CROSSING BARRIERS AND DEFEATING DEGENERATION

CORPORATE OVERVIEW
MARCH 2025

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 2025 and beyond; Denali’s ability to execute on its tailored commercial strategies and accelerate commercial launch readiness; the potential for Denali's product candidates to treat various neurodegenerative diseases including MPS I (Hurler Syndrome), MPS II (Hunter Syndrome), MPS IIIA (Sanfilippo Syndrome), PD, ALS, AD, FTD-GRN, UC, Gaucher's Disease, Pompe Disease, and related peripheral inflammatory diseases; 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 related to Denali's TransportVehicle™ (TV) platform, including the Enzyme TV (ETV), Antibody TV (ATV), Protein TV (PTV), and Oligonucleotide TV (OTV), and its therapeutic and commercial opportunities; plans, timelines, and expectations related to the ETV platform and ETV-enabled programs, including ETV:GAA, ETV:GCase, and ETV:IDUA, their therapeutic and commercial potential, and the timing and likelihood of planned regulatory filings; plans, timelines, and expectations relating to DNL310, including the ongoing Phase 1/2 study and Phase 2/3 COMPASS study, the timing of planned regulatory filings, and the timing, likelihood, and scope of regulatory approvals and commercial launch; plans, timelines, and expectations related to DNL126, including the timing and availability of data from the Phase 1/2 study and likelihood and pathway of regulatory approval; plans, timelines, and expectations related to the OTV and OTV-enabled programs, including OTV:MAPT and OTV:SNCA, their therapeutic and commercial potential, and the timing and likelihood of planned regulatory filings; plans, timelines, and expectations relating to ATV:Abeta, including its therapeutic potential and the timing of planned regulatory filings; plans, timelines, and expectations relating to DNL151, including enrollment in the Ph2B LUMA study and Ph2A BEACON study; plans and expectations regarding DNL593, including enrollment of Cohort B in the Ph1/2 study; plans, timelines, and expectations related to DNL758 and enrollment in the Ph2 RESOLUTE study; plans and expectations regarding Denali's global organization and clinical operations, the expected timing and likelihood of success of its commercial growth, and the potential value of Denali's programs, are forward-looking statements. Denali has based these forward-looking statements largely on its current expectations and projections about future events, and forward-looking statements regarding potential outcomes should not be interpreted as guarantees of future performance.

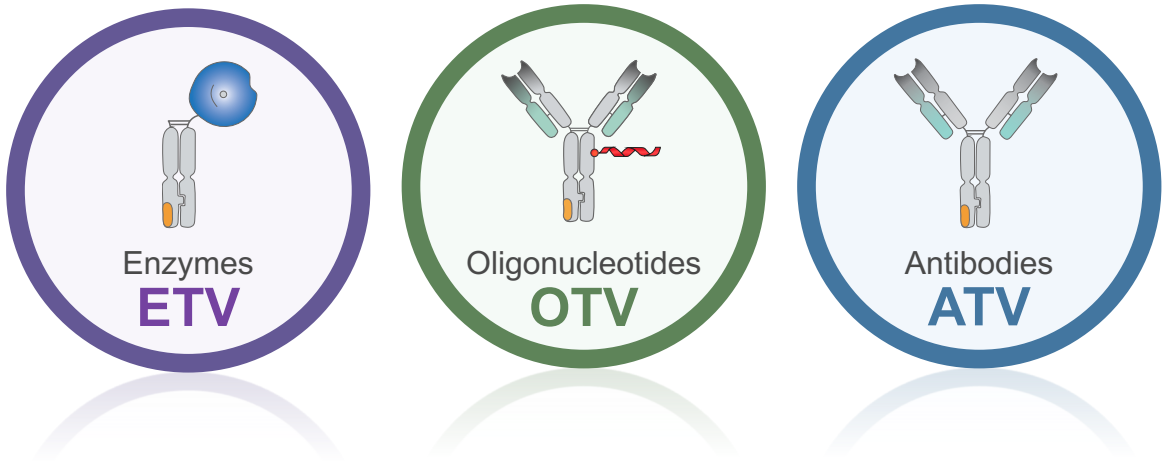
These forward-looking statements speak only as of the date of this presentation and are subject to a number of risks, uncertainties and assumptions, including but not limited to: the risk of the occurrence of any circumstance that could give rise to the termination of Denali’s agreements with its collaborators; Denali’s and its collaborators’ ability to complete the development and, if approved, commercialization of its product candidates; Denali’s and its collaborators’ ability to enroll patients in its ongoing and future clinical trials; Denali’s reliance on third parties for the manufacture and supply of its product candidates for clinical trials; Denali’s dependence on successful development of its blood-brain barrier platform technology and TV-enabled product candidates; Denali’s and its collaborators’ ability to conduct or complete clinical trials on expected timelines; the predictive value of Denali's biomarker selection; the occurrence of significant adverse events, toxicities or other undesirable side effects; the potential for clinical trials of Denali’s product candidates to differ from preclinical, early clinical, preliminary or expected results; the uncertainty that product candidates will receive regulatory approval or be commercialized; Denali’s ability to continue to create a pipeline of product candidates or develop commercially successful products; Denali’s ability to obtain, maintain, or protect intellectual property rights related to its product candidates; Denali's achievement of planned milestones and realization of value; implementation of Denali’s strategic plans for its business, product candidates, and blood-brain barrier platform technology; and other risks. In light of these risks, uncertainties and assumptions, the forward-looking statements in this press release are inherently uncertain and may not occur, and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements. Accordingly, you should not rely upon forward-looking statements as predictions of future events. Information regarding additional risks and uncertainties may be found in Denali’s most recent quarterly and annua reports filed with the Securities and Exchange Commission on Forms 10-Q and 10-K, respectively, as well as Denali’s future reports to be filed with the SEC. Denali does not undertake any obligation to update or revise any forward-looking statements, to conform these statements to actual results or to make changes in Denali’s expectations, except as required by law.

The product candidates being developed by Denali are investigational and their safety and efficacy profiles remain unestablished. Denali's product candidates have not been approved by any health authority for any use.

Accuracy of Data. This presentation contains statistical data based on independent industry publications or other publicly available information, as well as other information based on Denali’s internal sources. Denali has not independently verified the accuracy or completeness of the data contained in these industry publications and other publicly available information. Accordingly, Denali makes no representations as to the accuracy or completeness of that data.

DELIVERING A NEW CLASS OF THERAPEUTICS

The **TransportVehicle**™ (TV) enables a **new class of therapeutics** that cross the **blood-brain barrier (BBB)**



2025 Priorities

PREPARING TO LAUNCH

Potential launch of **tividenofusp alfa in MPS II** (Hunter syndrome)

EXPANDING ETV FRANCHISE

Realize potential of TV platform for **lysosomal storage diseases**

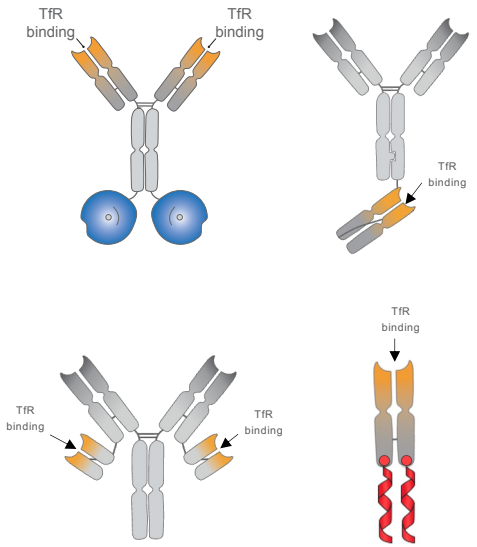
ADVANCING TV PORTFOLIO

Progress TV programs for **neurodegeneration** and other indications

Transforming treatment for people with rare and common diseases that impact the brain

SETTING THE BAR FOR BRAIN DELIVERY PLATFORMS

Conventional Fab Approaches



Illustrative examples of other BBB technologies using the Fab to bind TfR

Our Fc-based TransportVehicle™ (TV) is Designed and Engineered to Optimize Brain Delivery

BBB receptor binding site engineered into the **Fc for optimal properties and modularity**

Optimized Binding Affinity & Monovalency: Enhances brain delivery and limits receptor degradation

Conditional Effector Function: Avoids reticulocyte loss and potentially minimizes anemia liability

High Fidelity to Natural Protein: No appended sequences limits risk of immunogenicity and IRRs

Modularity: Enables broadest utility to transport biologics, such as enzymes, oligos, antibodies

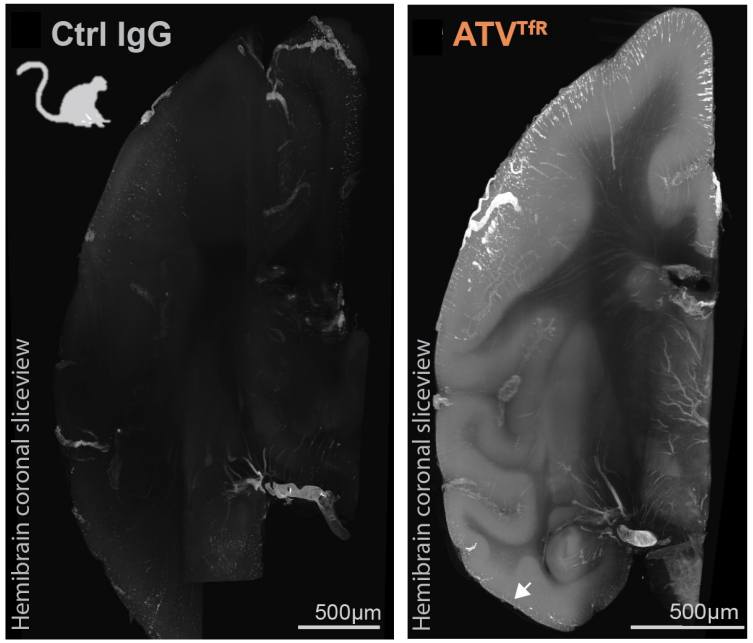
>350 Patents and Applications | **10** High Impact Publications | **3** Clinical Programs | **>10** Preclinical Programs

Leading BBB technology and broadest portfolio of TV-enabled therapeutics

BBB – blood-brain barrier; **TfR** – transferrin receptor; **IRRs** – infusion related reactions

OUR TV PLATFORM IS WELL CHARACTERIZED AND CLINICALLY VALIDATED

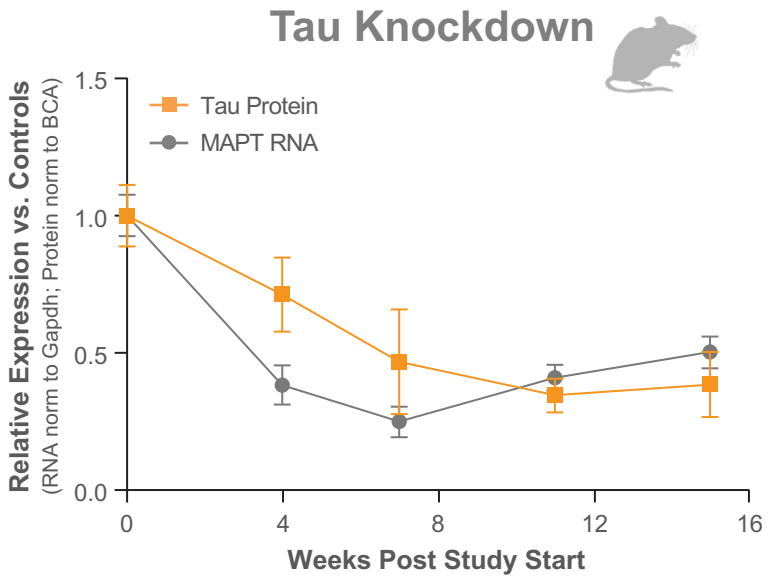
Biodistribution



Khoury et al. 2025 *Nature Communications*

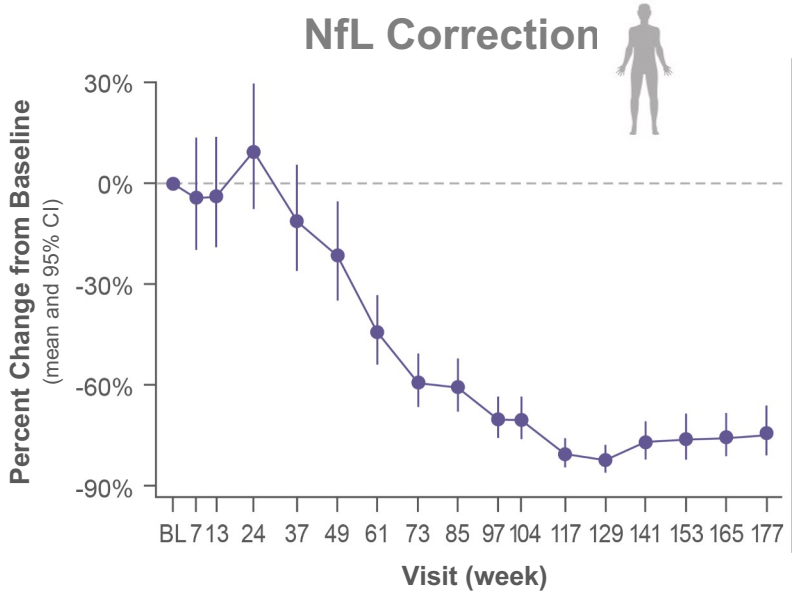
TV provides high and uniform deposition of ATV across the brain with systemic delivery

Target Engagement



TV enables sustained brain tau knockdown with OTV:MAPT systemic delivery

Disease Biomarker



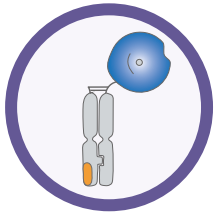
TV enables ETV:IDS to reduce serum NfL by >80%, achieving normal levels

TransportVehicle™ (TV) enables broader brain biodistribution, enhanced target engagement, and normalization of key disease biomarkers

NfL – neurofilament light, a marker of neurodegeneration; Source: tau – Denali data on file, NfL – adapted from SSIEM 2024

PREPARING FOR COMMERCIAL LAUNCH

Enzyme TransportVehicle™ (ETV): Expected Product Launches



Paving the Path with Tividenofusp alfa

- Market **leading profile** to treat MPS II phenotype spectrum
- Only candidate therapy to **normalize** key biomarkers, CSF HS, urine HS, and NfL, in a lysosomal storage disease
- Alignment with FDA on **accelerated approval path**
- BLA filing early 2025 and **preparing for U.S. launch**
- Ongoing Phase 2/3 COMPASS study to support global approval

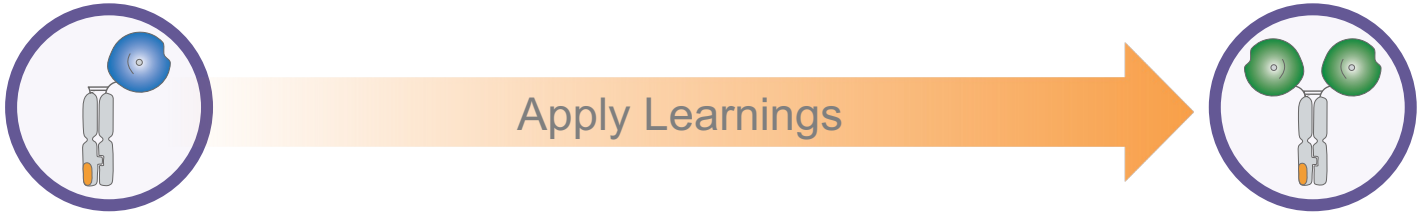
U.S. FDA Breakthrough Therapy Designation **Granted to Tividenofusp Alfa** for the Treatment of Hunter Syndrome (MPS II)

Validating the TransportVehicle™ platform and enabling a broad ETV portfolio

MPS II – Mucopolysaccharidoses Type II; **CSF HS –** cerebrospinal fluid heparan sulfate; **HS –** heparan sulfate; **NfL** – neurofilament light, a marker of neurodegeneration; **BLA –** Biologics License Application; **MPS IIIA –** Mucopolysaccharidoses Type IIIA; **START –** Support for clinical Trials Advancing Rare disease Therapeutics

TRANSITIONING TO COMMERCIAL STAGE

Enzyme TransportVehicle™ (ETV): Expected Product Launches



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Accelerating DNL126

- Achieved **biomarker proof-of-concept** in Phase 1/2
- Expanded study to support a potential **accelerated approval path** in MPS IIIA
- Selected for FDA **START program**
- Collaborating with FDA on path to approval

Validating the TransportVehicle™ platform and enabling a broad ETV portfolio

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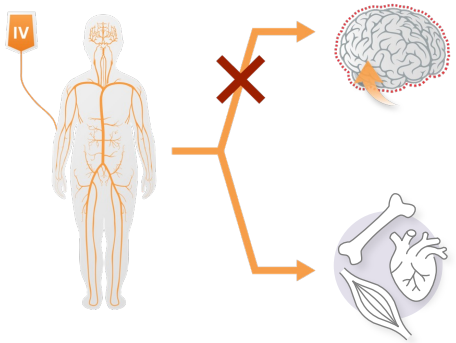
ETV FRANCHISE OPPORTUNITY IN LYSOSOMAL STORAGE DISEASES

Addressing High Unmet Need

LSDs are **single-enzyme deficiency** diseases

30,000 people with LSDs worldwide

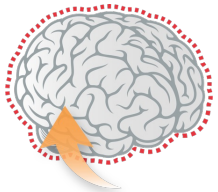
2/3 LSDs with **CNS manifestations**



Traditional ERTs partially address somatic but not CNS symptoms

~90% historical approval rate

Targeting Brain & Body with ETV



ETVs enable brain delivery of enzymes to address cognitive and behavioral symptoms

Potential to **enhance peripheral delivery**

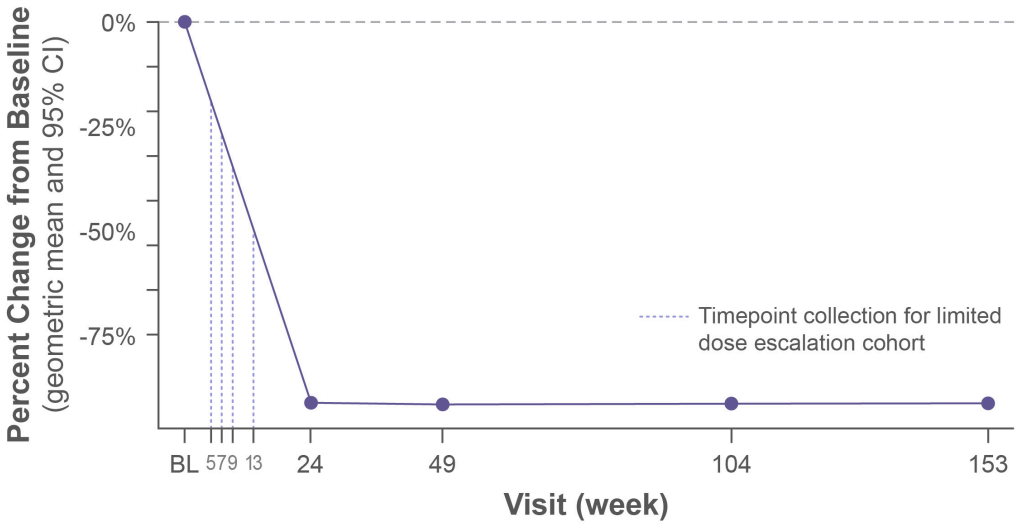
Goal is to treat the **full disease spectrum**

ETV – enzyme transport vehicle; **LSDs –** lysosomal storage diseases; **CNS –** central nervous system; **ERTs –** enzyme replacement therapies

TIVIDENOFUSP ALFA PHASE 1/2 IN MPS II: BRAIN BIOMARKERS

CSF Heparan Sulfate

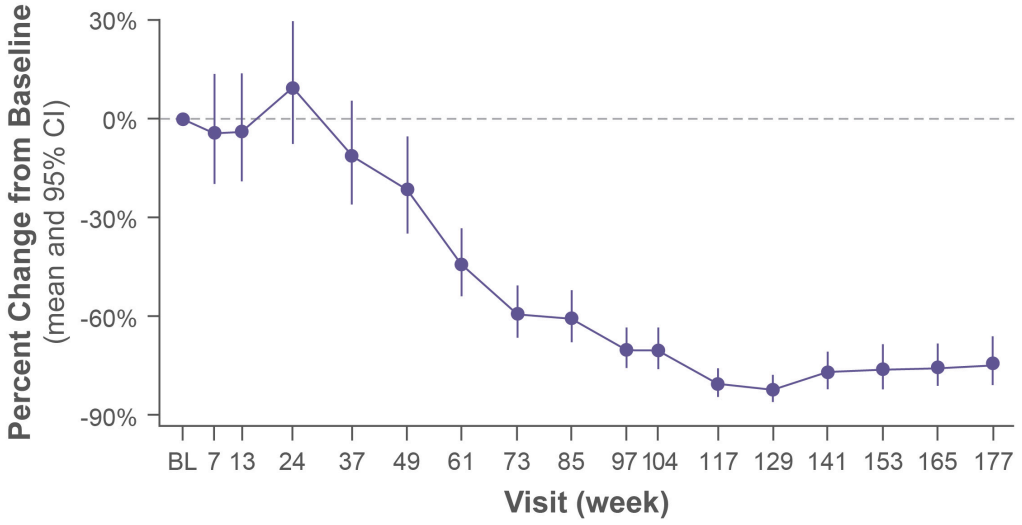
Biomarker of neuronopathic disease



Robust reduction from baseline in CSF HS with the majority of participants in the normal range after treatment

Serum NfL

Biomarker of neuronal damage



Robust reduction from baseline in serum NfL with the majority of participants reaching the normal range by Week 104

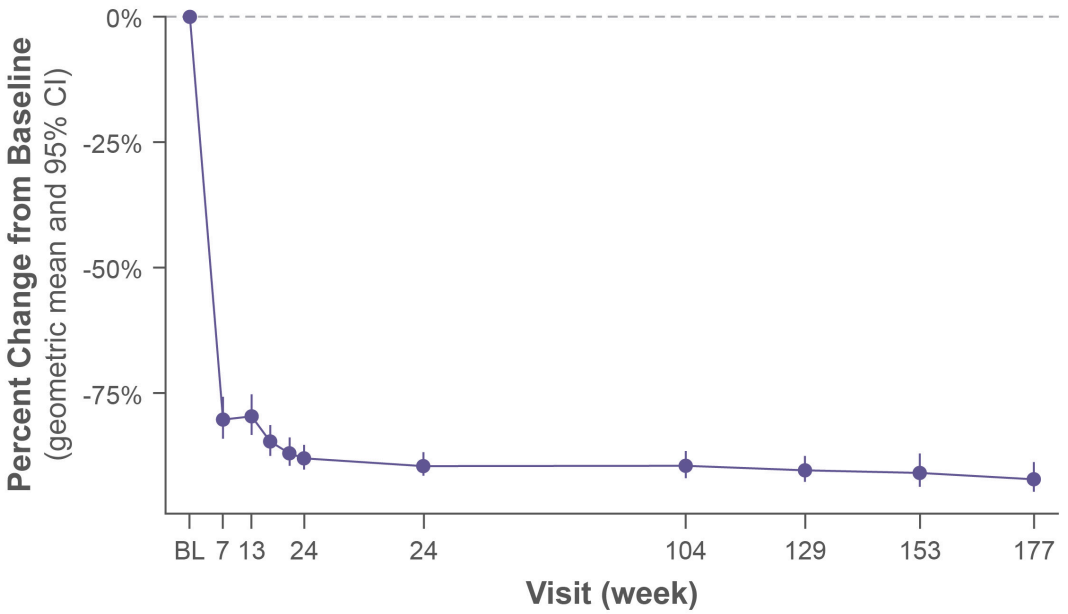
First and only therapy in development for MPS II to achieve normalization of key biomarkers

MPS II – Mucopolysaccharidoses Type II; **CSF –** cerebrospinal fluid; **NfL** – neurofilament light; Source: WORLD 2025

TIVIDENOFUSP ALFA PHASE 1/2 IN MPS II: PERIPHERAL EFFECTS

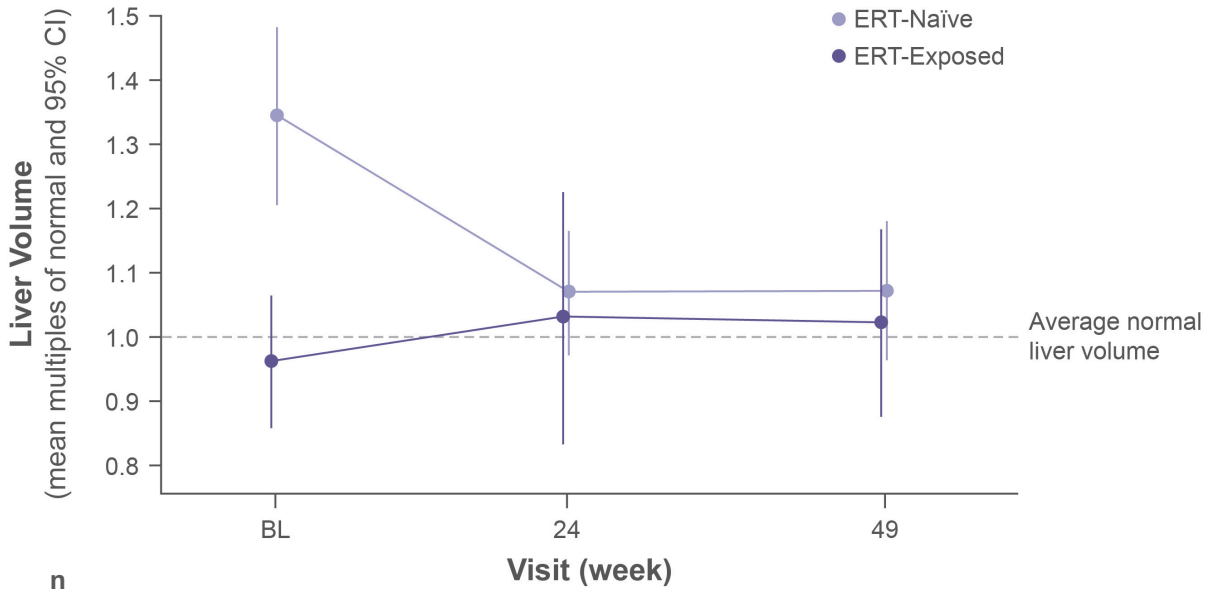
Urine Heparan Sulfate

Biomarker of peripheral disease



Liver Volume

Peripheral clinical outcome



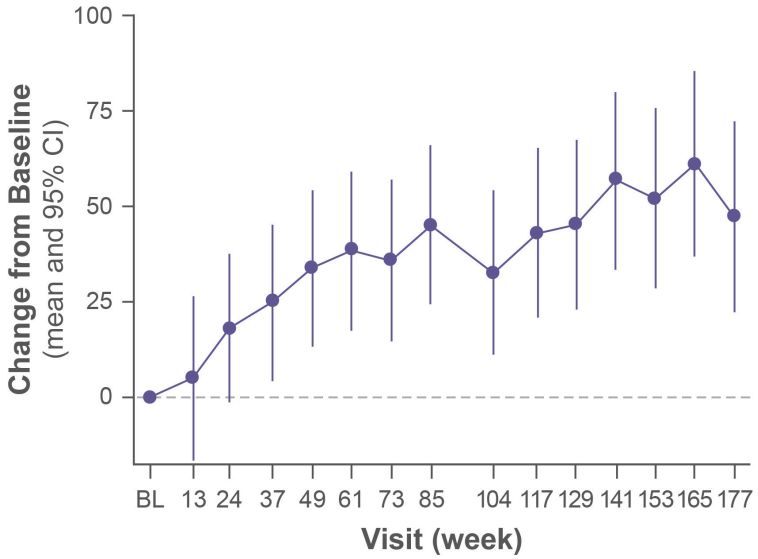
n			
ERT-Naïve	14	12	11
ERT-Exposed	7	6	3

Achievement of normalization of peripheral effects suggests additional effects after switching from idursulfase to treatment with tividenofusp alfa

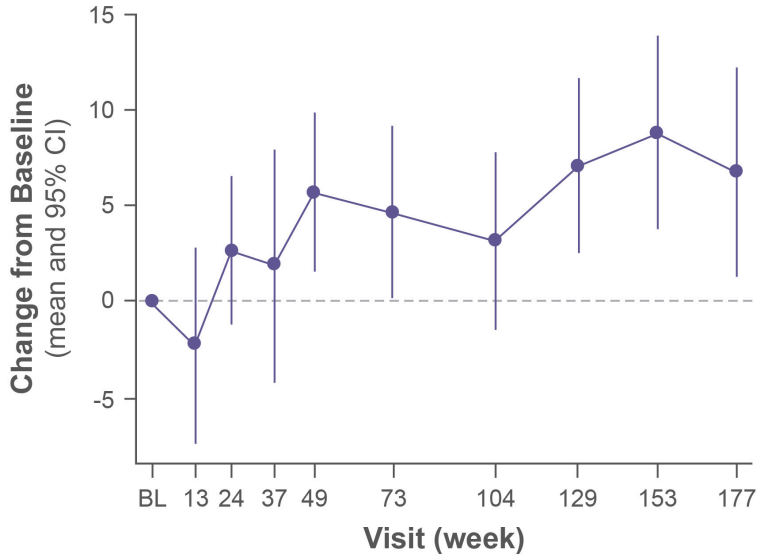
MPS II – Mucopolysaccharidoses Type II; **ERT –** enzyme replacement therapy; **CI –** confidence interval; Source: WORLD 2025

TIVIDENOFUSP ALFA PHASE 1/2 IN MPS II: CLINICAL OUTCOMES

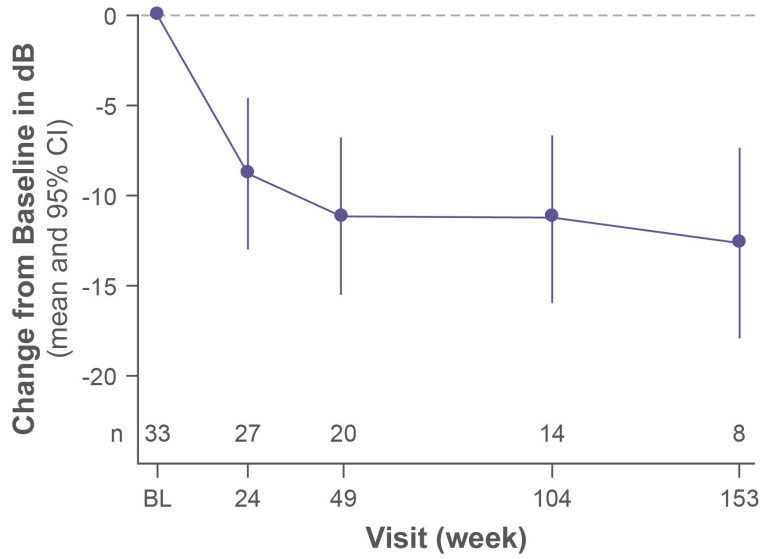
Vineland-3 Adaptive Behavior Raw Composite



BSID-III Cognitive Raw Score



Pure Tone Average



While on tividenofusp alfa, clinical outcomes showed skill gains relative to baseline in most participants on measures of adaptive behavior and cognition as well as hearing threshold improvement from baseline in all tested frequencies

Data supports impact on clinical outcomes important to individuals and families with MPS II

MPS II – Mucopolysaccharidoses Type II; **CI –** confidence interval; **BSID-III –** Bayley Scales of Infant and Toddler Development-Third Edition; Source: WORLD 2025

TIVIDENOFUSP ALFA PHASE 1/2 IN MPS II: SAFETY

	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
  - 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

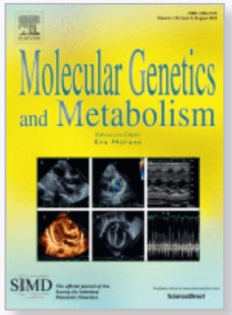
Phase 1/2 safety and clinical data supports broad indication for treatment of full spectrum of MPS II

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.

LEADERSHIP AND COLLABORATION IN TRANSFORMING MPS TREATMENT

Data Driven and Action Oriented to Deliver Meaningful Impact for Patients

Workshop, February 2024



Review Article

Community consensus for Heparan sulfate as a biomarker to support accelerated approval in Neuronopathic Mucopolysaccharidoses

Muenzer et al. 2024 *Mol. Genet. Metab.*

Accelerating a Path to New Treatments for Rare Neuropathic MPS Diseases

Carole Ho, MD
Feb 2024, *BioSpace*

Eliza, living with MPS IIIA

Dominic, living with MPS II

We acknowledge the collective efforts advocating for faster, science-driven, paths to effective treatments for rare diseases that contribute to this opportunity and potentially others

MPS II: PATIENTS, PRESCRIBERS, PRODUCT OPPORTUNITY IN U.S.

MPS II Landscape

Patients & Prescribers

- 400-500 patients
- 80-100 centers of excellence
- Extended health care team
- Weekly contact with patients

Opportunity

- Normalize disease biomarkers
- Address neuronopathic and peripheral disease
- Slow/stop degeneration
- Replace idursulfase as standard of care

Prelaunch Activities

Awareness

- Ongoing dialogue with prescribers; full coverage by MSL team
- Engaging with payers
- Educating on unmet need across the phenotype spectrum
- Demonstrating differentiated therapeutic profile

Access & Support

- Building a suite of patient support services and capabilities to enable broad access to tividenofusp alfa

Team

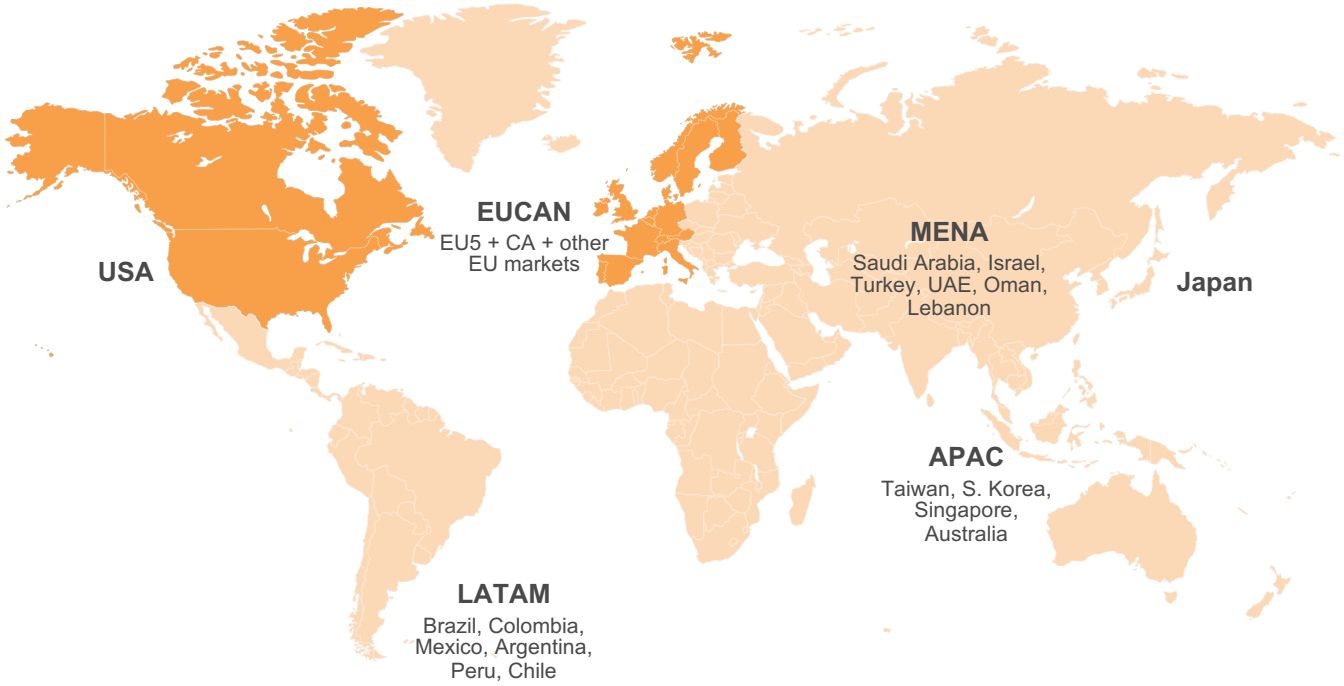
- Building a right-sized team in commercial and medical affairs to support tividenofusp alfa and additional ETV launches

Preparing to launch tividenofusp alfa for MPS II in late 2025 / early 2026

MPS II – Mucopolysaccharidoses Type II; **MSL –** medical science liaison; **ETV –** enzyme transport vehicle

MPS II GLOBAL MARKET OPPORTUNITY

Total Addressable Market ~2,000 Worldwide*

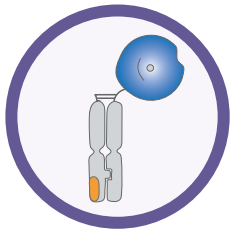
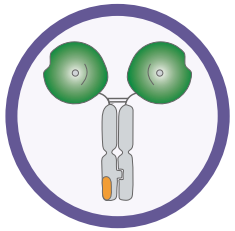
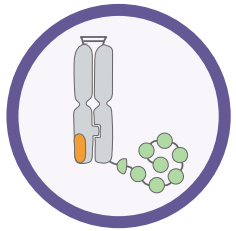
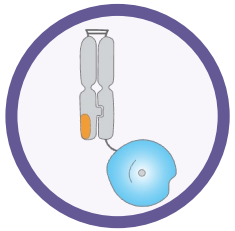
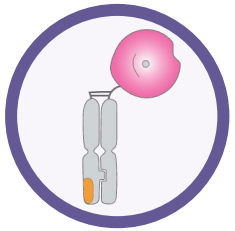
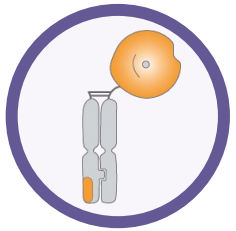


Strategically Build & Collaborate

- **Invest in key markets** with the highest opportunity: **USA / EUCAN**
- **Maximize global reach and value** with potential distributors (or local partners) to accelerate access to medicine for patients and time to revenue in anchor markets

*Excluding China and India; **MPS II** – Mucopolysaccharidoses Type II

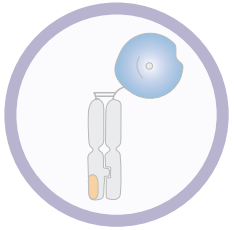
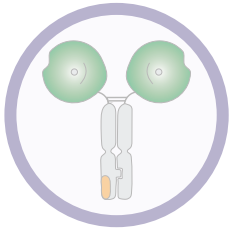
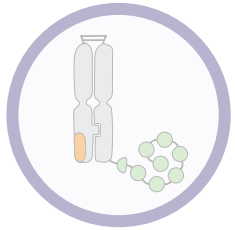
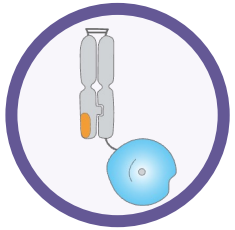
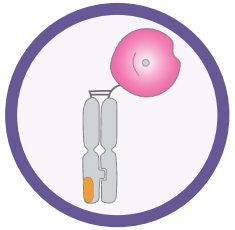
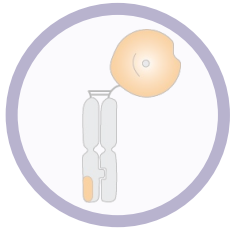
EXPANDING OUR ETV DEVELOPMENT FRANCHISE

	Tividenofusp alfa (ETV:IDS; DNL310)	ETV:SGSH (DNL126)	PTV:PGRN (DNL593)	ETV:GAA (DNL952)	ETV:GCase (DNL111)	ETV:IDUA (DNL622)
						
	MPS II (Hunter syndrome)	**MPS IIIA** (Sanfilippo syndrome)	**FTD-GRN** (Frontotemporal dementia)	**Pompe Disease**	**Parkinson's and Gaucher**	**MPS I** (Hurler syndrome)
Patients WW[1]	**~2,000**	**~1,500+**	**~25,000+**	**~5,000 – 10,000**	**~300,000+ (GBA-PD) ~10,000 – 15,000 (GD)**	**~1,500+**
Status	Phase 2/3 BLA filing[2]	Phase 1/2	Phase 1/2	IND-enabling	IND-enabling	IND-enabling

We are developing the next generation of enzyme replacement therapies designed to treat brain and body manifestations of serious genetic diseases

WW – worldwide; **BLA –** biologics license application; **IND –** investigational new drug application; **GBA-PD** – Parkinson's Disease with GBA mutation; **GD** – Gaucher's Disease; **1.** Excluding China and India; **2.** Expected filing of BLA under accelerated approval pathway in early 2025.

EXPANDING OUR ETV DEVELOPMENT FRANCHISE

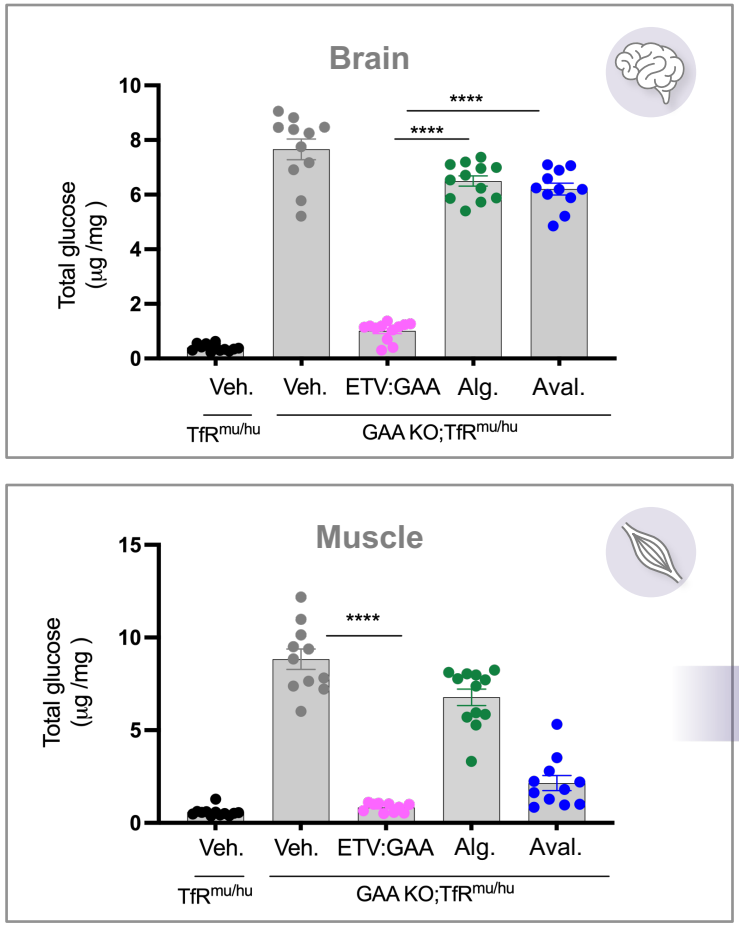
	Tividenofusp alfa (ETV:IDS; DNL310)	ETV:SGSH (DNL126)	PTV:PGRN (DNL593)	ETV:GAA (DNL952)	ETV:GCase (DNL111)	ETV:IDUA (DNL622)
						
	MPS II (Hunter syndrome)	**MPS IIIA** (Sanfilippo syndrome)	**FTD-GRN** (Frontotemporal dementia)	**Pompe Disease**	**Parkinson's and Gaucher**	**MPS I** (Hurler syndrome)
Patients WW[1]	~2,000	~1,500+	~25,000+	~5,000 – 10,000	~300,000+ (GBA-PD) ~10,000 – 15,000 (GD)	~1,500+
Status	Phase 2/3 BLA filing[2]	Phase 1/2	Phase 1/2	IND-enabling	IND-enabling	IND-enabling

We are developing the next generation of enzyme replacement therapies designed to treat brain *and* body manifestations of serious genetic diseases

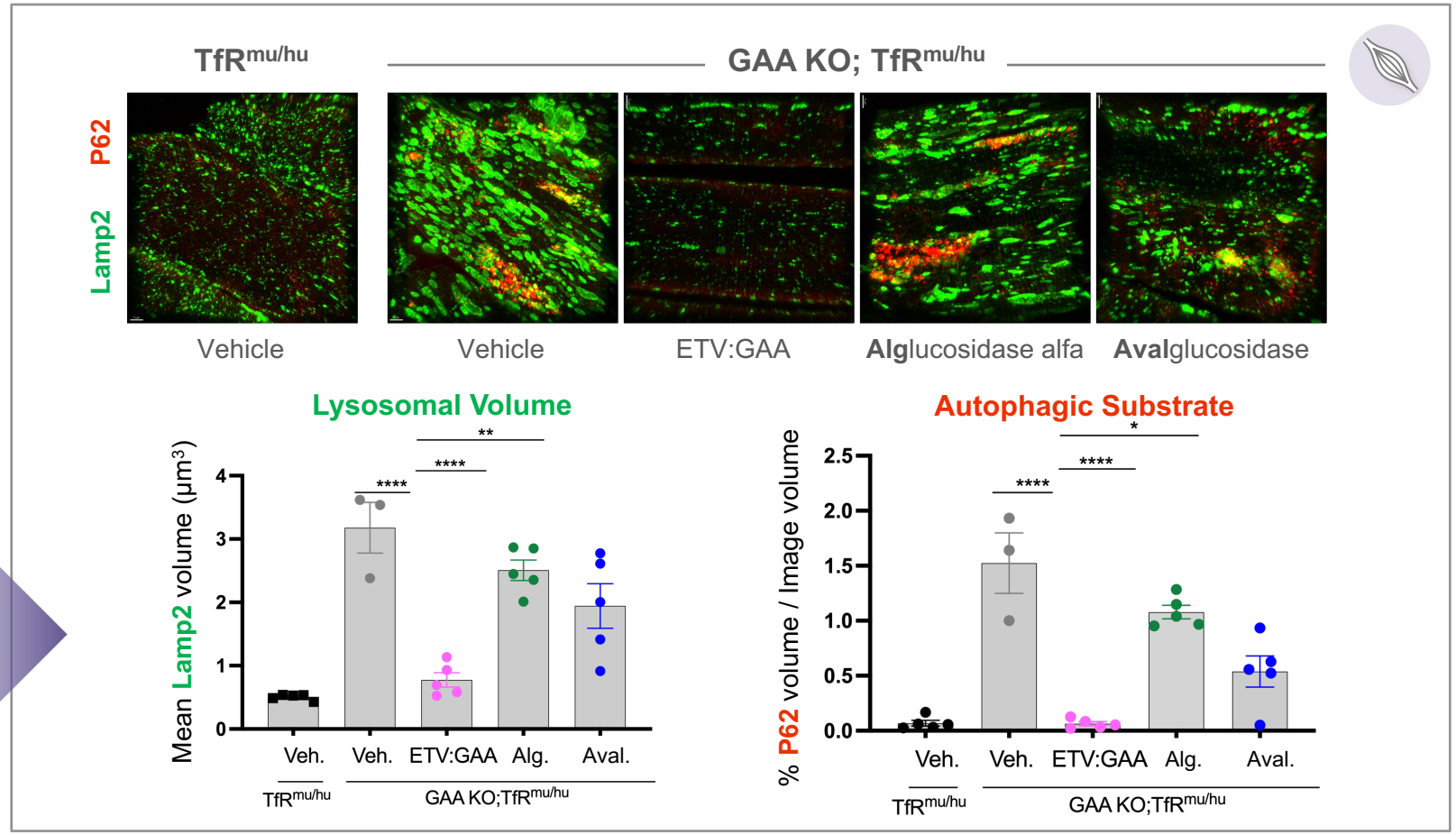
WW – worldwide; **BLA –** biologics license application; **IND –** investigational new drug application; **GBA-PD** – Parkinson's Disease with GBA mutation; **GD** – Gaucher's Disease; **1.** Excluding China and India; **2.** Expected filing of BLA under accelerated approval pathway in early 2025.

ETV:GAA IS SUPERIOR TO STANDARD OF CARE IN BRAIN AND MUSCLE

Correction of Glycogen Load



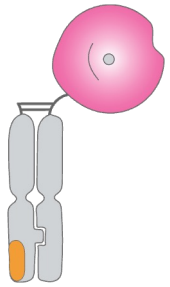
Reduction of Lysosomal Volume and Autophagy in Muscle



ETV:GAA shows superior reduction of key biomarkers compared to standard of care

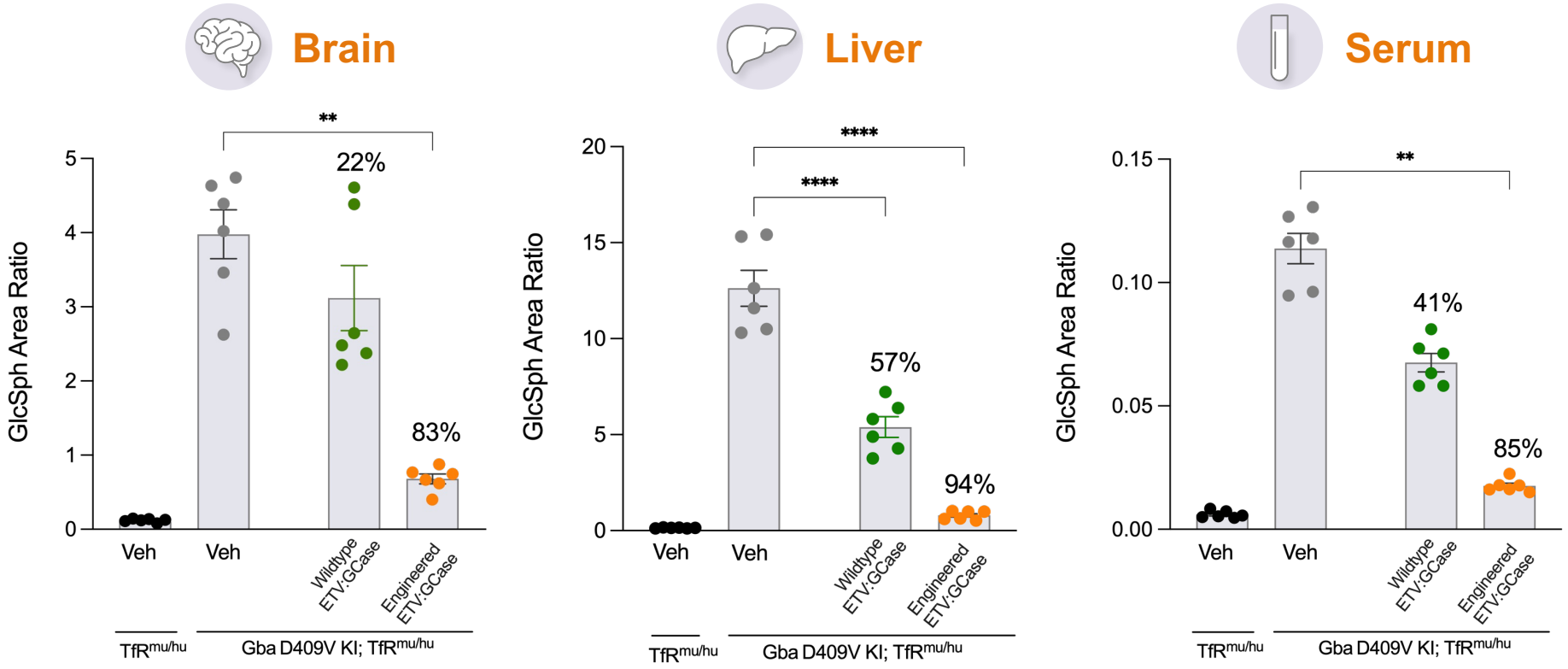
Standard of care: Alg. – alglucosidase alfa; **Aval.** – avalglucosidase alfa-ngpt

ENGINEERED ETV:GCase SHOWS IMPROVED SUBSTRATE REDUCTION



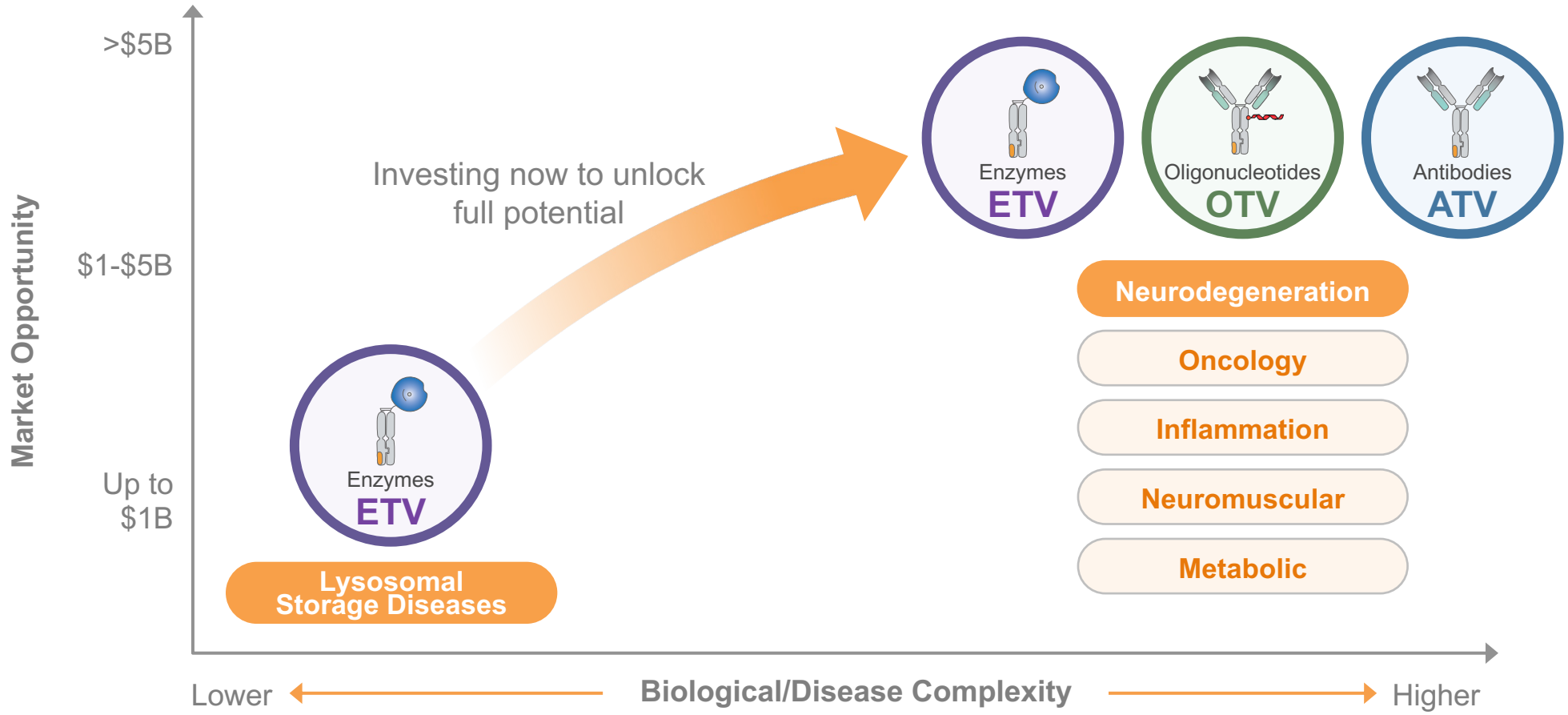
- Coupling GCase with **TV** enables **brain delivery**
- **Engineered** GCase **improves potency** in CNS and periphery

Reduction of GlcSph Substrate in Brain and Periphery



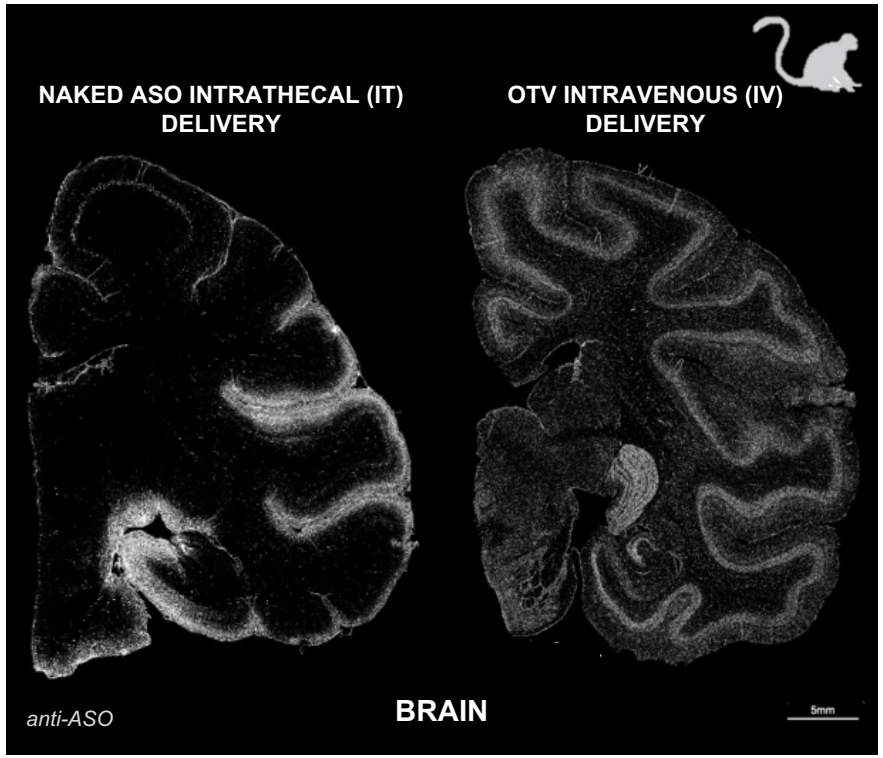
Engineered ETV:GCase may enable highly stable and potent brain-penetrant enzyme replacement therapy for Parkinson's disease and Gaucher

CAPTURING THE FULL POTENTIAL OF THE TRANSPORTVEHICLE™ (TV)

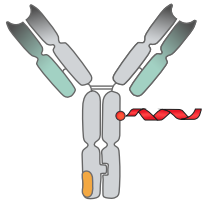


Each TV Franchise has a market potential of $3B+
Expect to file 1-2 INDs per year over the next 3 years

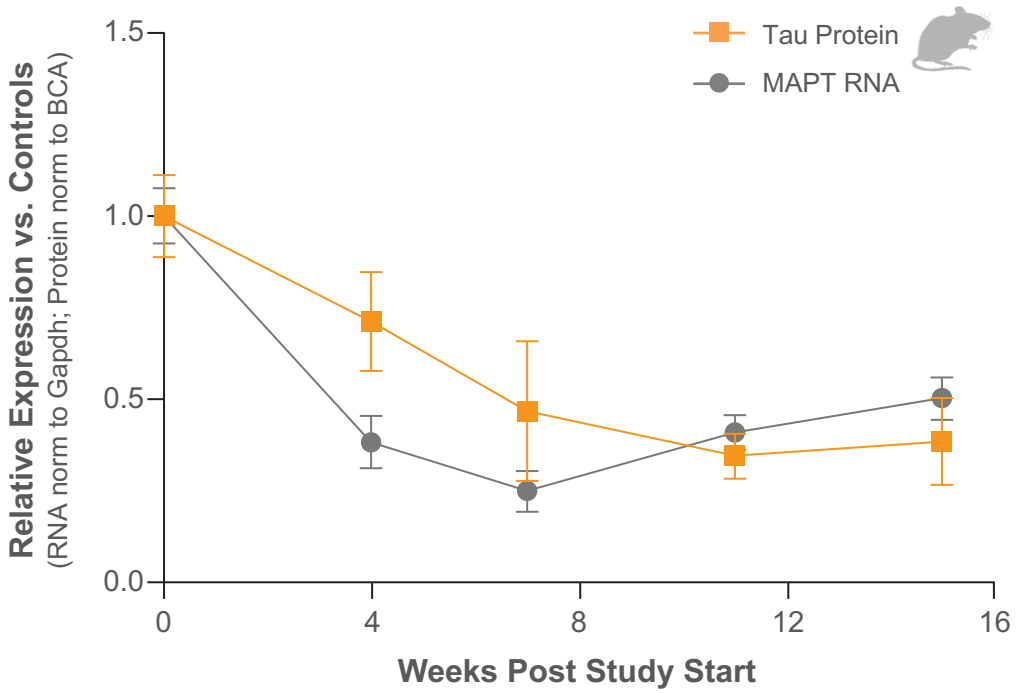
DEVELOPING A FIRST-IN-CLASS ANTI-TAU THERAPY WITH OTV:MAPT



Barker et al. 2024 *Sci. Transl. Med.*



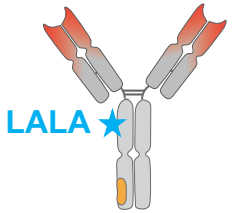
OTV provides **uniform ASO deposition** in the brain with intravenous (IV) delivery



- Brain MAPT RNA and tau protein knockdown persists for >15 weeks following four IV doses of OTV:MAPT
- Extended knockdown duration of action enables less frequent maintenance dosing

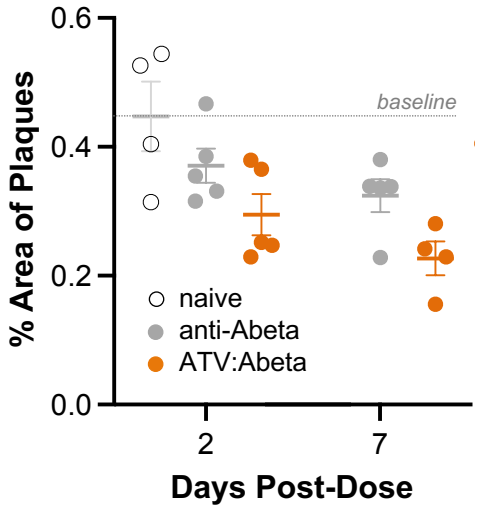
Robust and sustained reduction in tau protein with OTV:MAPT

DEVELOPING A BEST-IN-CLASS ANTI-AMYLOID THERAPY WITH ATV:Aβ

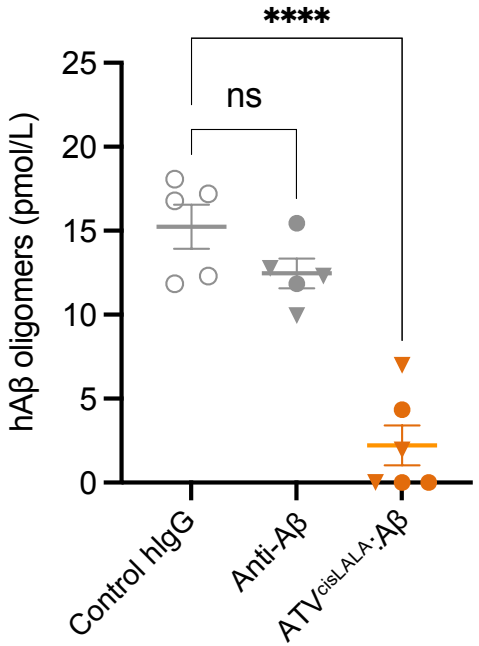


Greater Reductions in Oligomeric Aβ and Plaque and Less ARIA with ATV:Aβ

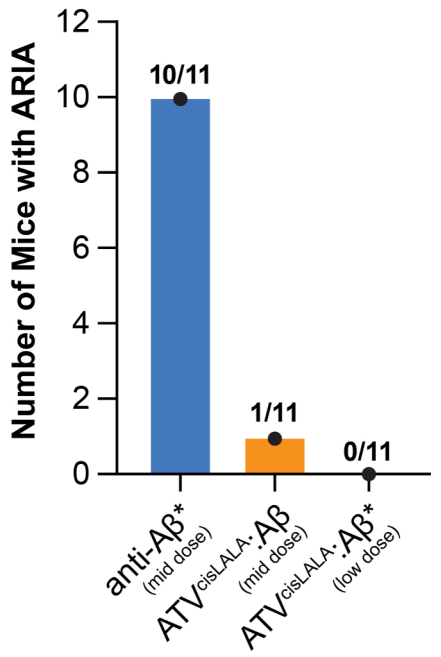
Aβ Plaque Load
Single, mid dose,
APP^{SAA} KI[1]



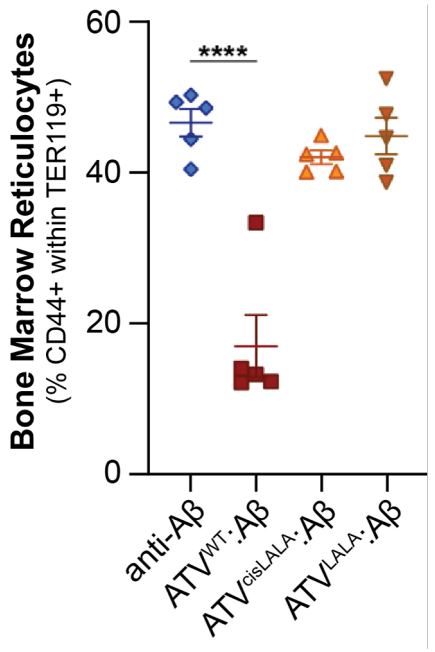
Oligomeric Aβ Load
Single, mid dose,
APP^{SAA} KI[2]



ARIA-Like MRI Events
Weekly dosing x 11 wks,
5xFAD TfR$^{mu/hu}$ KI[3]



Reticulocyte Numbers
Single dose
TfR$^{mu/hu}$ KI[3]



ATV:Aβ may enable better efficacy and safety in treating Alzheimer's disease as compared to conventional anti-Abeta therapy

1. Xia et al., *Molecular Neurodegeneration* 2022; **2.** Denali data on file; **3.** Pizzo et al., *bioRxiv* 2024; *At experimental doses selected to yield equivalent brain exposure and plaque reduction
ATV – Antibody Transport Vehicle; **Aβ** – Amyloid beta; **huIgG** – Human immunoglobulin G; **ARIA** – Amyloid related imaging abnormalities; **MRI** – Magnetic resonance imaging

PORTFOLIO EXECUTION ACROSS AN ARRAY OF RARE AND COMMON DISEASES

	Discovery	IND-Enabling	Clinical	Regulatory Filing
Neurodegeneration		DNL952 (ETV:GAA) Pompe Disease	DNL126 (ETV:SGSH) MPS IIIA (Sanfilippo Syndrome)	Tividenofusp alfa (DNL310)* MPS II (Hunter Syndrome)
Lysosomal Storage Diseases		DNL111 (ETV:GCase) Parkinson's / Gaucher Diseases	DNL593 / TAK-594 (PTV:PGRN) FTD-GRN	
Oncology		DNL622 (ETV:IDUA) MPS I (Hurler Syndrome)	BIIB122 (LRRK2 inhibitor) Parkinson's Disease	
Inflammation		DNL628 (OTV:MAPT) Alzheimer's Disease	Eclitasertib (SAR443122) Ulcerative Colitis	
Neuromuscular		DNL422 (OTV:SNCA) Parkinson's Disease		
Metabolic		DNL921 (ATV:Abeta) Alzheimer's Disease		

ETV Enzyme TransportVehicle™
OTV Oligonucleotide TransportVehicle™
ATV Antibody TransportVehicle™
SM Small Molecule

Broad portfolio across TV franchises with substantial opportunity for expansion

*Expect to file biologics license application under accelerated approval pathway in early 2025

OUR PURPOSE: CROSSING BARRIERS & DEFEATING DEGENERATION

2025 Priorities

PREPARE TO LAUNCH

Potential launch of **tividenofusp alfa in MPS II** (Hunter syndrome)

EXPAND ETV FRANCHISE

Realize potential of TV platform for **lysosomal storage diseases**

ADVANCE TV PORTFOLIO

Progress TV programs for **neurodegeneration** and other indications

Deliver Meaningful Medicines

Dominic, living with MPS II

Seth, living with ALS

Allan, living with PD

Denali Team at AD Walk

Transforming treatment for people with rare and common diseases that impact the brain


THANK YOU