310 on CSF biomarkers
	  • CSF GAGs
	• Effect of DNL310 on neurobehavioral parameters
	  • Adaptive behavior testing: Vineland Adaptive Behavior Scales
	  • Neurocognitive testing: BSID, KABC, WISC
	• Effect of DNL310 on peripheral manifestations of disease
	  • Urine GAGs
	  • Liver/spleen volume
	• Clinician and caregiver reported outcomes: Global Impression Scales
	
	Key Safety Assessments
	• Treatment-emergent adverse events
	• Infusion-related reactions
	• Laboratory abnormalities

DOSING SCHEMA



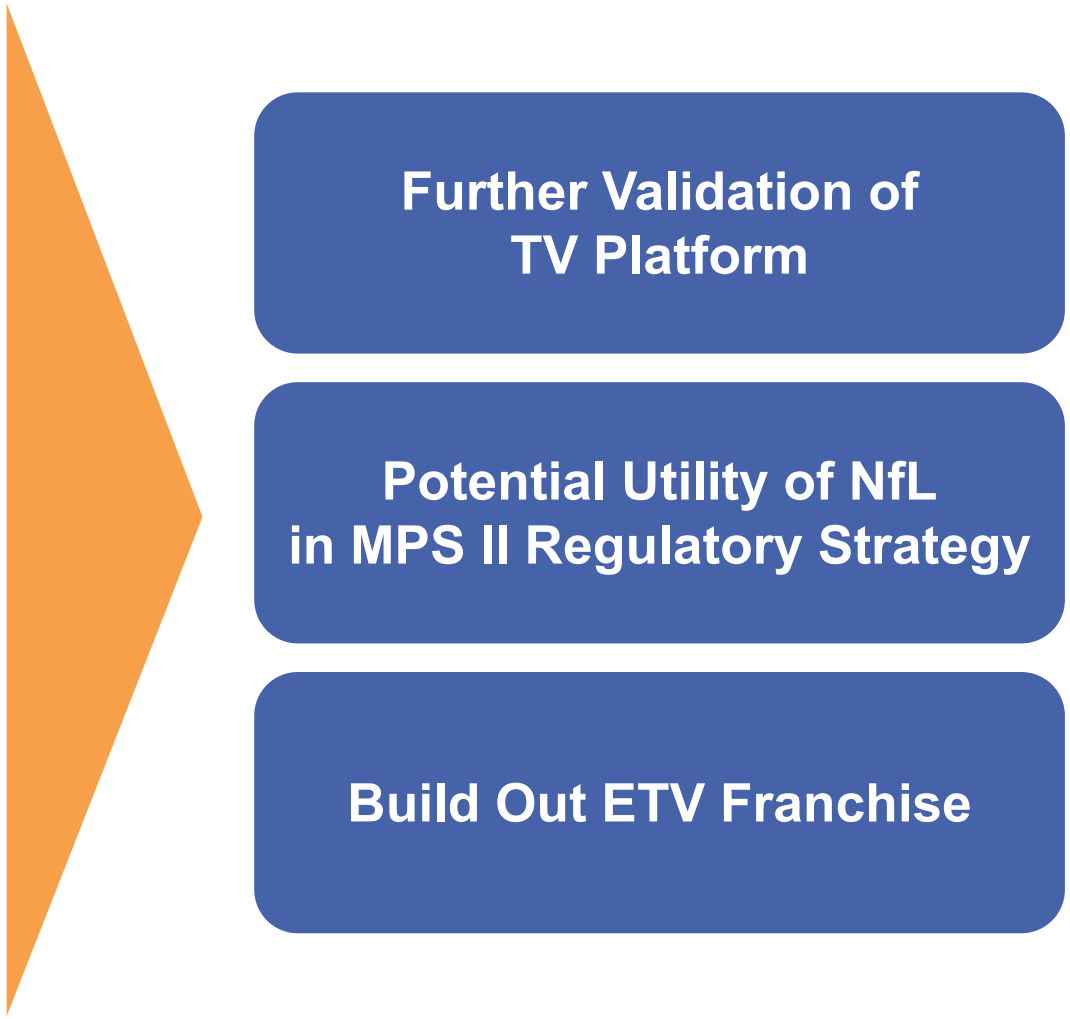
Closing Remarks

Ryan Watts, PhD, Chief Executive Officer

SUMMARY & CONCLUSIONS

DNL310 (ETV:IDS) DEVELOPMENT

- Biochemical: Rapid and sustained normalization of CSF heparan sulfate to normal healthy levels
- Cellular: Improvement in lysosomal function biomarkers
- **Neuronal: Robust reduction in NfL**
- Clinical: Positive changes across measures of exploratory clinical outcomes, including adaptive behavior, cognition, and auditory brainstem response
- Improved peripheral activity
- Safety and tolerability profile, with up to two years of treatment, consistent with current standard of care
- Global Phase 2/3 COMPASS ongoing



OUR PURPOSE: DEFEAT DEGENERATION

Thank you to all those who are part of Denali's purpose, especially our patients and their families

LYSOSOMAL STORAGE DISEASE

RARE NEURODEGENERATIVE DISEASES (ALS, FTD)

PARKINSON'S DISEASE

ALZHEIMER'S DISEASE

Denali

The name captures the formidable challenges in fighting neurodegenerative diseases but also the unprecedented opportunities enabled by new scientific insights and technologies. With a relentlessly committed team and rigorous effort, breakthroughs appear to be within reach.

Q&A