DENALI

Corporate Overview

September 2023

Disclaimers

Forward-Looking Statements. This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements do not relate strictly to historical or current facts and they may be accompanied by such words as “anticipate,” “believe,” “could,” “estimate,” “expected,” “forecast,” “intend,” “may,” “plan,” “potential,” “possible,” "future," “will” and other words and terms of similar meaning. All statements other than statements of historical facts contained in this presentation, including, without limitation, statements regarding future results of operations and financial position of Denali Therapeutics Inc. (“Denali” or the “Company”); Denali’s business strategy and business plans, expected progress and expansion, and expected key milestones for Denali's therapeutic portfolio in 2023 and beyond; Denali’s ability to execute on its tailored commercial strategies and accelerate commercial launch readiness in key markets, including the US and China; expectations relating to the prevalence and potential for Denali's product candidates to treat various neurodegenerative diseases including MPS I, MPS II (Hunter Syndrome), MPS IIIA (Sanfilippo Syndrome), ALS, MS, PD, AD, FTD-GRN, CLE, UC, and related peripheral inflammatory diseases; expectations and timelines related to planned preclinical studies and clinical trials and the expectations regarding the timing and availability of results and data from such studies and trials; plans, timelines, expectations, and current and future therapeutic and commercial opportunities related to Denali's Transport Vehicle (TV) platform, including its Enzyme Transport Vehicle (ETV), Antibody Transport Vehicle (ATV), Protein Transport Vehicle (PTV), and Oligonucleotide (OTV) technologies, and other programs enabled by these platforms, as well as potential targets, therapeutic areas, and differentiation strategies; plans, timelines, and expectations relating to DNL310, including safety profile and exploratory clinical outcomes data from the ongoing Phase 1/2 study, enrollment in the Phase 2/3 COMPASS study, and planned regulatory filings and registration potential; plans, timelines and expectations related to DNL126, including its therapeutic potential and the timing of recruitment activities for the planned Ph 1/2 study; Denali's and Takeda's plans and expectations regarding DNL593, including enrollment in the ongoing Ph 1/2 Part B trial; expectations and potential benefits relating to ATV:Abeta for the potential treatment of AD; expectations and timelines related to OTV-enabled programs, including their therapeutic and registrational potential; plans, timelines, and expectations relating to the Biogen-led development of BIIB122/DNL151, including for the Phase 2b trial, as well as other LRRK2 inhibitor molecules; plans, timelines, and expectations related to DNL343, including the timing and availability of data from the ongoing Healey trial and success of the selected model; Denali's and Sanofi's plans, timelines, and expectations related to DNL788 and DNL758, including with respect to the availability of data and recruitment of patients for current trials and potential completion dates; the potential benefits and results of the collaborations with Denali’s partners, including Biogen, Sanofi, and Takeda, and the amounts and likelihood of receipt of milestone payments; plans and expectations regarding Denali's global organization, including the expansion of its medical affairs and clinical operations, the growth of its in-house clinical manufacturing capabilities, and the expected timing and likelihood of success of its commercial growth; and timing and expectations regarding potential additional BBB transporters; are forward-looking statements. Denali has based these forward-looking statements largely on its current expectations and projections about future events.

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OUR FOCUS AND STRATEGIC PRINCIPLES

OUR FOCUS

Defeat Degeneration

Lysosomal Storage Diseases

Rare Neurodegenerative Diseases (ALS, FTD)

Parkinson's Disease

Alzheimer's Disease

OUR SCIENTIFIC PRINCIPLES

Increase Likelihood of Success

Degenogene Pathways

Brain Delivery

Biomarker-Driven Development

OUR BUSINESS PRINCIPLES

Create Value

Broad Portfolio

Integrated Global Capabilities

Strategic Partnering

OUR SCIENCE: BBB PLATFORMS AND DEGENOGENE PATHWAYS

Published May 27, 2020

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

BLOOD-BRAIN BARRIER

Brain delivery of therapeutic proteins using an Fc fragment blood-brain barrier transport vehicle in mice and monkeys

Published Sept 2, 2021

Cell — CellPress

Article

Rescue of a lysosomal storage disorder caused by *Grn* loss of function with a brain penetrant progranulin biologic

Published March 4, 2020

CellPress — Neuron Article

TREM2 Regulates Microglial Cholesterol Metabolism upon Chronic Phagocytic Challenge

Published May 27, 2020

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

BLOOD-BRAIN BARRIER

Brain delivery and activity of a lysosomal enzyme using a blood-brain barrier transport vehicle in mice

Published July 22, 2020

International Journal of *Molecular Sciences* — MDPI

Article

Characterization of Fluid Biomarkers Reveals Lysosome Dysfunction and Neurodegeneration in Neuronopathic MPS II Patients

Published October 22, 2020

CellPress — Neuron Article

Small-Molecule Modulation of TDP-43 Recruitment to Stress Granules Prevents Persistent TDP-43 Accumulation in ALS/FTD

Published April 8, 2020

NATURE REVIEWS | DRUG DISCOVERY

Leveraging preclinical models for the development of Alzheimer disease therapeutics

Published July 30, 2020

International Journal of *Molecular Sciences* — MDPI

Article

High-Throughput Liquid Chromatography–Tandem Mass Spectrometry Quantification of Glycosaminoglycans as Biomarkers of Mucopolysaccharidosis II

Published June 8, 2020

nature neuroscience

Alzheimer's-associated PLCγ2 is a signaling node required for both TREM2 function and the inflammatory response in human microglia

Published Sept 4, 2019

Neuron — CellPress

Review

Emerging Microglia Biology Defines Novel Therapeutic Approaches for Alzheimer's Disease

Published October 8, 2021

JCI insight

Iduronate-2-sulfatase transport vehicle rescues behavioral and skeletal phenotypes in a mouse model of Hunter syndrome

Published June 8, 2022

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

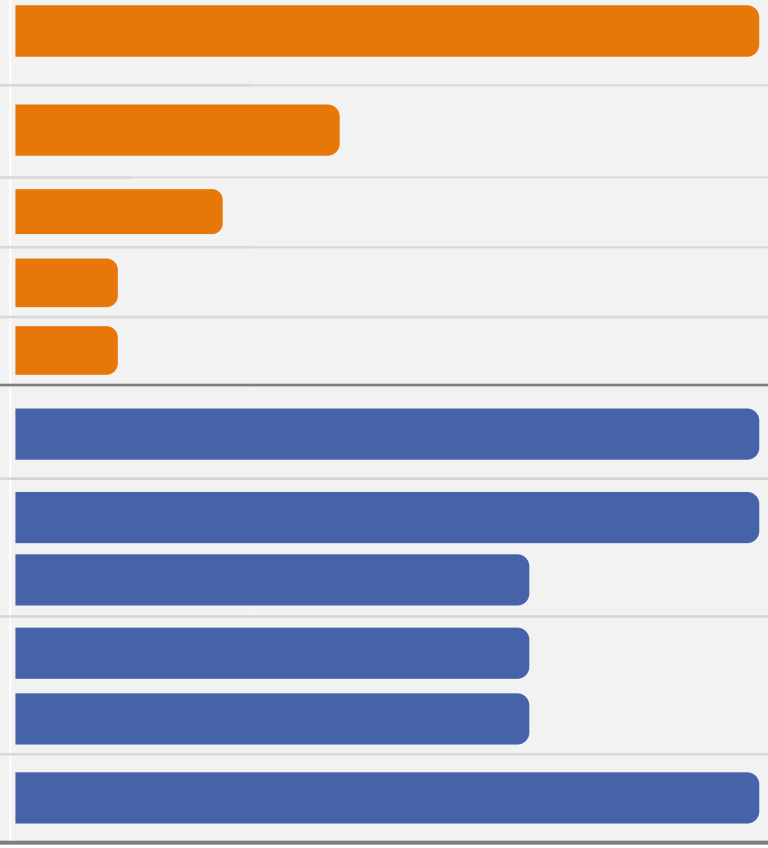
PARKINSON'S DISEASE

Preclinical and clinical evaluation of the LRRK2 inhibitor DNL201 for Parkinson's disease

Denali scientists have generated more than 20 publications and 90 granted patents worldwide

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)		
	PGRN	Lysosomal Function	**TAK-594/DNL593** (PTV:PGRN)	Frontotemporal Dementia-Granulin (FTD-GRN)		Takeda
	Sulfamidase	Lysosomal Function	**DNL126** (ETV:SGSH)	MPS IIIA (Sanfilippo)		
	Alpha-L-iduronidase	Lysosomal Function	**DNL622** (ETV:IDUA)	MPS I (Hurler)		
	Multiple	Multiple	**OTV:Multiple**	Multiple		
SMALL MOLECULE	LRRK2	Lysosomal Function	**BIIB122/DNL151** (LRRK2 inhibitor)	Parkinson's Disease		Biogen
	RIPK1 (CNS)	Glial Biology	**SAR443820/DNL788** (RIPK1 inhibitor)	Amyotrophic Lateral Sclerosis (ALS) Multiple Sclerosis (MS)		sanofi
	RIPK1 (Peripheral)	Other	**SAR443122/DNL758** (RIPK1 inhibitor)	Cutaneous Lupus Erythematosus (CLE) Ulcerative Colitis (UC)		sanofi
	eIF2B	Cellular Homeostasis	**DNL343** (eIF2B activator)	Amyotrophic Lateral Sclerosis (ALS)		



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

OUR STRATEGIC PARTNERSHIPS

CO-DEVELOPMENT & CO-COMMERCIALIZATION PARTNERSHIPS

Biogen

- **LRRK2** inhibitor for Parkinson's and **ATV:Abeta**
- $1.025B upfront (cash/equity) and $2B in milestones
- LRRK2: 50/50 profit share in US, 40/60 in China

SANOFI

- **RIPK1** inhibitors for neurological and peripheral inflammatory indications
- $125M upfront and $1.1B in milestones
- 50/50 profit share in US/China (CNS)

Takeda

- **PTV:PGRN** and **ATV:TREM2**
- $150M upfront (cash/equity) and $1B in milestones
- 50/50 profit share worldwide

$1.3B — **Total upfront payments**[1]

>$3B — **Total earned & potential milestones**

~50% — **Profit sharing in key geographies**

Strategic collaborations facilitate development of a broad portfolio while maintaining commercial upside

1) Upfront payments include cash and equity

OUR VISION: COMMERCIAL ORGANIZATION TO SERVE PATIENTS

>30,000 patients WW*
$500M-1B+ per indication

LYSOSOMAL STORAGE DISEASES

(e.g., MPS II, MPS IIIA)

>500,000 patients WW*
$1-5B per indication

RARE NEURODEGENERATIVE DISEASES

(e.g., ALS, FTD)

>50M patients WW*
>$5B per indication

COMMON NEURODEGENERATIVE DISEASES

(e.g., Parkinson's, Alzheimer's)

Build in-house infrastructure

Strategically partner

- Market-based strategic plans for DNL310 & DNL343
- Patients & community engagement in MPS II and ALS
- Expand medical affairs & commercial teams
- Co-commercialize partnered assets (PD, FTD and AD) in US and China
- Execute to deliver on our patient promise

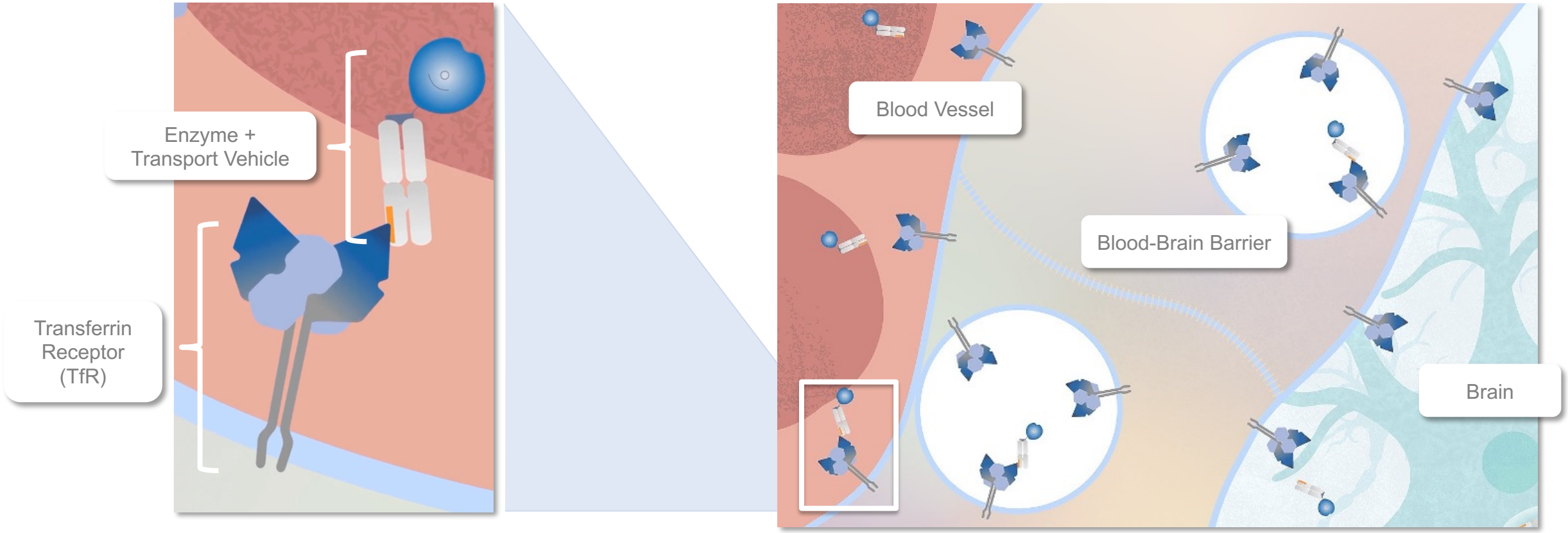
Accelerate commercial launch readiness in key markets

* Denali estimates of world-wide aggregate prevalence


OUR TV PLATFORM FOR BRAIN
DELIVERY OF BIOTHERAPEUTICS

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

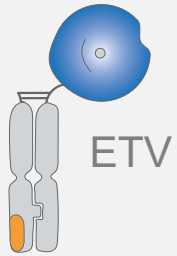


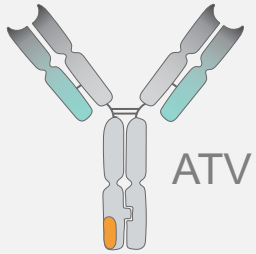
https://www.denalitherapeutics.com/patients

TRANSPORT VEHICLE ENABLES MODALITY-OPTIMIZED BRAIN DELIVERY

Enzyme Transport Vehicle

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



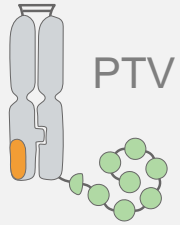


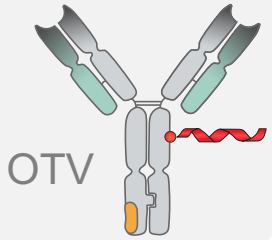
Antibody Transport Vehicle

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

Protein Transport Vehicle

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





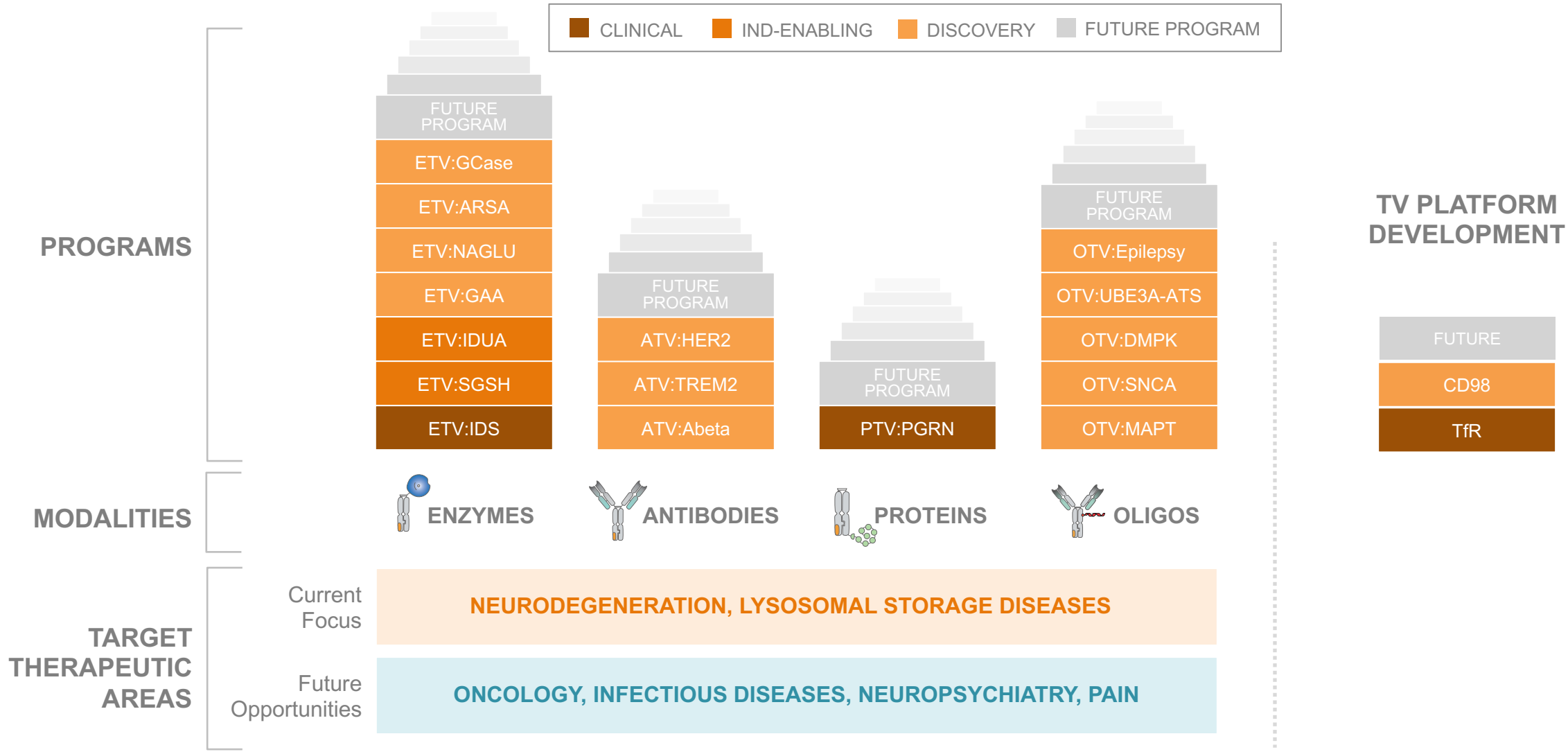
Oligonucleotide Transport Vehicle

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

Each TV modality is a platform opportunity

TV PLATFORM OPPORTUNITIES DRIVE SUSTAINABLE VALUE CREATION

Each TV modality is a platform opportunity

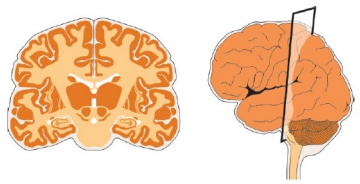


DEVELOPING A THERAPY FOR MPS II (HUNTER SYNDROME)

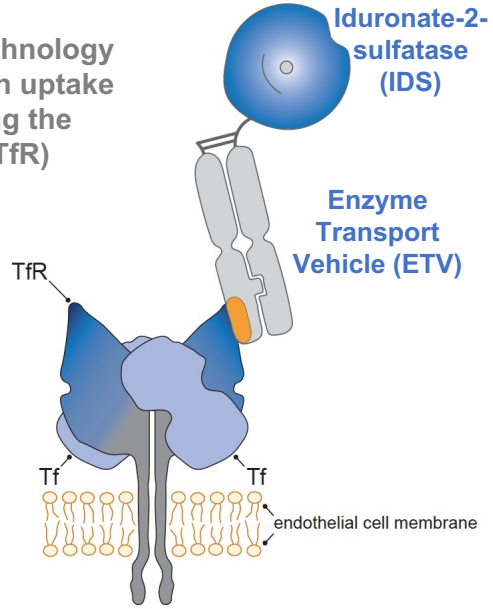
DNL310 (ETV:IDS) is an investigational iduronate-2-sulfatase (IDS) fusion protein engineered to treat both the brain and physical manifestations of mucopolysaccharidosis type II (MPS II) with a **single weekly IV infusion**

Enzyme Transport Vehicle (ETV)

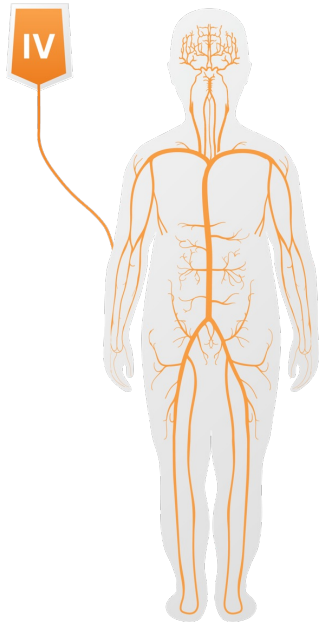
Transport Vehicle (TV) technology optimized to improve brain uptake of biotherapeutics using the transferrin receptor (TfR)



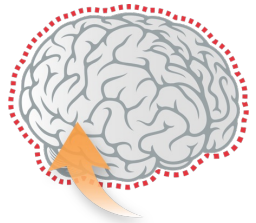
Capillary TfR expression in the brain facilitates widespread biodistribution of TV and enzyme



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 (ETV:IDS) 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.

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

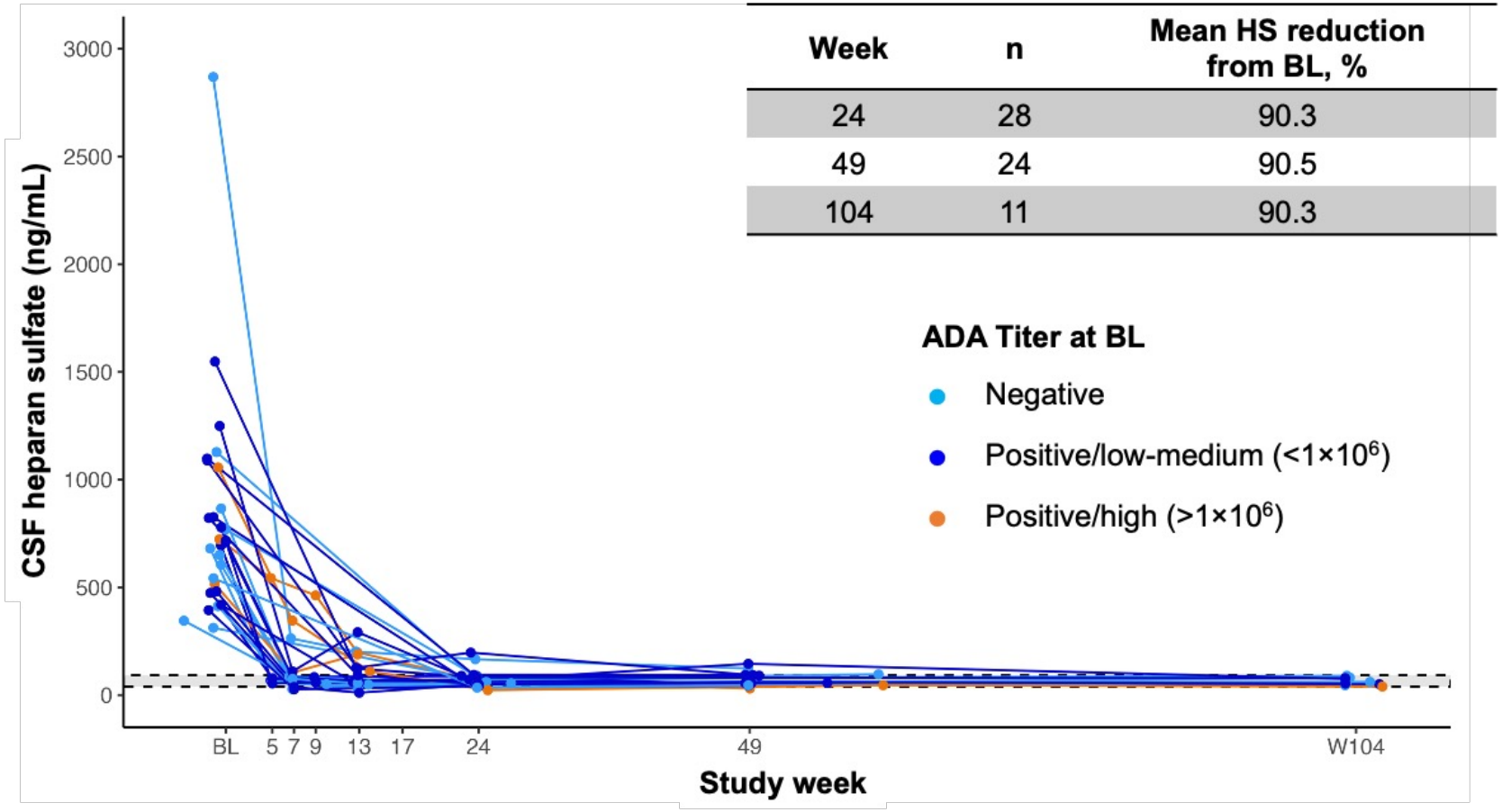
CNS involvement

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

DNL310 PHASE 1/2 STUDY 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

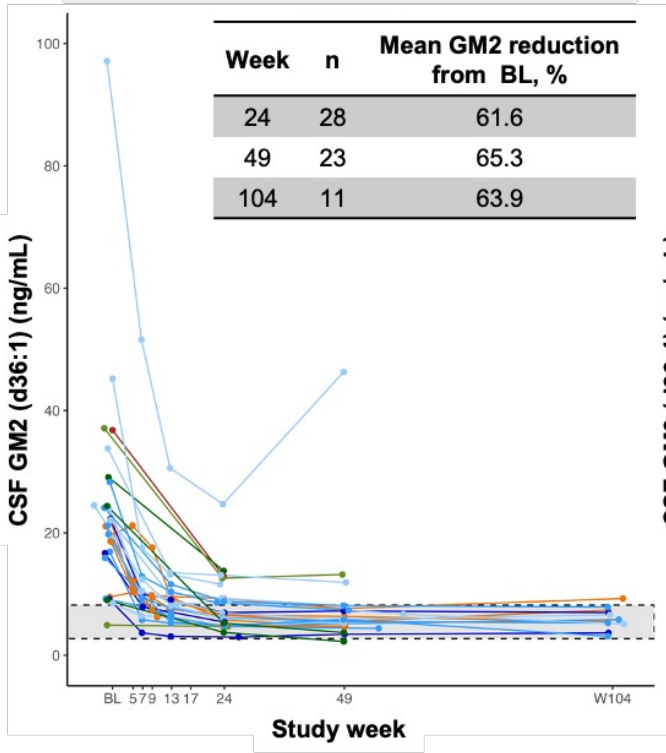
ADA, anti-drug antibody; BL, baseline; CSF, cerebral spinal fluid; HS, heparan sulfate.
[a]Preliminary normal range (10th and 90th percentile) determined using 30 healthy adult CSF samples (age range, 18-81 years; median, 52 years). Total CSF GAG levels were similar in adults and children (Hendriksz 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.

Source: Burton B, et al. SSIEM 2023

DNL310 PHASE 1/2 STUDY BIOMARKERS: CSF LYSOSOMAL LIPIDS

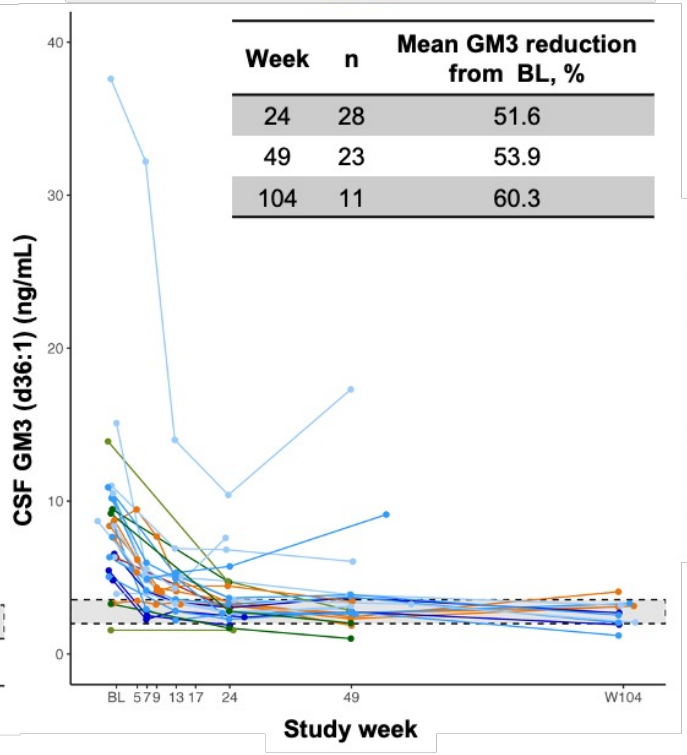
GM2[a]

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



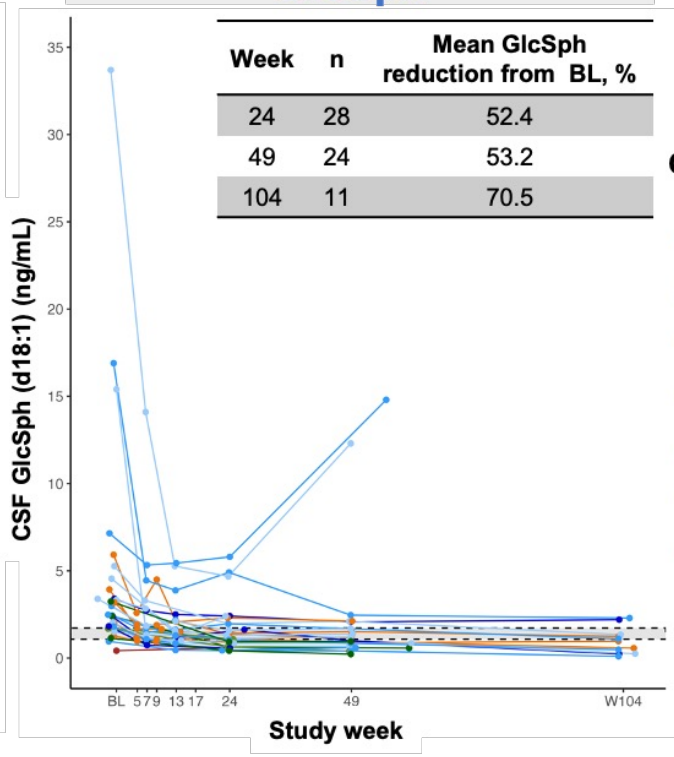
GM3[a]

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



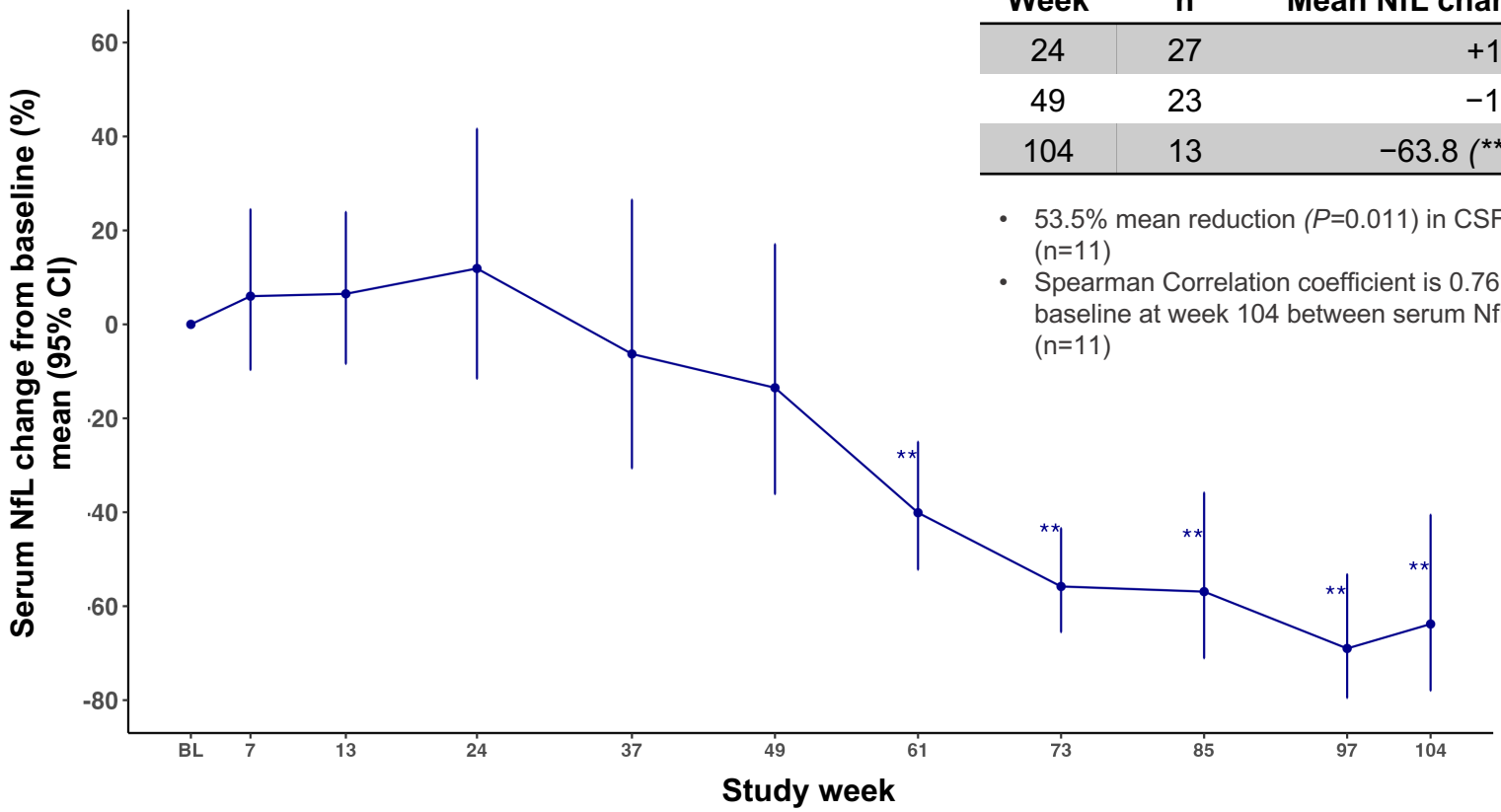
Cohort	Dose (mg/kg)
A	3-30
B1	3-15
B2	7.5-15
B3	15
C	15
D	15
E	15

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.

Source: Burton B, et al. SSIEM 2023

DNL310 PHASE 1/2 STUDY 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.

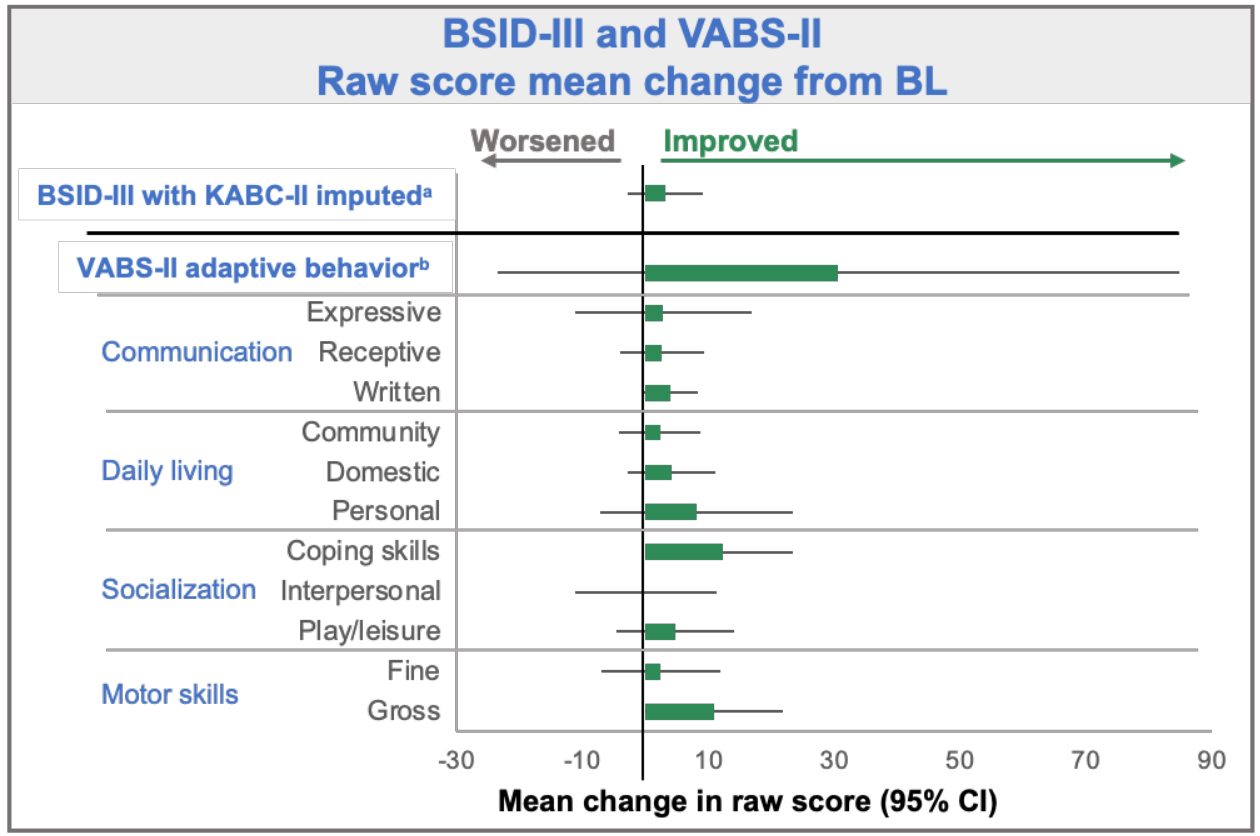
Source: Burton B, et al. SSIEM 2023

NEUROFILAMENT (NfL): A MARKER OF NEUROAXONAL DAMAGE

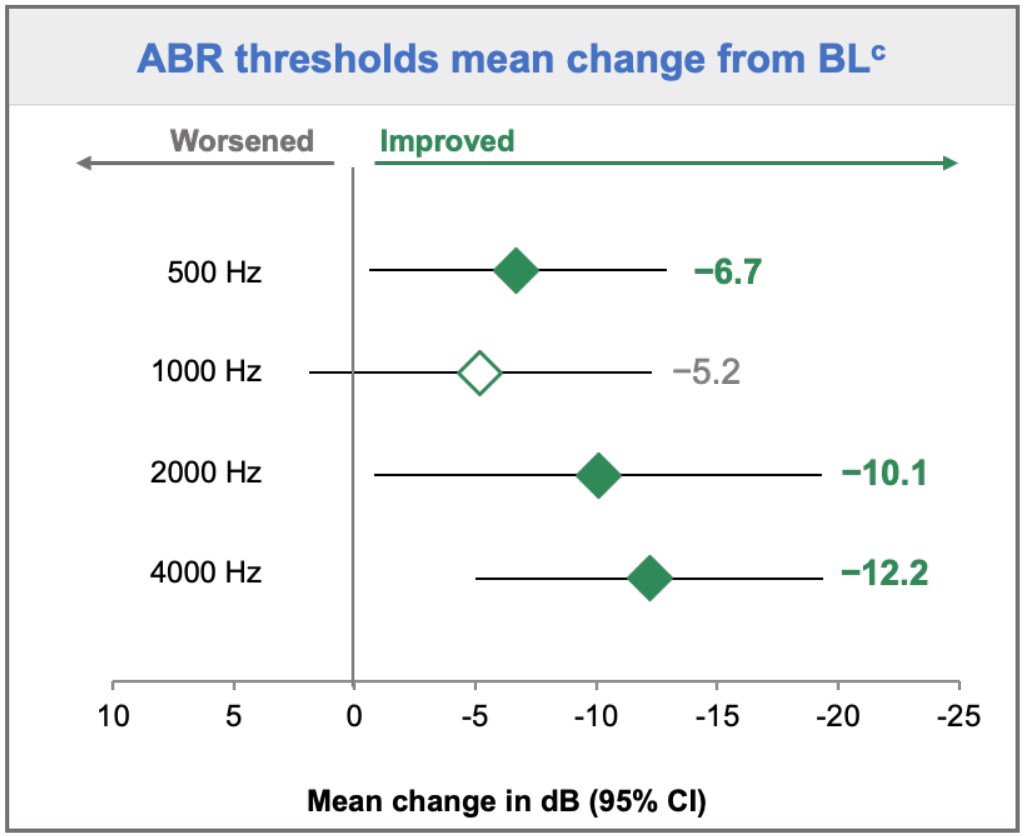
Indication	NfL elevation disease vs. non-disease control	Therapeutic	NfL reduction on treatment	FDA approval
CLN2[a]	~50-fold (plasma)	cerliponase alfa	~85% (plasma @ 3 yrs)	✓
SMA Type 1[b]	~30-fold (CSF)	nusinersen	75% (CSF @ ~ Wk 12)	✓
SOD1 ALS[c,d]	~4-fold (serum)	tofersen	55% (plasma @ Wk 28)	✓ Accelerated 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 PHASE 1/2 STUDY: CLINICAL OUTCOMES AT WEEK 49



(n=16)



(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.

Source: Burton B, et al. SSIEM 2023

DNL310 PHASE 1/2 STUDY 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

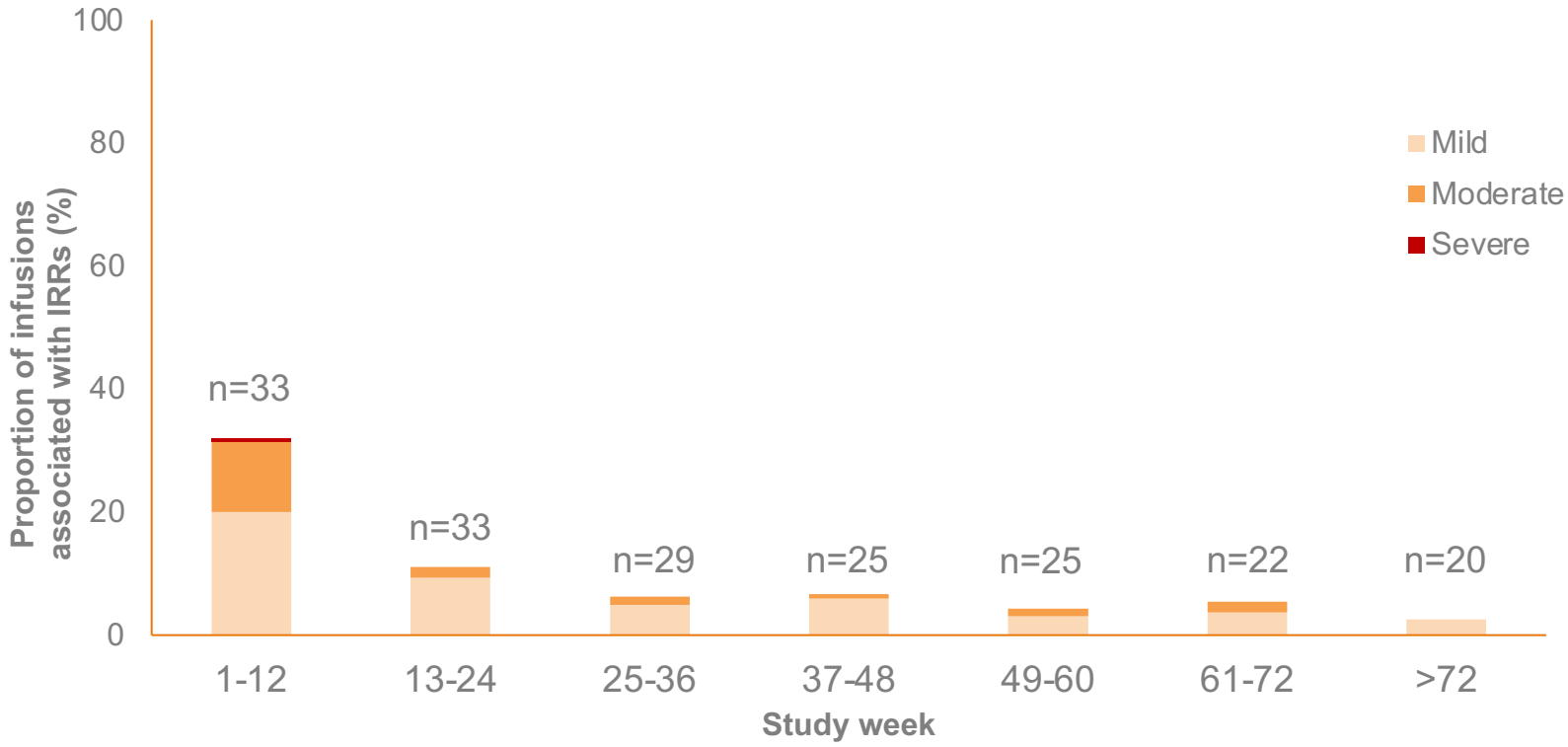
Safety profile reflects median treatment duration of 91 weeks in 33 study participants; maximum treatment duration: 135 weeks
Independent Data Monitoring Committee recommended continuing study without modifications (May 2023)

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.

Source: Burton B, et al. SSIEM 2023

DNL310 PHASE 1/2 STUDY SAFETY: IRRS



Total number of infusions during the study: 2471

Tolerance to DNL310 occurred with longer-term dosing

IRR, infusion-related reaction.

Source: Burton B, et al. SSIEM 2023

DNL310 PHASE 1/2 STUDY: 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.

Source: Burton B, et al. SSIEM 2023

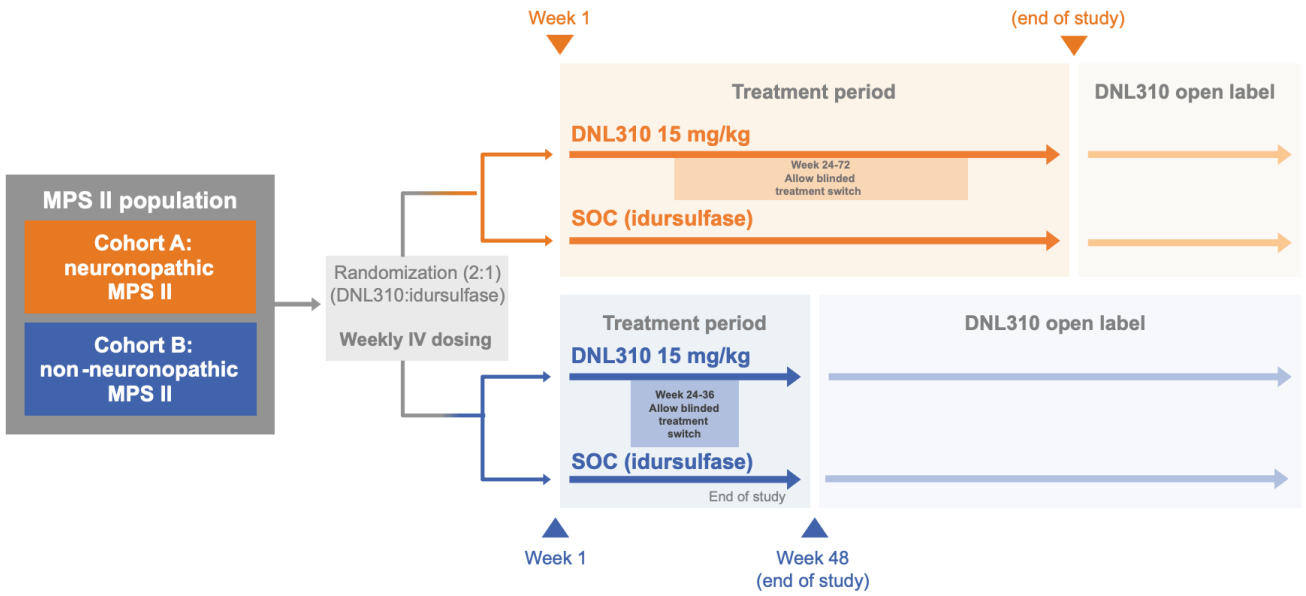
DNL310 PHASE 2/3 STUDY DESIGN IN PEDIATRIC MPS II PATIENTS

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) MPSII 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

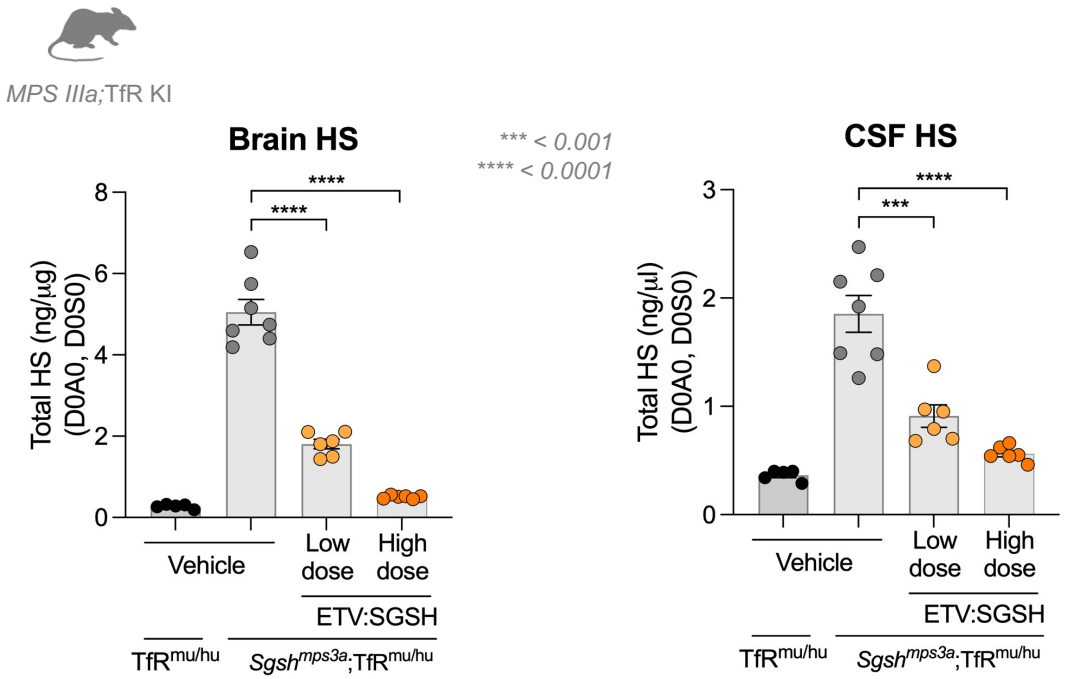


DNL126 (ETV:SGSH): EXPANDS ETV PLATFORM FOR MPS IIIA

Addressing cognitive, behavioral & physical manifestations of Sanfilippo syndrome Type A

- Rare lysosomal storage disease (LSD) that causes neurodegeneration; no treatments
- Caused by genetic mutations that result in a reduction in the activity of SGSH
- SGSH is an enzyme responsible for degrading heparan sulfates (HS) in the lysosome
- HS accumulation leads to lysosomal dysfunction
- DNL126 is designed to replace SGSH in the brain and throughout the body

IV DNL126 treatment reduces HS in a dose-dependent manner in brain and CSF



Recruiting activities for the Phase 1/2 study beginning in 2H23

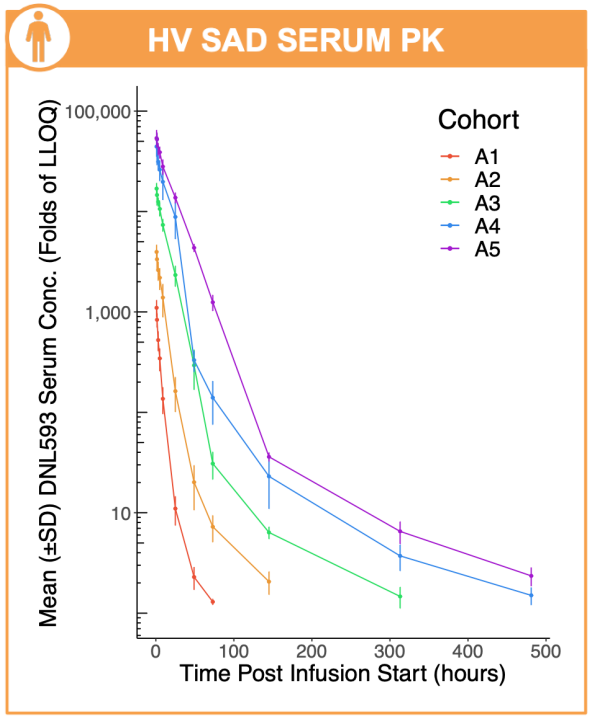
ETV:SGSH=Enzyme Transport Vehicle N-Sulfoglucosamine Sulfohydrolase; MPS=mucopolysaccharidoses; CSF=cerebrospinal fluid; IND=investigational new drug

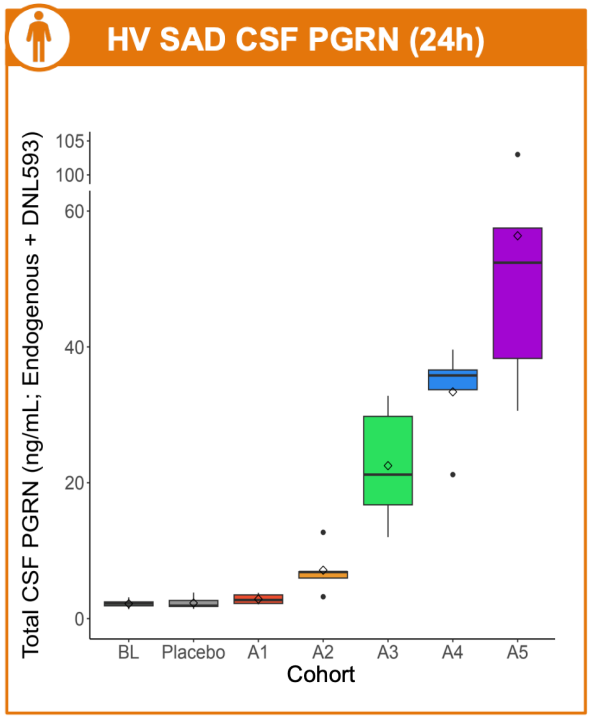
DNL593 (PTV:PGRN): PGRN BRAIN DELIVERY FOR FTD-GRN

Brain delivery of progranulin (PGRN) designed to treat FTD-GRN

- FTD is the most common dementia in people under 60; no approved therapies
- FTD-GRN is associated with PGRN deficiency; accounts for 5-10% of FTD
- Single doses of DNL593 in HVs led to dose-dependent increases in CSF PGRN and were generally well tolerated
- Data support enrolling participants with FTD-GRN in Part B (multiple ascending doses)
- Co-development/co-commercialization with Takeda

Dose-dependent increase in CSF PGRN in HV with IV DNL593 further validates TV for BBB crossing



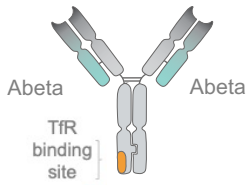


Recruitment of participants with FTD-GRN in Part B (ascending multiple doses) of the Phase 1/2 study is ongoing

PTV:PGRN=Protein Transport Vehicle:Progranulin; FTD-GRN-frontotemporal dementia granulin; CSF=cerebrospinal fluid; HVs=healthy volunteers

ATV:ABETA FOR ALZHEIMER'S DISEASE (AD)

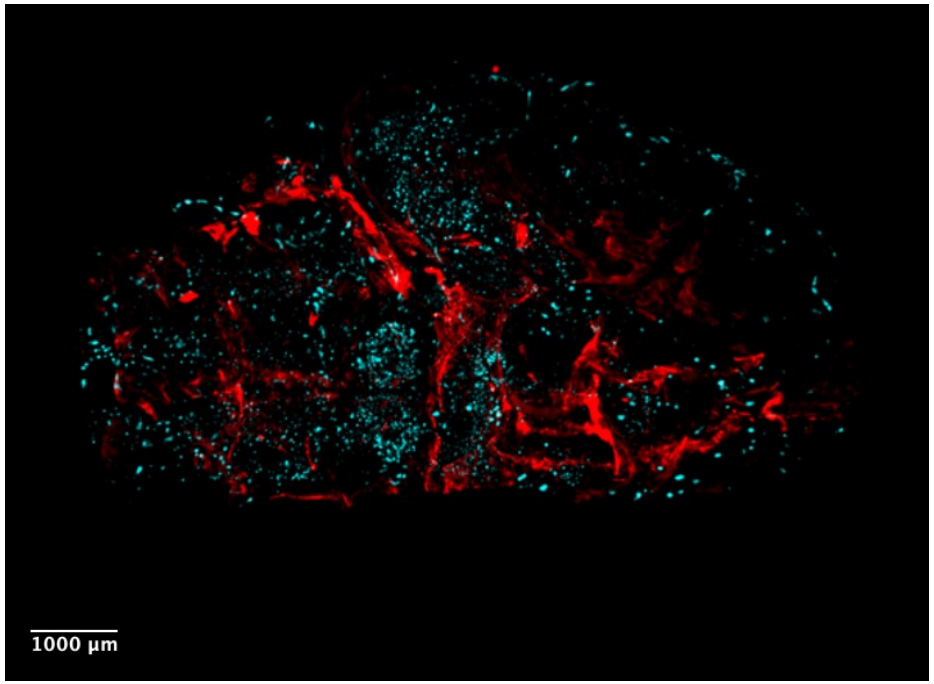
ATV:Abeta shows broad parenchymal plaque binding with minimal perivascular distribution

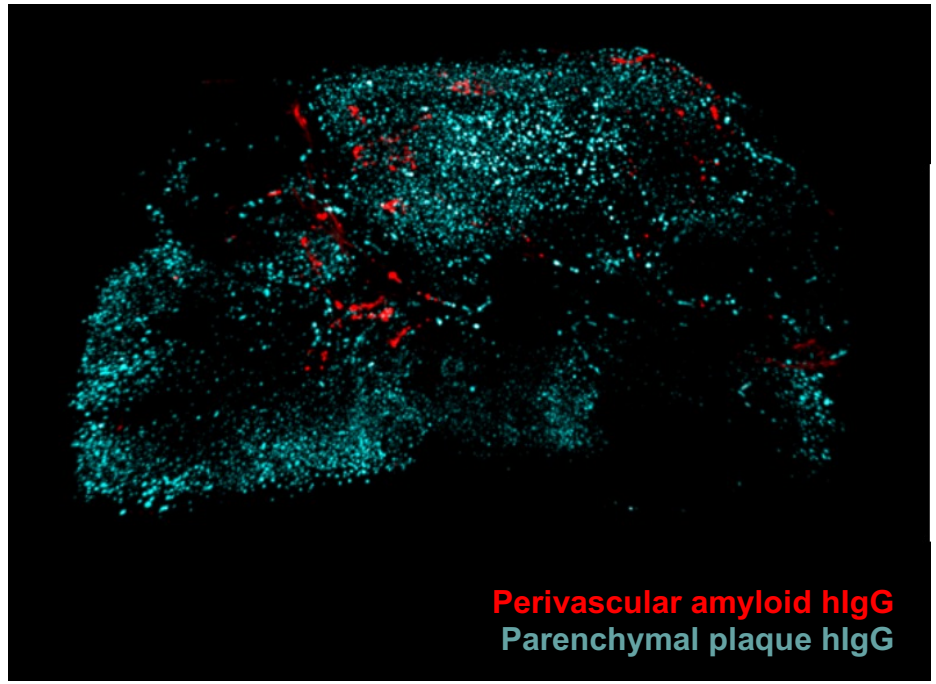


Anti-Abeta

ATV:Abeta

5xFAD;TfR KI





iDISCO whole brain image 24h post 10mg/kg single dose in AD mouse model

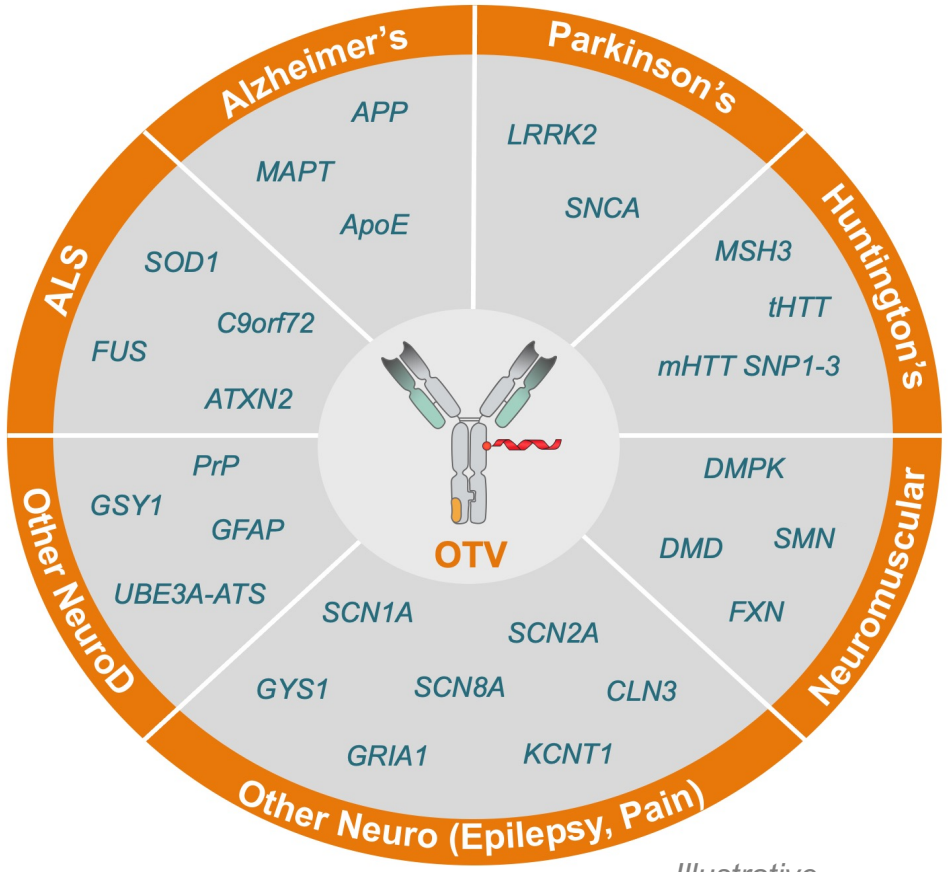
Biogen has opted-in to the ATV:Abeta program (April 2023) and now leads development and commercialization

OTV IS DESIGNED TO ENHANCE CNS DELIVERY OF OLIGONUCLEOTIDES

Therapeutic oligonucleotides have the potential to address challenging targets

- Oligonucleotide Transport Vehicle (OTV) is designed to:
  - Enable superior biodistribution of ASOs across brain regions
  - Provide superior knockdown of target gene expression across all cell types
  - Enable IV dosing
- OTV opens a large potential indication space in neurodegeneration and beyond
- Multiple OTV programs progressing toward IND-enabling studies
- OTV manuscript posted on bioRxiv April 28, 2023 (Barker SJ et al.)

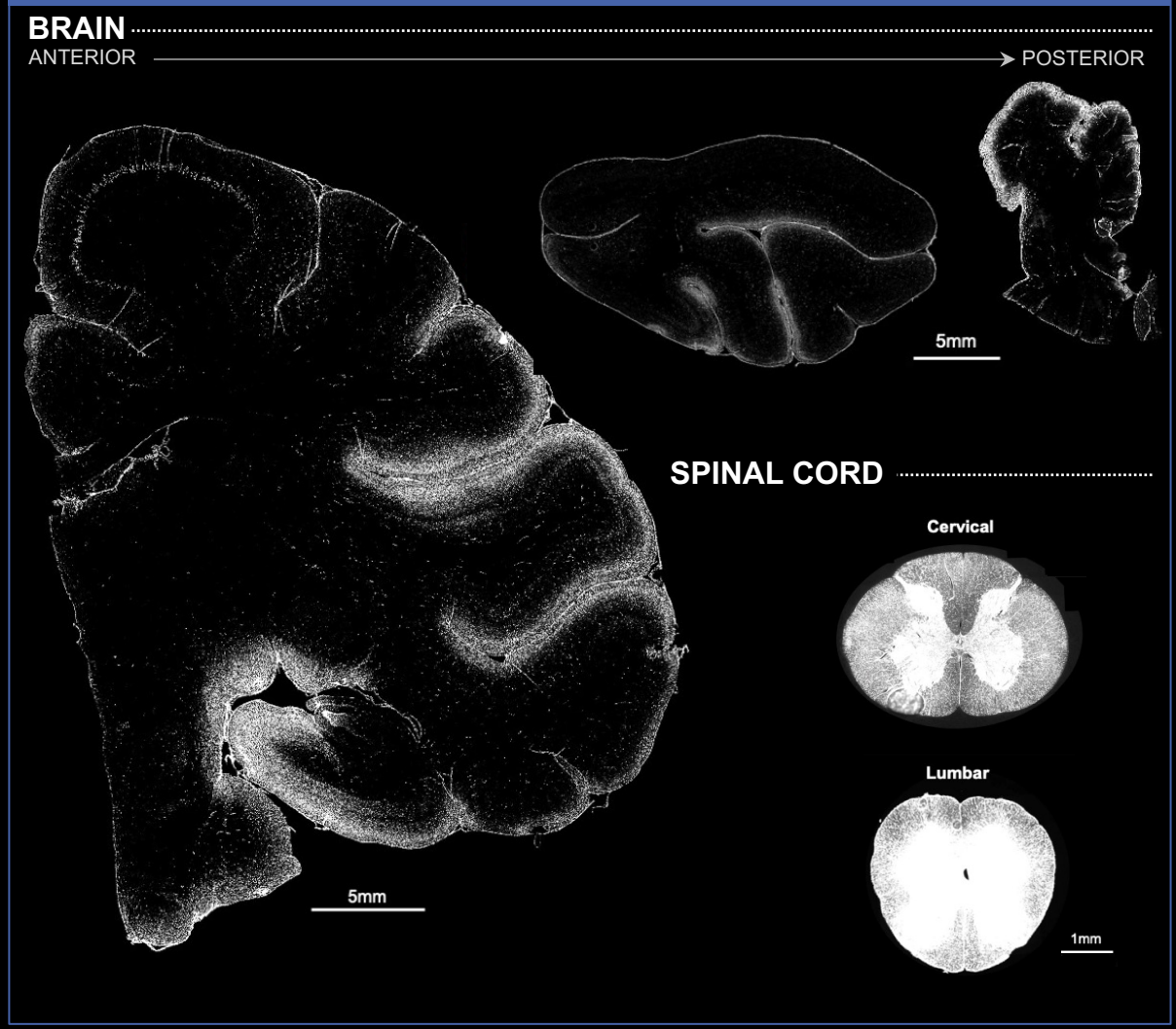
OTV has potential to revolutionize ASOs/oligos for treating CNS disease



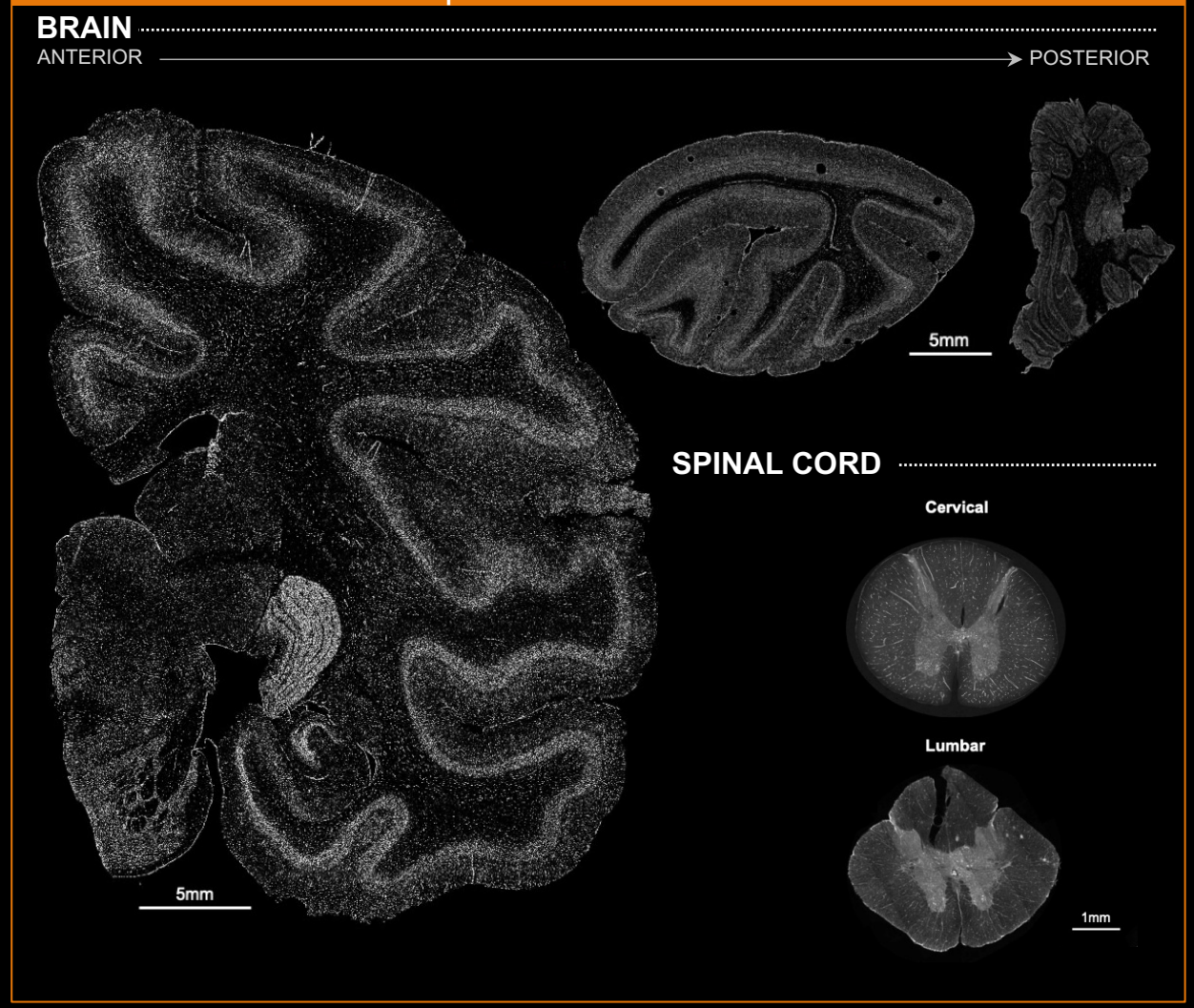
Illustrative

OTV PROVIDES UNIFORM ASO DEPOSITION ACROSS THE CNS WITH IV DELIVERY

NAKED ASO INTRATHECAL (IT) DELIVERY
Limited ASO Biodistribution



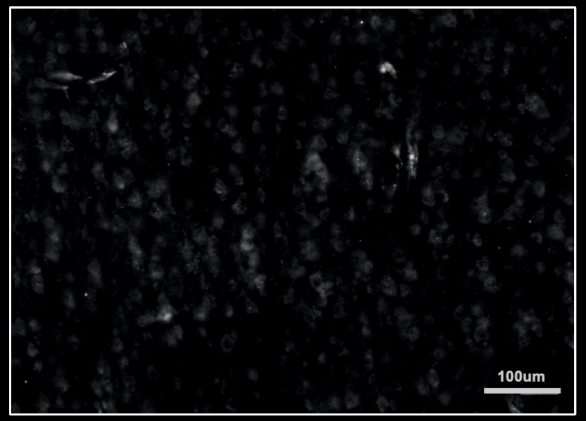
OTV INTRAVENOUS (IV) DELIVERY
Widespread ASO Biodistribution



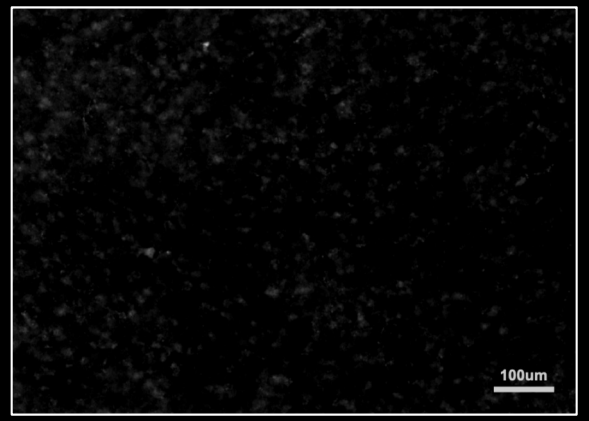
OTV PROVIDES UNIFORM ASO DEPOSITION ACROSS THE CNS WITH IV DELIVERY

NAKED ASO INTRATHECAL (IT) DELIVERY
Limited ASO Biodistribution

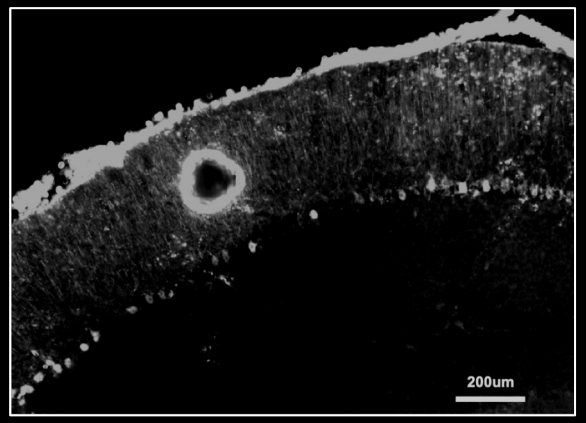
CORTEX



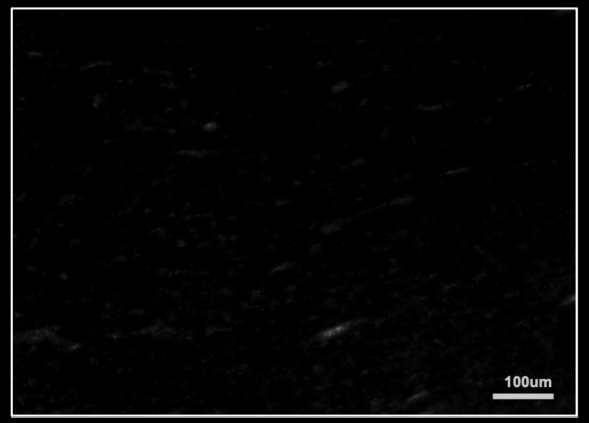
STRIATUM



CEREBELLUM

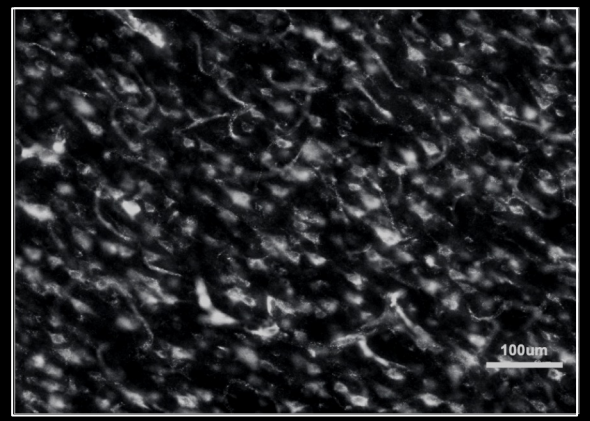


WHITE MATTER



OTV INTRAVENOUS (IV) DELIVERY
Widespread ASO Biodistribution

CORTEX



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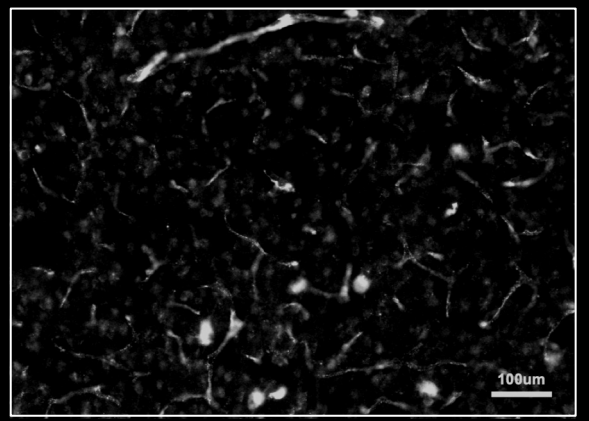

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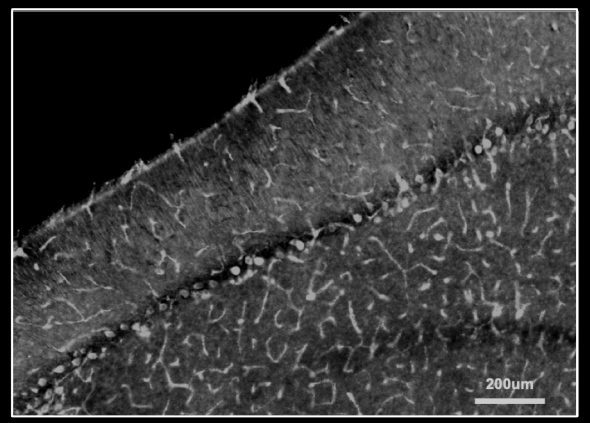
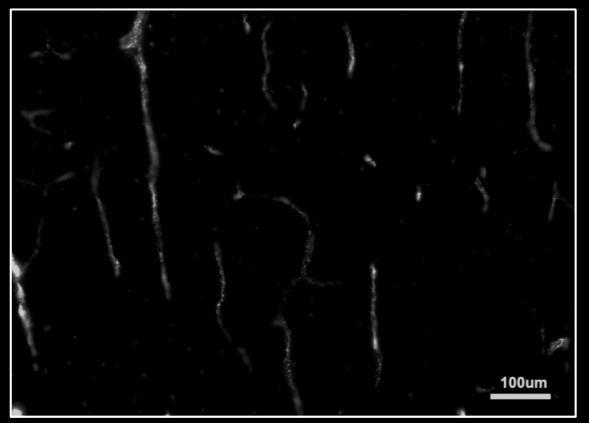


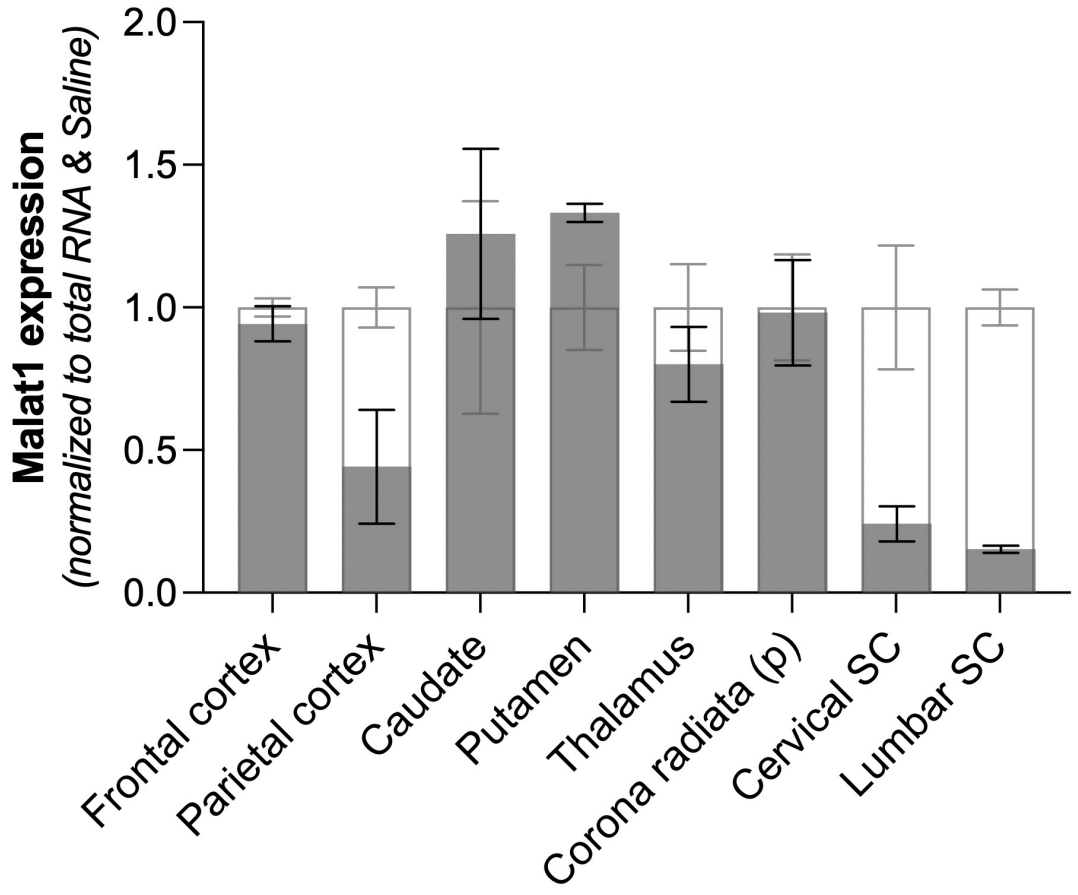
WHITE MATTER



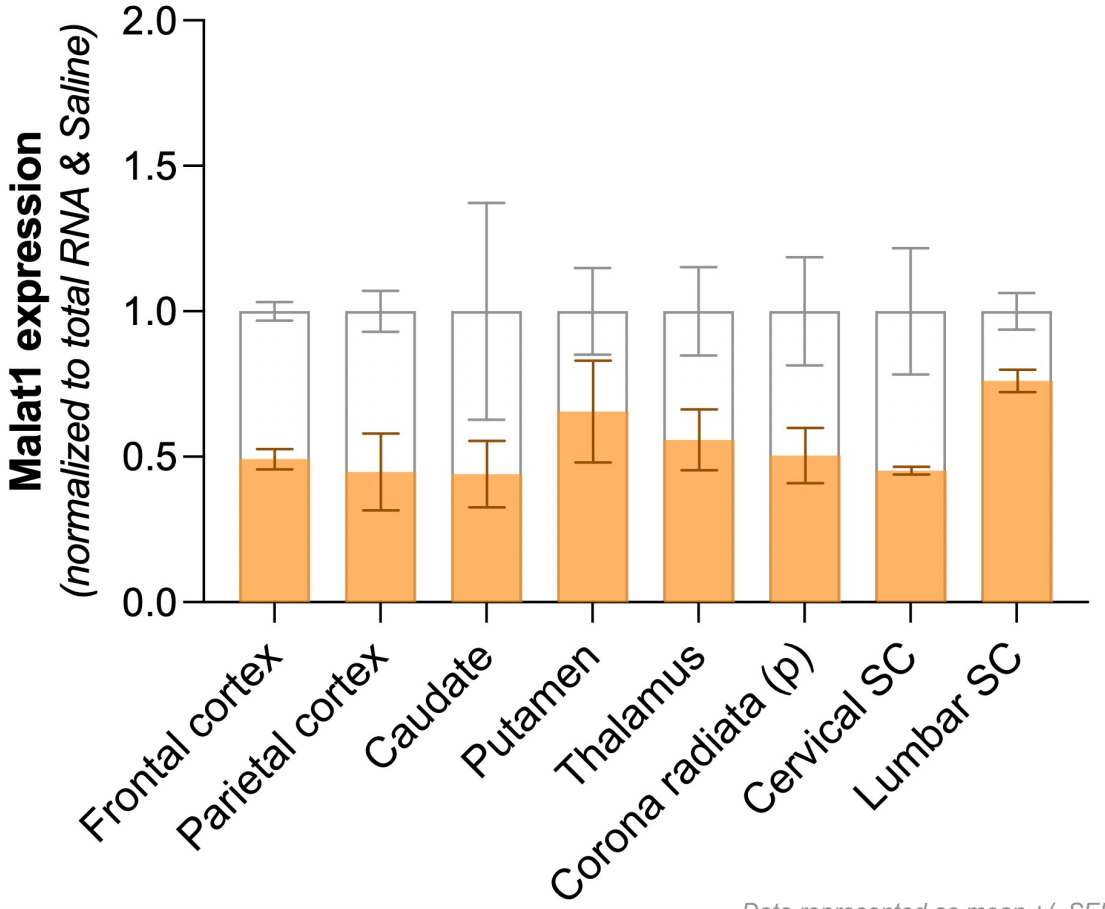
anti-ASO

OTV ENABLES MORE UNIFORM KNOCKDOWN OF TARGET GENE EXPRESSION

NAKED ASO INTRATHECAL (IT) DELIVERY



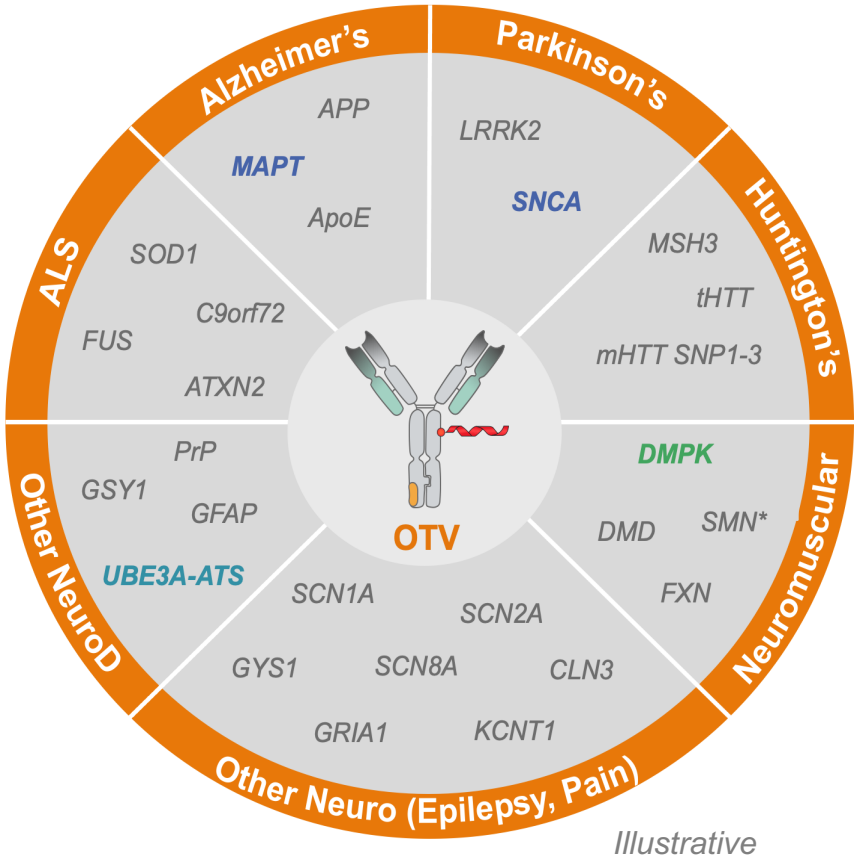
OTV INTRAVENOUS (IV) DELIVERY



Data represented as mean +/- SEM; n=3

IV OTV shows uniform knockdown across the CNS compared to IT ASO

OTV TARGET SELECTION



Illustrative

OTV in IND-Enabling stage with near-term focus on acceleration of two targets to clinical testing

TARGET	INDICATION	PREVALENCE	DIFFERENTIATION STRATEGY
COMMON NEURODEGENERATIVE DISEASES			
MAPT	Alzheimer's Disease	6-10M cases US	Uniform knockdown of MAPT across the CNS to effectively reduce all forms of Tau protein & decrease aggregates
SNCA	Parkinson's Disease	1M cases US	Uniform knockdown of SNCA across the CNS to effectively reduce all forms of α-Syn protein & decrease aggregates
RARE CNS DISEASES			
UBE3A-ATS	Angelman's Syndrome	1.5-3K cases US (<8yo)	Uniform knockdown of UBE3A-ATS via systemic route to increase normal UBE3A protein levels throughout the CNS
Epilepsy Target 1	Epilepsy	1-15K cases US	Undisclosed
NEUROMUSCULAR DISEASES			
DMPK	Myotonic Dystrophy Type 1	*Adult* 40K cases US *Congenital* ~600 cases US	Knockdown of DMPK in periphery and CNS to reduce toxic RNA foci & allow MBNL proteins to resume normal splicing


DENALI
OUR BRAIN-PENETRANT SMALL MOLECULE PROGRAMS

BIIB122 (LRRK2 INHIBITOR): TARGETING THE LYSOSOME IN PD

Targeting LRRK2 may impact the underlying biology and slow the progression of PD

- 10M+ people with Parkinson's disease (PD) WW
- Mutations in LRRK2 are one of the most common genetic risk factors for PD
- Increased LRRK2 kinase activity is thought to impair lysosomal function and contribute to PD
- Denali conducted extensive Phase 1/1b testing with LRRK2 inhibitors in 300+ individuals*
- BIIB122 achieved ≥80% pS935 inhibition (target engagement biomarker) at doses of ≥ 225 mg
- Biogen is leading operational execution of the Phase 2b LUMA Study

Phase 2b LUMA Study of BIIB122 in PD patients with and without LRRK2 mutations

	Phase 2b LUMA Study
PD patient pop.	Early-stage, idiopathic and pathogenic LRRK2 variants
Dosing	225 mg oral once daily BIIB122 vs. placebo
Primary endpoint	Assessed using MDS-UPDRS
No. participants	640 (320 per arm)
Treatment period	48 weeks (min)
Study initiation	May 2022

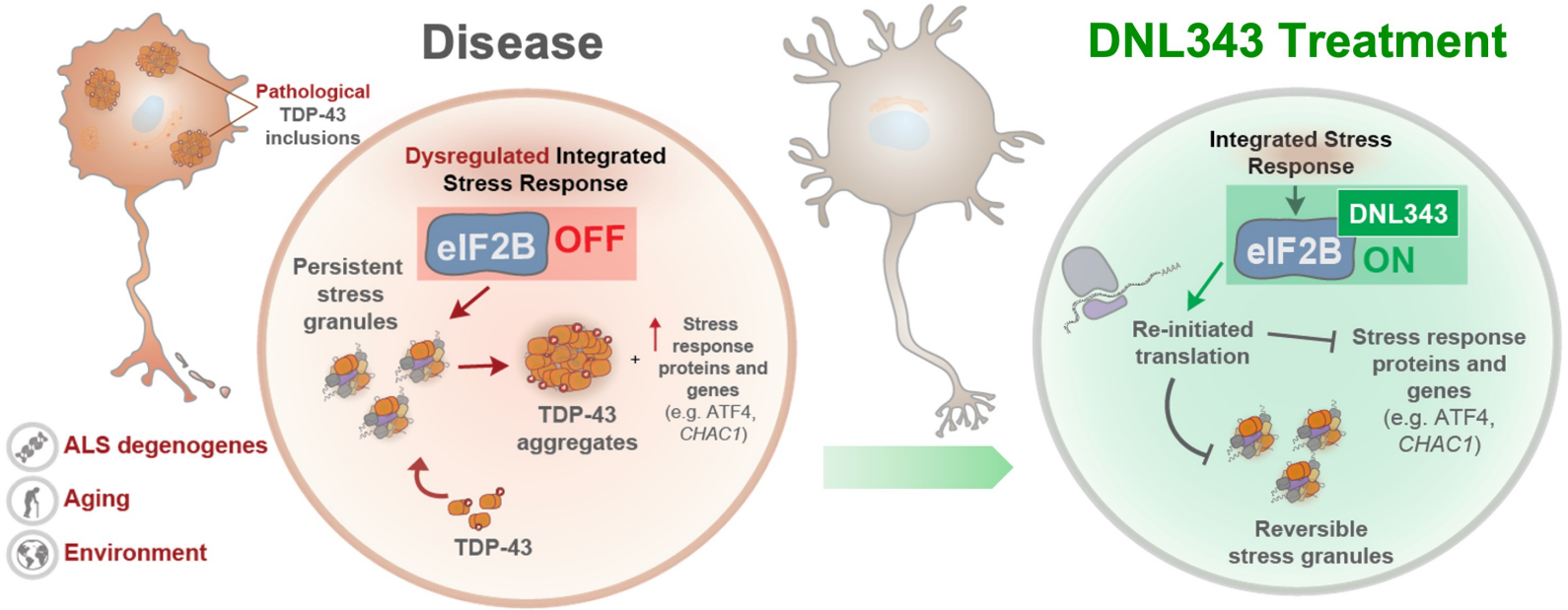
DENALI THERAPEUTICS Biogen

*Phase 1/1b program for BIIB122 and DNL201

LRRK2=leucine-rich repeat kinase 2; WW=worldwide; MDS-UPDRS=Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale

EIF2B ACTIVATION HAS POTENTIAL TO SLOW NEURODEGENERATION IN ALS

In ALS, TDP-43 pathology is linked to cellular dyshomeostasis resulting from chronic activation of the Integrated Stress Response (ISR) via inactivation of the eukaryotic initiation factor 2b (eIF2B)

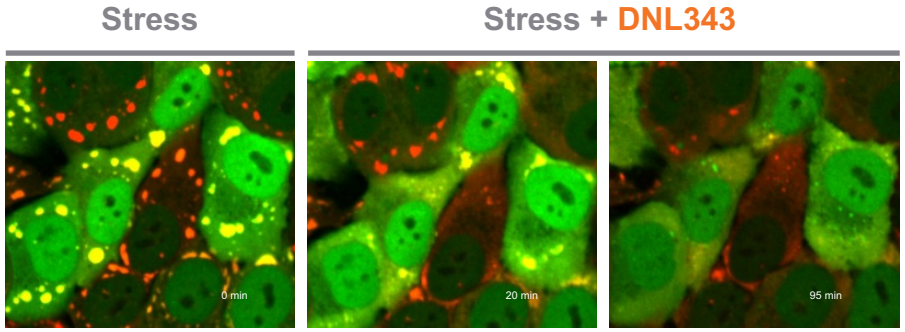


DNL343 is an eIF2B agonist designed to inhibit the ISR and restore cells to a healthy state

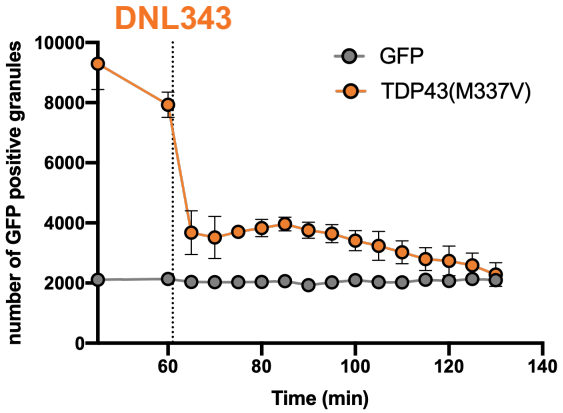
TDP-43: transactive response DNA binding protein 43 kDa; ATF4: Activating Transcription Factor 4; CHAC1: ChaC Glutathione Specific Gamma-Glutamylcyclotransferase 1

DNL343 EFFECTS IN NEURONS AND IPSC-DERIVED NEURONS

DNL343 EFFECTS IN NEURONS

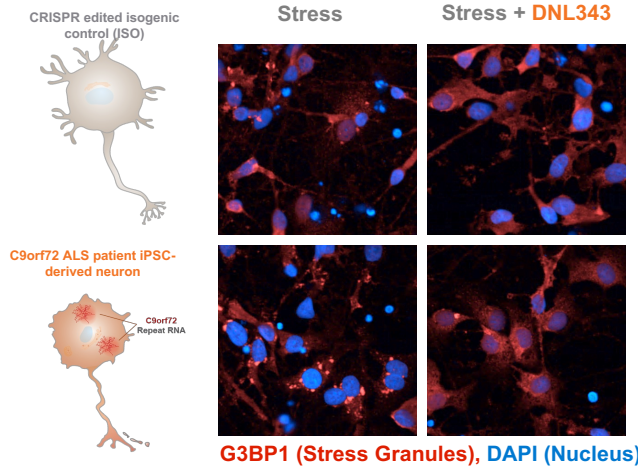


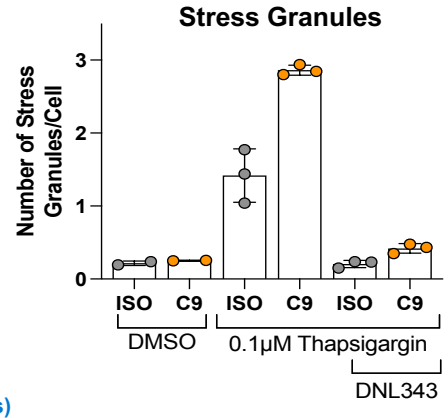
G3BP1 (Stress Granules) GFP-TDP-43$^{\Delta NLS, M337V}$
Co-localization of TDP-43 in Stress Granules



During cell stress TDP-43 localizes to stress granules in neuroglioma H4 cells and DNL343 dissolves these structures

DNL343 EFFECTS IN iPSC-DERIVED NEURONS





C9orf72 patient-derived neurons have increased stress granules. DNL343 prevents this effect.

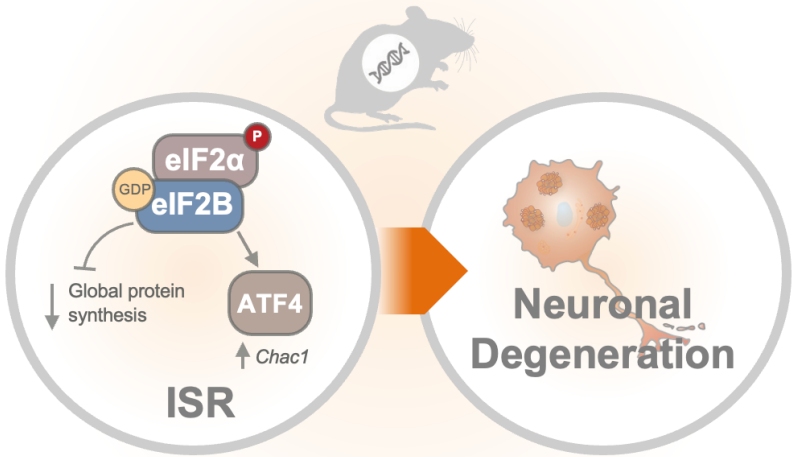
IN VITRO STUDY DESIGN

- GFP-TDP43$^{\Delta NLS, M377V}$/mCherry-G3BP1-expressing H4 cells were treated with sodium arsenite for 1h followed by addition of 1μM DNLS or DMSO. Cells were imaged every 5 mins and the number of GFP^{+} puncta were quantified
- Forebrain neurons were differentiated from C9orf72-repeat containing patient iPSCs or isogenic control and matured for 2 weeks. Cells were pretreated with either DMSO or 1 μM DNL343 for 30 min followed by 2h thapsigargin treatment. Cells were then fixed and stained for G3BP1 and stress granules were quantified.

Acronyms: NLS, nuclear localization sequence, G3BP1, Ras GTPase-activating protein-binding protein 1

DNL343 EFFECTS IN NEURONS AND IPSC-DERIVED NEURONS

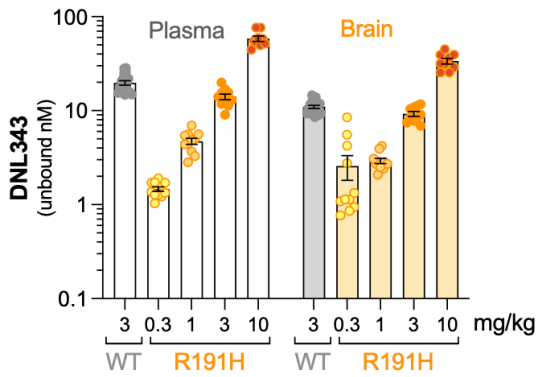
THE eIF2Bε R191H MODEL



The EIF2Bε R191H mouse models the consequences of ISR activation & is an ideal model to test DNL343 mechanism of action

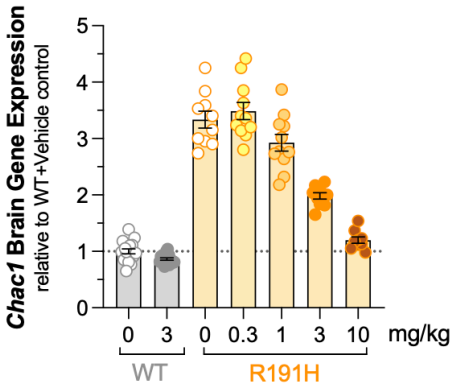
EIF2α, eIF2B, eukaryotic translation initiation factor 2α and 2B respectively; ISR, integrated stress response

DNL343 EXPOSURE



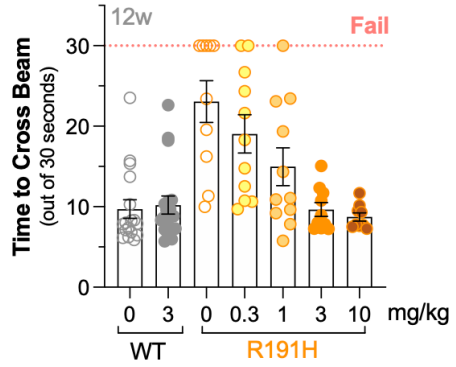
DNL343 achieved comparable exposure in the brain & plasma

ISR PATHWAY



Dose dependent modulation of brain ISR gene marker

MOTOR FUNCTION



Dose dependent restoration of motor function

DNL343 is BBB penetrant and achieved CNS pathway modulation in association with functional correction in an in vivo model

IN VIVO STUDY DESIGN

Wild-type and R191H mice self-administered chow-formulated DNL343 (*ad libitum*) for 13 weeks at doses ranging from 0.3 to 10 mg/kg daily, which led to a dose-dependent increase in exposures in the plasma and brain. Pathway modulation and functional effects were evaluated at the end of the dosing period. Data are presented as mean +/- SEM

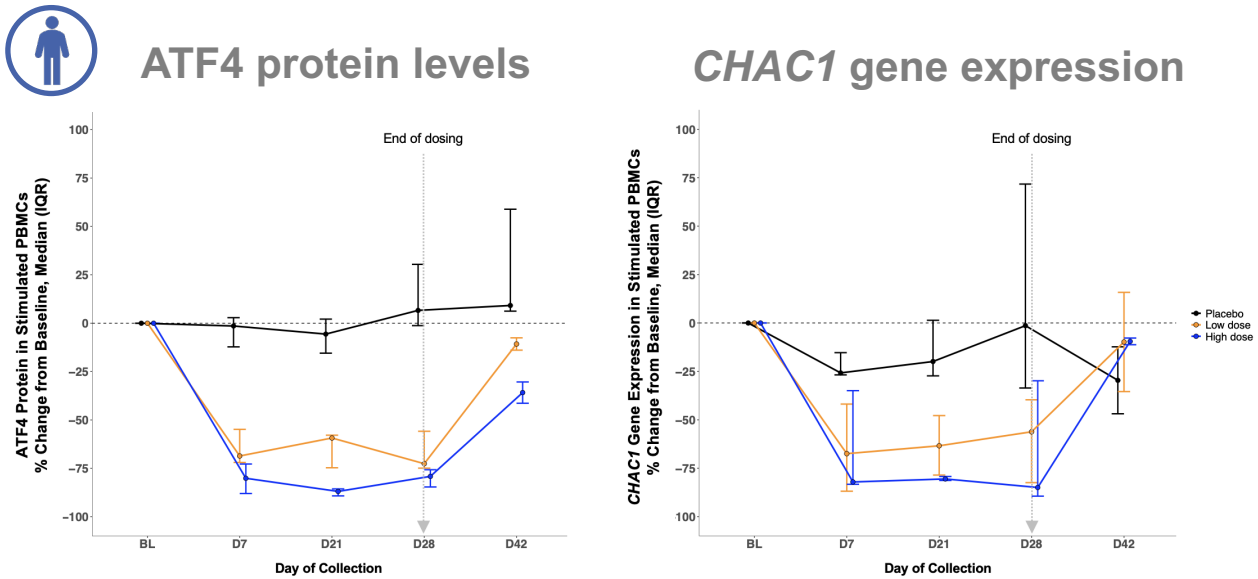
DNL343 (eIF2B ACTIVATOR): INHIBITING THE ISR PATHWAY IN ALS

By inhibiting the ISR pathway, DNL343 is intended to prevent or slow ALS progression

- ALS is a fatal neurodegenerative disease with TDP-43 inclusion pathology in 95% of patients
- Chronic activation of the integrated stress response (ISR) may contribute to ALS
- DNL343 is a small molecule that activates eIF2B, a key ISR regulator
- DNL343 inhibits ISR stress granule formation in cellular models
- DNL343 promotes neuroprotection in animal models

eIF2B=eukaryotic initiation factor 2B; ISR=integrated stress response; ALS=amyotrophic lateral sclerosis; TDP-43=TAR DNA-binding protein 43

28-day dosing with DNL343 reduced ISR biomarkers in blood samples* from ALS patients (Phase 1b)



*Fresh PBMCs were collected and stimulated ex vivo for each time point indicated for a subset of patients (per dose group: n=5-7 through day 28 and 2-3 for day 42). Experiments using cryopreserved PBMCs were also performed and showed similar results.

Dosing with DNL343 in Phase 2/3 HEALEY Platform Trial in ALS initiated May 2023

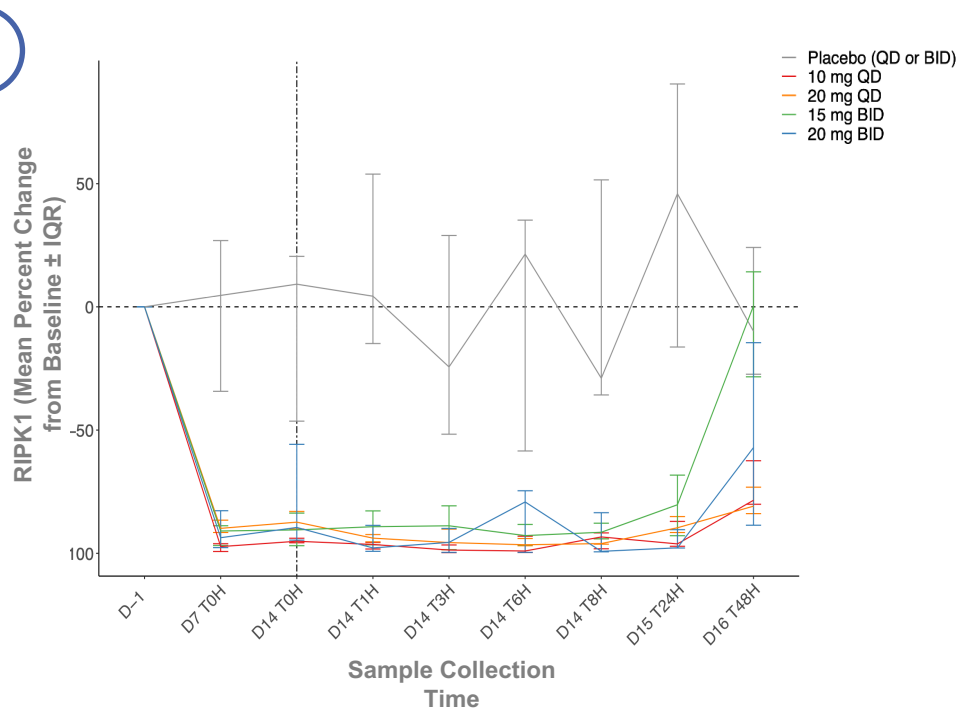
RIPK1 INHIBITORS: TARGETING INFLAMMATION AND CELL DEATH

RIPK1 is a critical signaling protein in a canonical inflammatory and cell death pathway

- Increased RIPK1 activity drives neuroinflammation and cell necroptosis and contributes to neurodegeneration
- RIPK1 inhibition achieved beneficial effects in preclinical models of ALS, multiple sclerosis and other diseases
- Denali and Sanofi have a strategic collaboration to develop and commercialize RIPK1 inhibitors
- Robust target engagement goals and safety goals achieved in Phase 1 studies for SAR443820 (CNS penetrant) and SAR443122 (peripherally restricted)

RIPK1= receptor-interacting serine/threonine-protein kinase 1; ALS=amyotrophic lateral sclerosis; MS=multiple sclerosis; CLE=cutaneous lupus erythematosus; UC=ulcerative colitis

93% to 99% RIPK1 inhibition achieved in Phase 1 after multiple doses of SAR443820*



*Range of maximum median inhibition of pS166-RIPK1 levels in blood cells from HVs in the Phase 1 study

Sanofi is conducting four Phase 2 studies: SAR443820 in ALS and MS + SAR443122 in CLE and UC

DENALI THERAPEUTICS sanofi

OUR PRIORITIES

1 Clinical Execution

- 4 late-stage programs enrolling studies in MPS II, 2x ALS, and PD
- Multiple earlier-stage trials designed for biomarker PoC
- Expansion of clinical operations and medical affairs in Europe
- Building out clinical manufacturing capabilities

2 TV Expansion

- Clinical data from 3 TV-platform enabled programs
- Fourth TV-enabled program advancing towards clinical testing
- Selected OTV targets provides broad range of opportunities
- Expand TV platform potential with additional BBB transporter

3 Commercial Readiness

- Define go-to-market strategies in the US and key global markets
- Outreach to patients and communities in MPS II and ALS to understand unmet needs
- Establish critical medical affairs and commercial capabilities to prepare for early filing scenarios

TV=Transport Vehicle; OTV=Oligonucleotide Transport Vehicle; MPS= mucopolysaccharidoses; ALS=amyotrophic lateral sclerosis; PD=Parkinson's disease; PoC=proof of concept

$1.19B in cash and investments (as of 6/30/23)

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.


THANK YOU