



CROSSING BARRIERS AND DEFEATING DEGENERATION

SEPTEMBER 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.

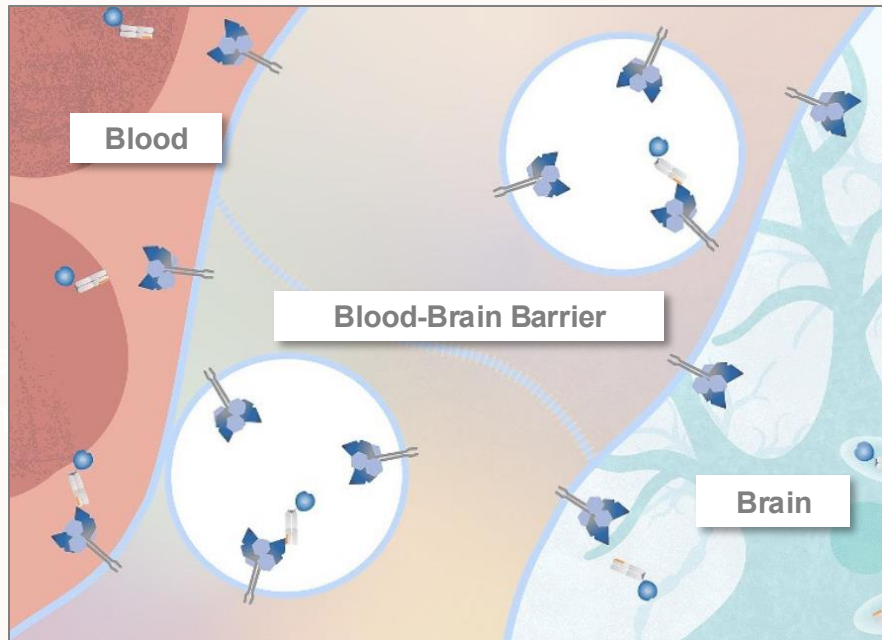
These forward-looking statements speak only as of the date of this presentation and are subject to a number of risks, uncertainties and assumptions, including but not limited to: the risk of the occurrence of any circumstance that could give rise to the termination of Denali’s agreements with its collaborators; 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 annual 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.

OUR PURPOSE: CROSSING BARRIERS & DEFEATING DEGENERATION

Crossing Barriers



Taking on the **blood-brain barrier challenge** to enable delivery of medicines to the brain at scale

Defeating Degeneration



Dominic, living with MPS II



Seth, living with ALS



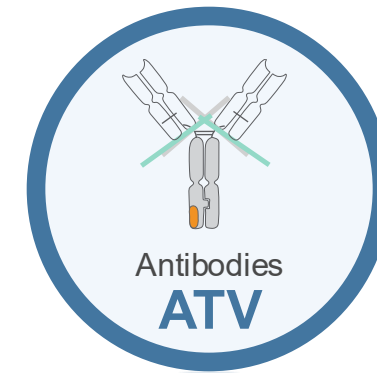
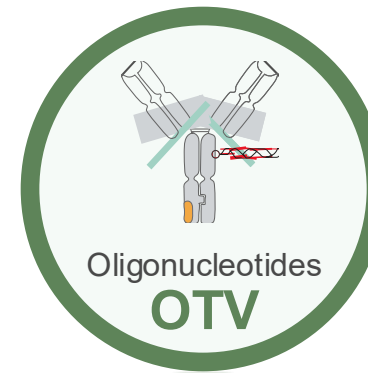
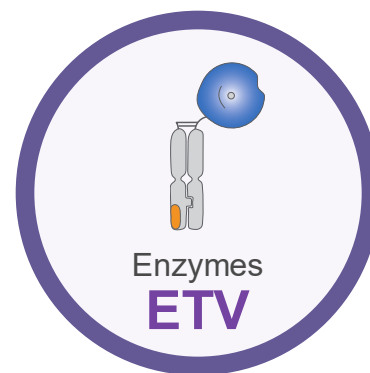
Allan, living with PD



Denali Team at AD Walk

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**

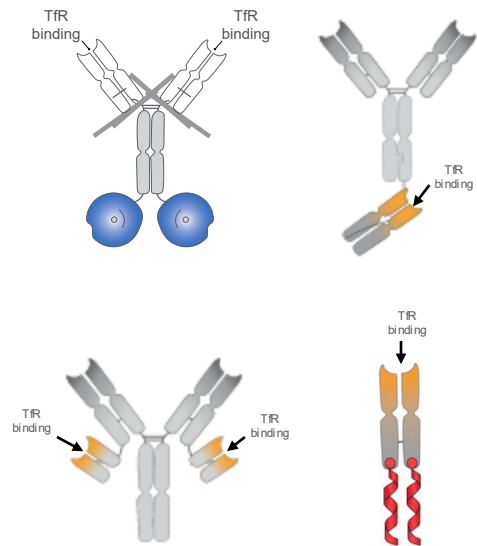
ADVANCING TV PORTFOLIO

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

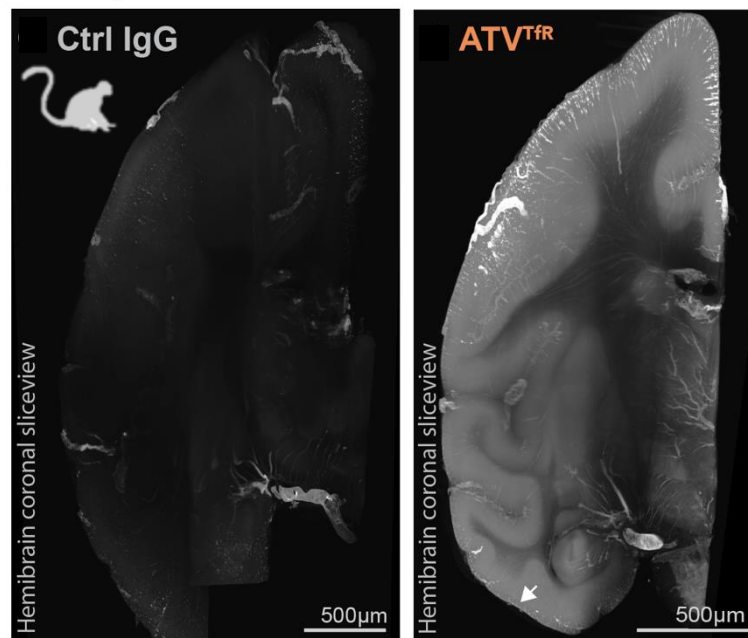
3 Clinical Programs

>10 Preclinical Programs

Leading BBB technology and broadest portfolio of TV-enabled therapeutics

OUR TV PLATFORM IS WELL CHARACTERIZED AND CLINICALLY VALIDATED

Biodistribution

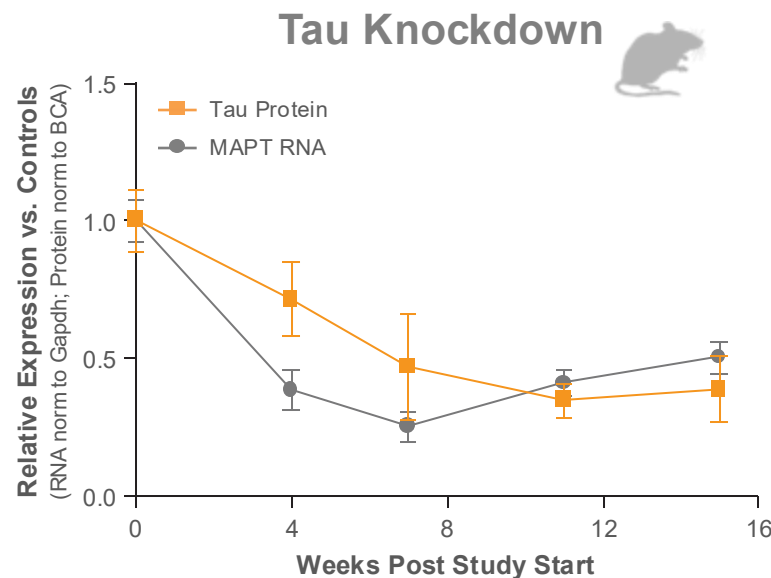


Khoury et al. 2025 *Nature Communications*



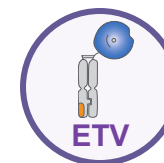
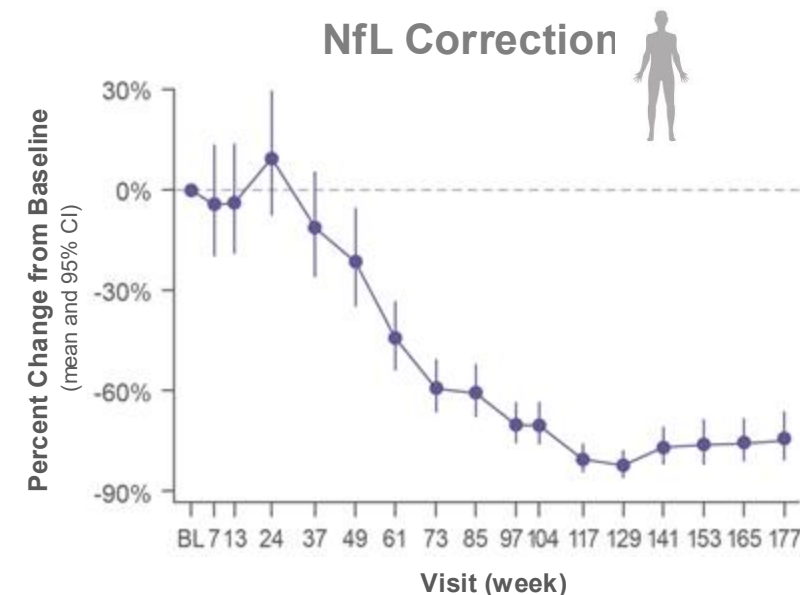
TV provides high and uniform deposition of **ATV** across the brain with systemic delivery

Target Engagement



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

Disease Biomarker

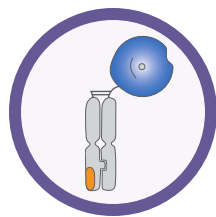


TV enables **ETV:IDS** to reduce serum NfL by >80%, achieving normal levels

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

PREPARING FOR **COMMERCIAL LAUNCH**

Enzyme **TransportVehicle**™ (ETV): Expected Product Launches



Paving the Path with **Tividenofusp alfa**

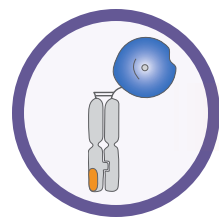
- Market **leading profile** to treat MPS II phenotype spectrum
- Only candidate therapy to **normalize** key biomarkers, CSF HS, urine HS, and NfL, in a lysosomal storage disease
- BLA granted Priority Review with a **PDUFA target action date** of January 5, 2026, for accelerated approval decision
- 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)

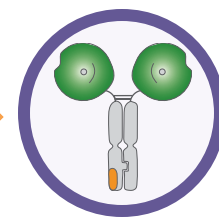
Validating the TransportVehicle™ platform and enabling a broad ETV portfolio

TRANSITIONING TO **COMMERCIAL STAGE**

Enzyme **TransportVehicle**™ (ETV): Expected Product Launches



Apply Learnings



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
- BLA granted Priority Review with a **PDUFA target action date** of January 5, 2026, for accelerated approval decision
- Ongoing Phase 2/3 COMPASS study to support global approval

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

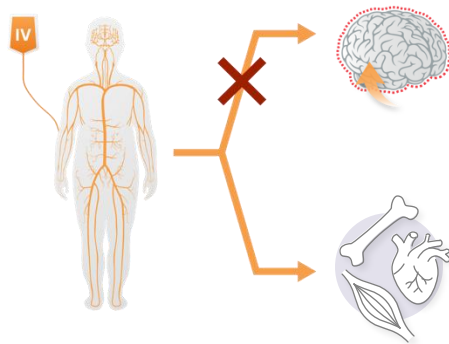
ETV FRANCHISE OPPORTUNITY IN **LYSOSOMAL STORAGE DISEASES**

Addressing High Unmet Need

LSDs are **single-enzyme deficiency** diseases

30,000 people with LSDs worldwide

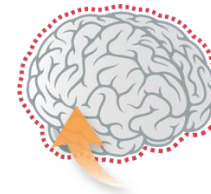
2/3 LSDs with **CNS** manifestations



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



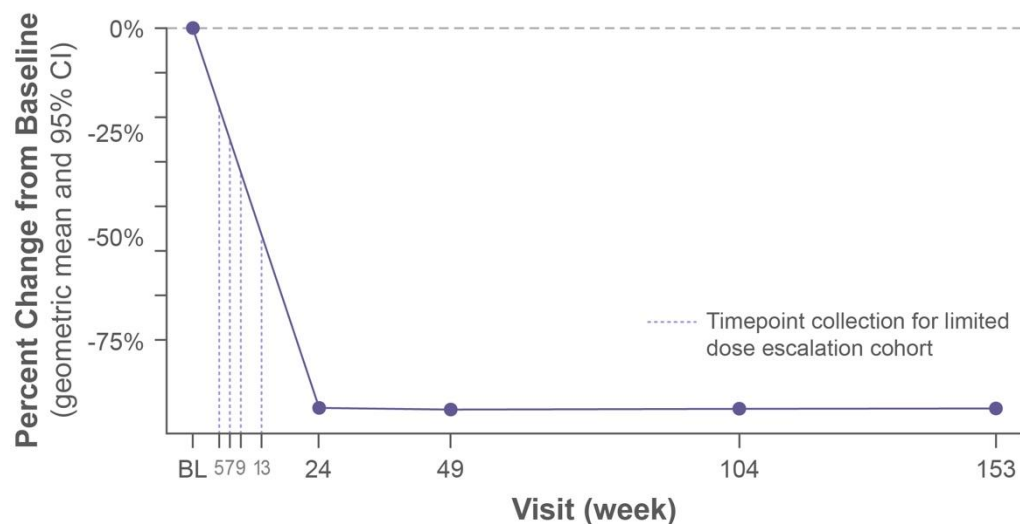
Potential to **enhance
peripheral delivery**

Goal is to treat the
full disease spectrum

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

CSF Heparan Sulfate

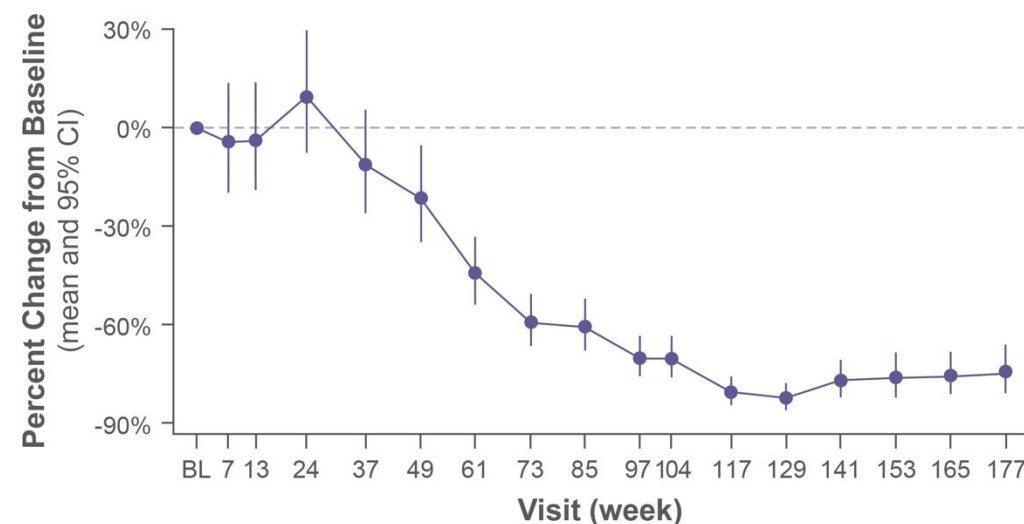
Biomarker of neuronopathic disease



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

Serum NfL

Biomarker of neuronal damage



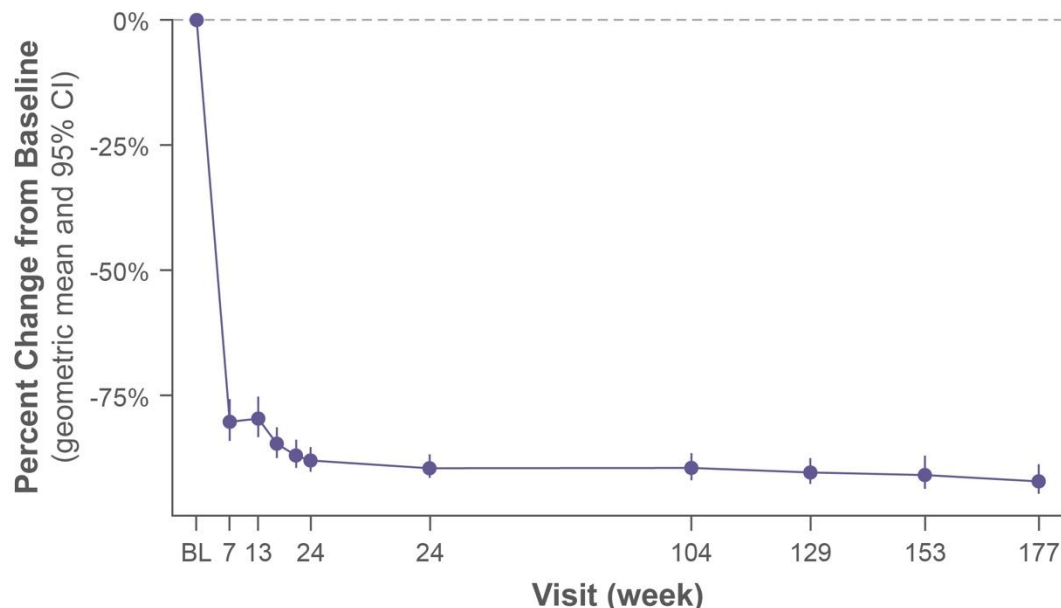
Robust reduction from baseline in serum NfL with the majority of participants reaching the normal range by Week 104

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

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

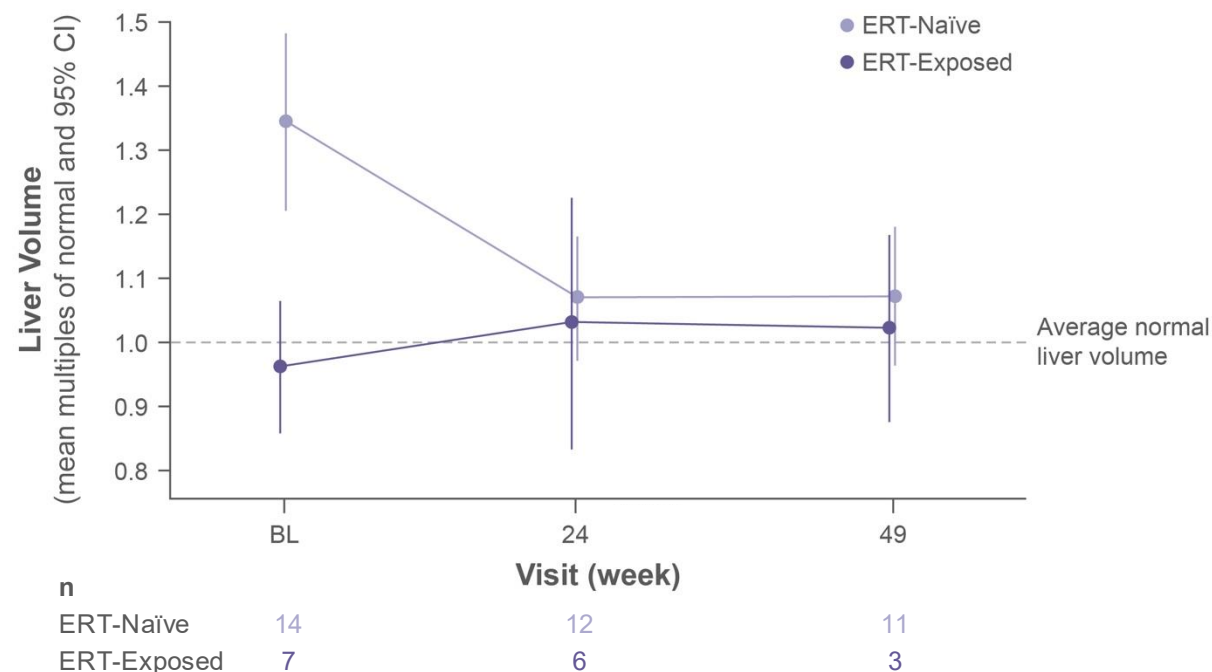
Urine Heparan Sulfate

Biomarker of peripheral disease



Liver Volume

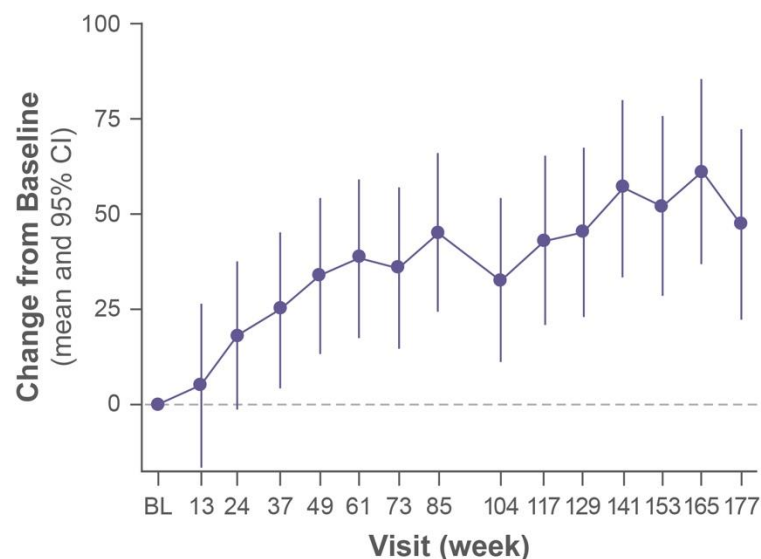
Peripheral clinical outcome



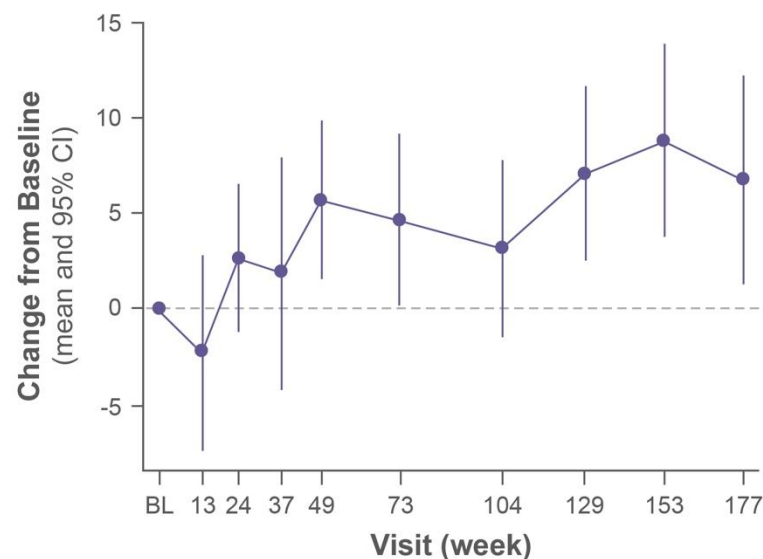
Achievement of normalization of peripheral effects suggests additional effects after switching from idursulfase to treatment with tvidenofusp alfa

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

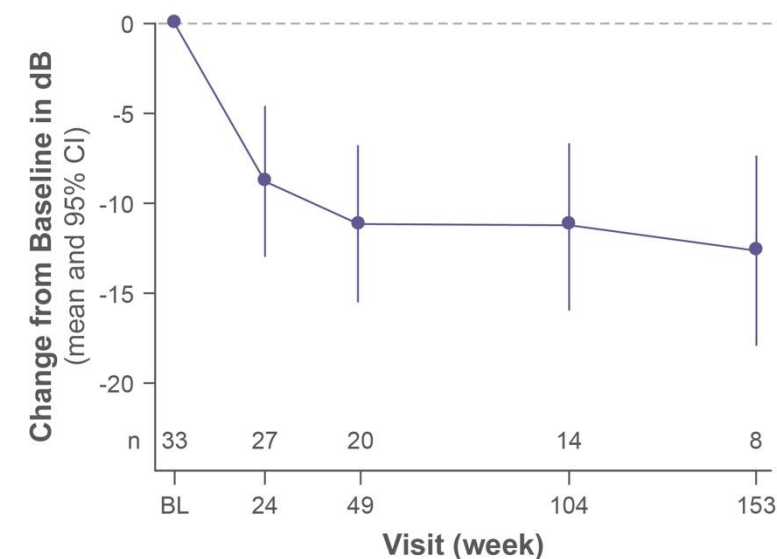
Vineland-3 Adaptive Behavior Raw Composite



BSID-III Cognitive Raw Score



Pure Tone Average



While on tividenufusp 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

TIVIDENOFUSP ALFA PHASE 1/2 IN MPS II: SAFETY

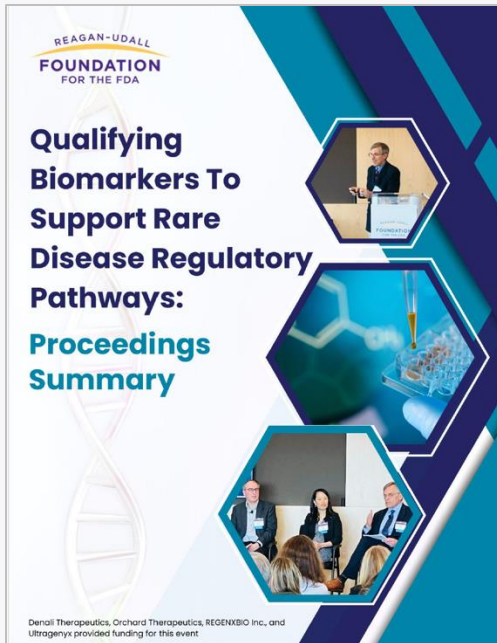
	24-Week Treatment Period (BL to W24), n = 47	All Periods (BL to W261), n = 47
TEAE,^a n (%)	47 (100)	47 (100)
Mild	8 (17.0)	2 (4.3)
Moderate	35 (74.5)	32 (68.1)
Severe ^b	4 (8.5)	13 (27.7)
Serious TEAE, n (%)	6 (12.8)	18 (38.3)
Treatment-Related Serious TEAE	3 (6.4)	3 (6.4)
Fatal TEAE, n (%)	0	0
TEAE 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

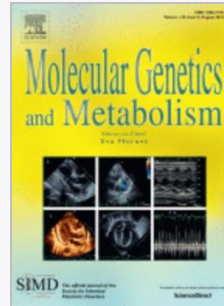
Phase 1/2 safety and clinical data supports broad indication for treatment of full spectrum of MPS II

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.*



Advocates, Academics, Industry, & FDA



Eliza, living with MPS IIIA

Accelerating a Path to New Treatments for Rare Neuropathic MPS Diseases

Carole Ho, MD
Feb 2024, *BioSpace*



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.

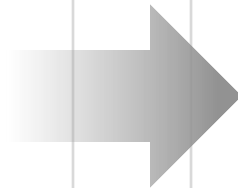
MPS II Landscape

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 tvidenofusp alfa

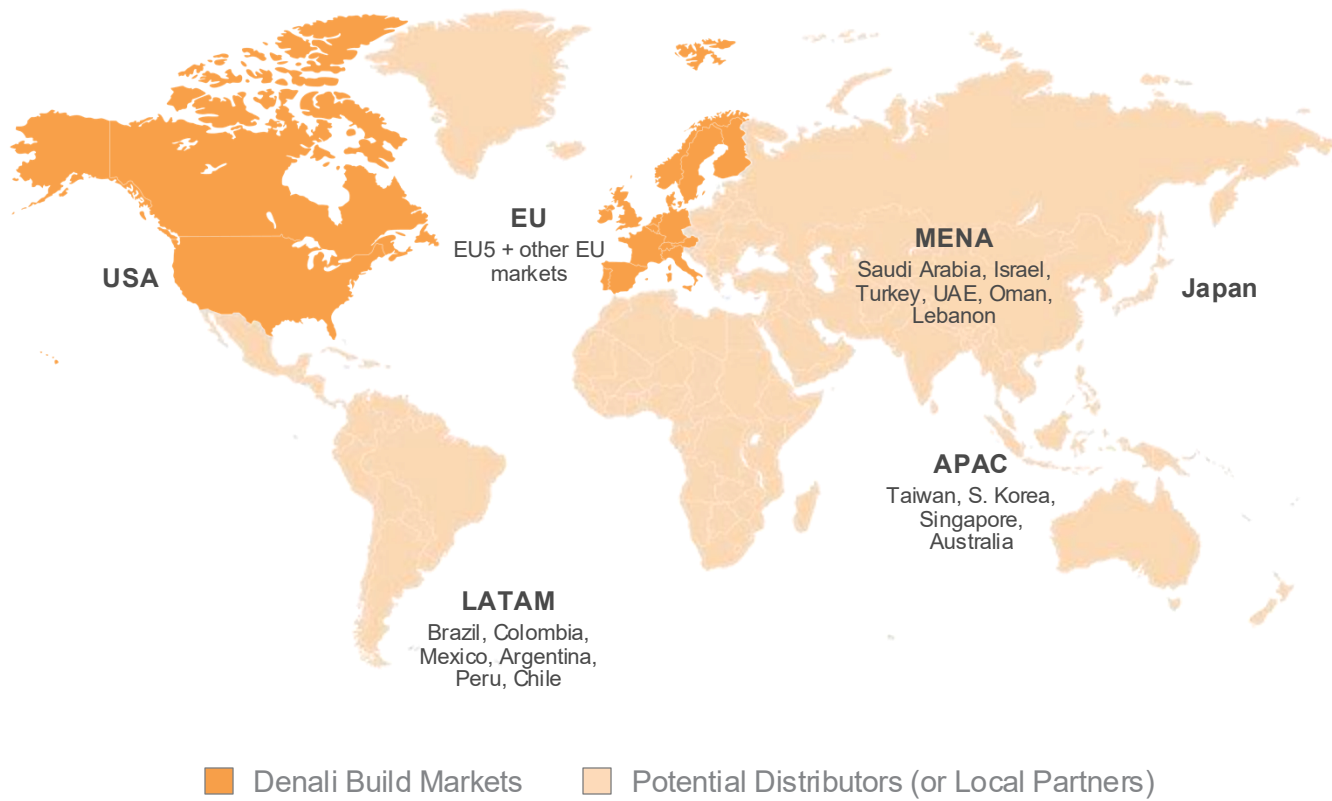
Team

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

Preparing for potential U.S. launch of tvidenofusp alfa for MPS II (Hunter syndrome)

MPS II GLOBAL MARKET OPPORTUNITY

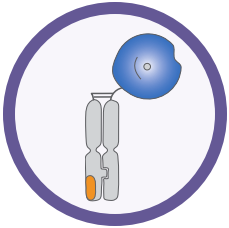
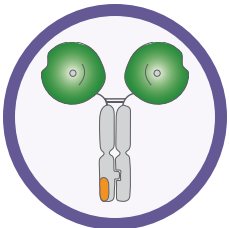
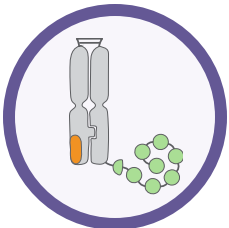
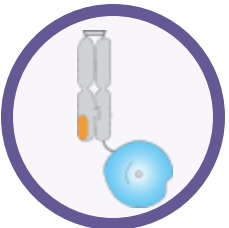
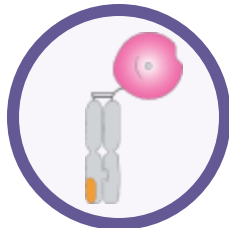
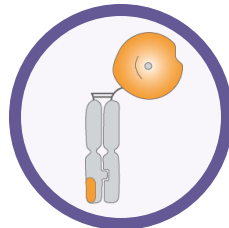
Total Addressable Market ~2,000 Worldwide*



Strategically Build & Collaborate

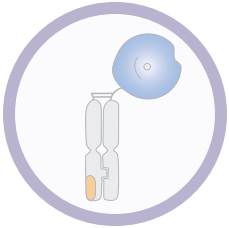
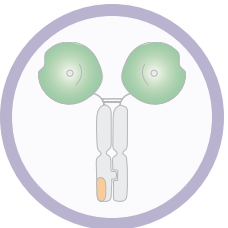
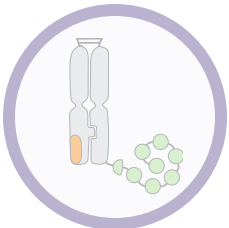
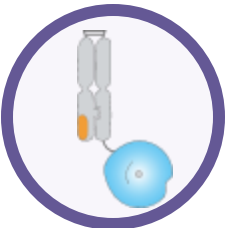
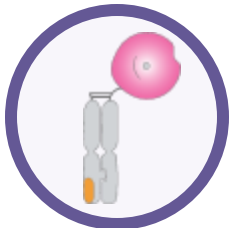
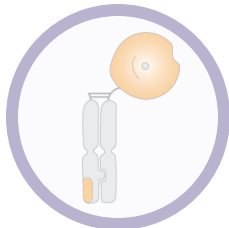
- Invest in key markets with the highest opportunity: **USA / EU**
- Maximize global reach and value with potential distributors (or local partners) to accelerate access to medicine for patients and time to revenue in anchor markets

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

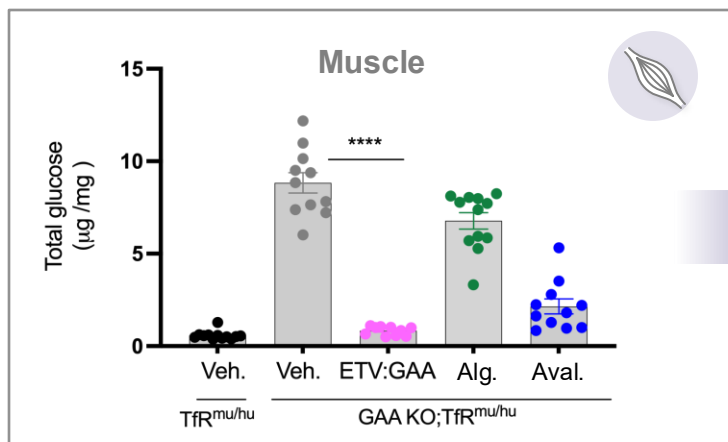
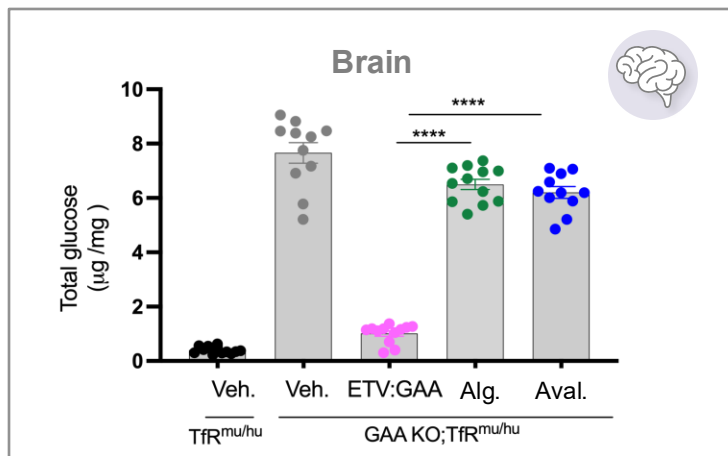
EXPANDING OUR ETV DEVELOPMENT FRANCHISE

	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 WW¹	~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

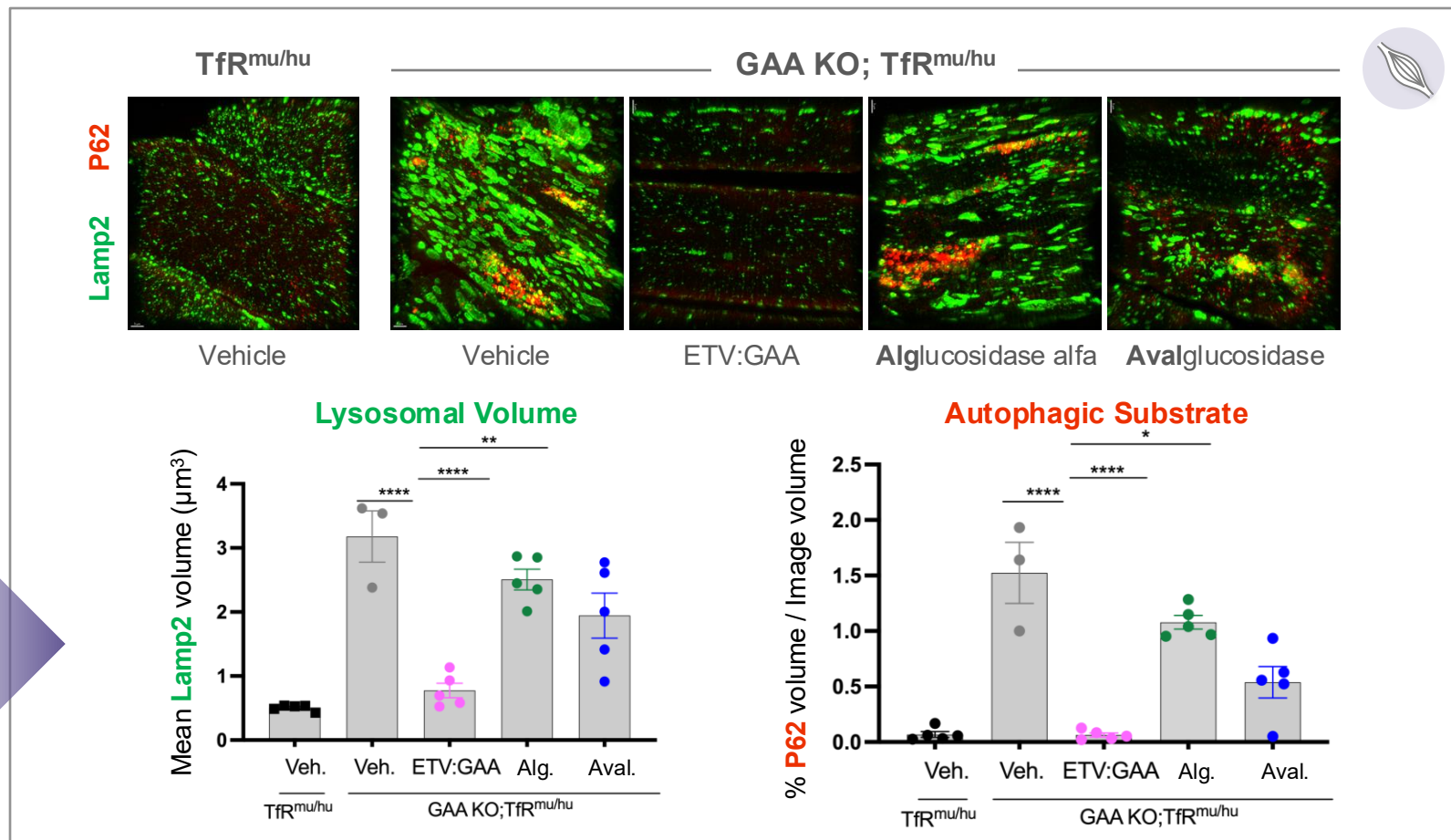
We are developing the next generation of enzyme replacement therapies designed to treat brain *and* body manifestations of serious genetic diseases

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

Correction of Glycogen Load



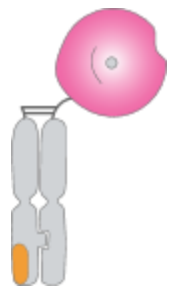
Reduction of Lysosomal Volume and Autophagy in Muscle



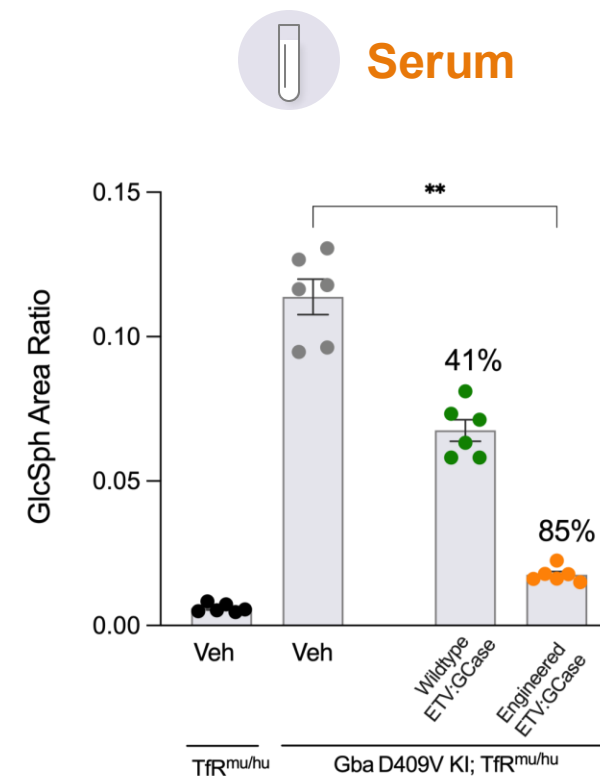
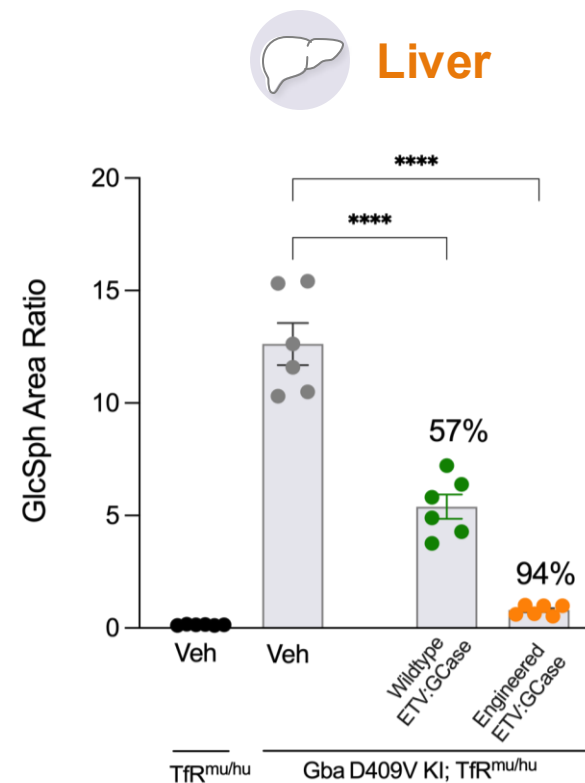
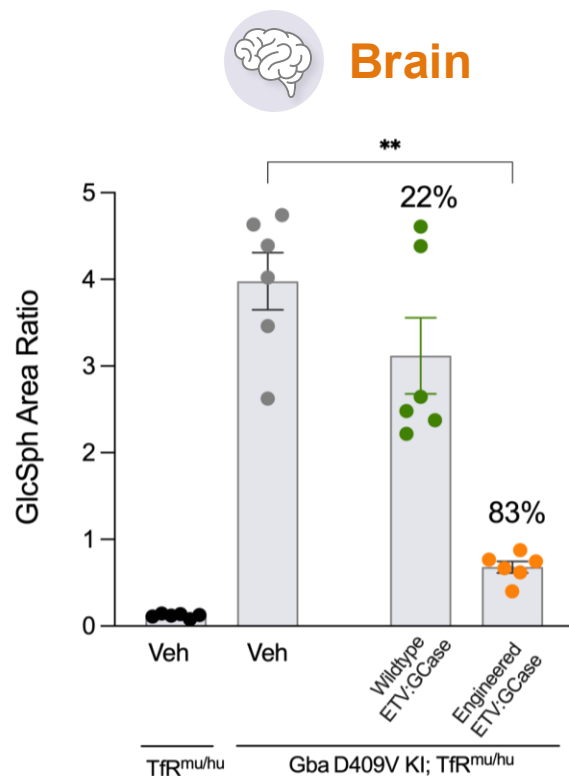
ETV:GAA shows superior reduction of key biomarkers compared to standard of care

ENGINEERED ETV:GCase SHOWS IMPROVED SUBSTRATE REDUCTION

Reduction of GlcSph Substrate in Brain and Periphery

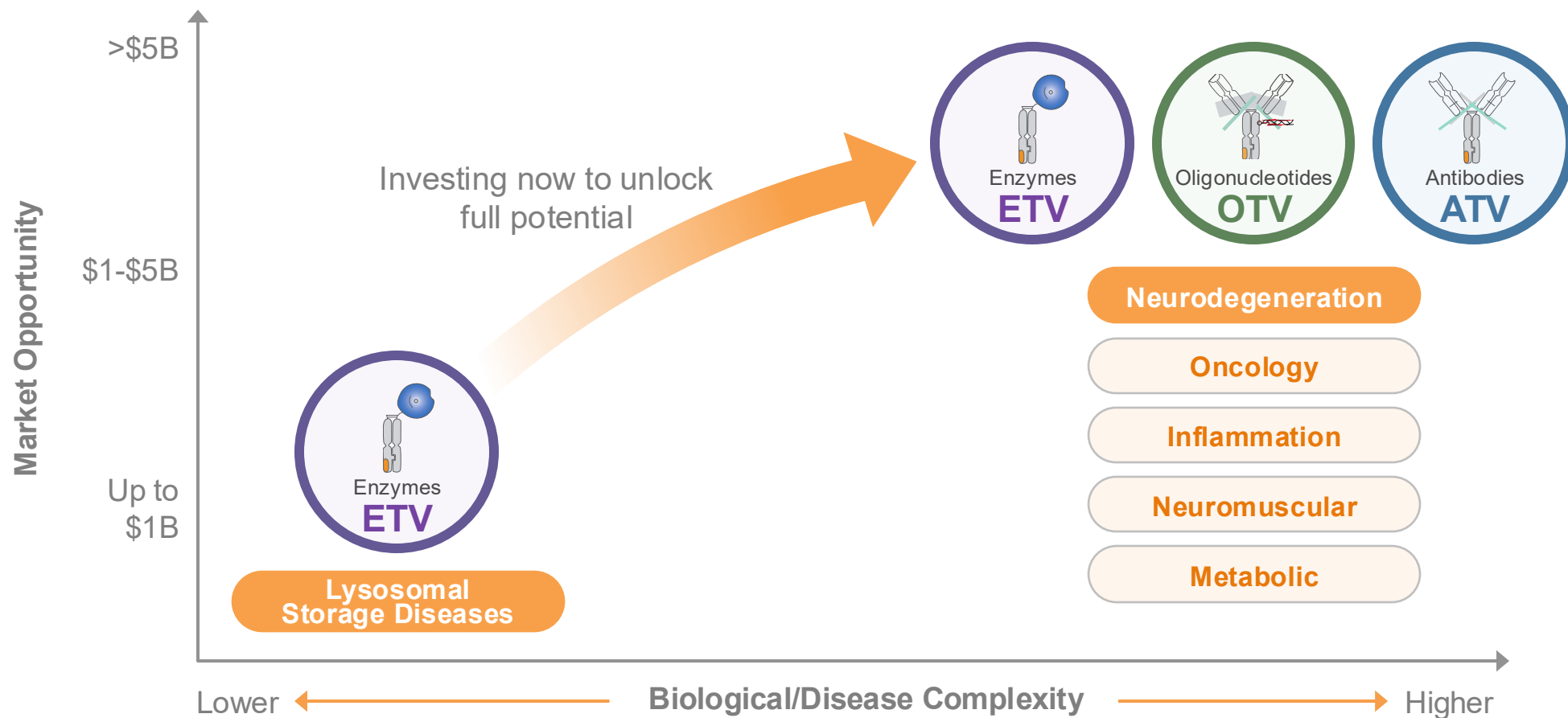


- Coupling GCase with **TV** enables **brain delivery**
- **Engineered** GCase improves **potency** in CNS and periphery



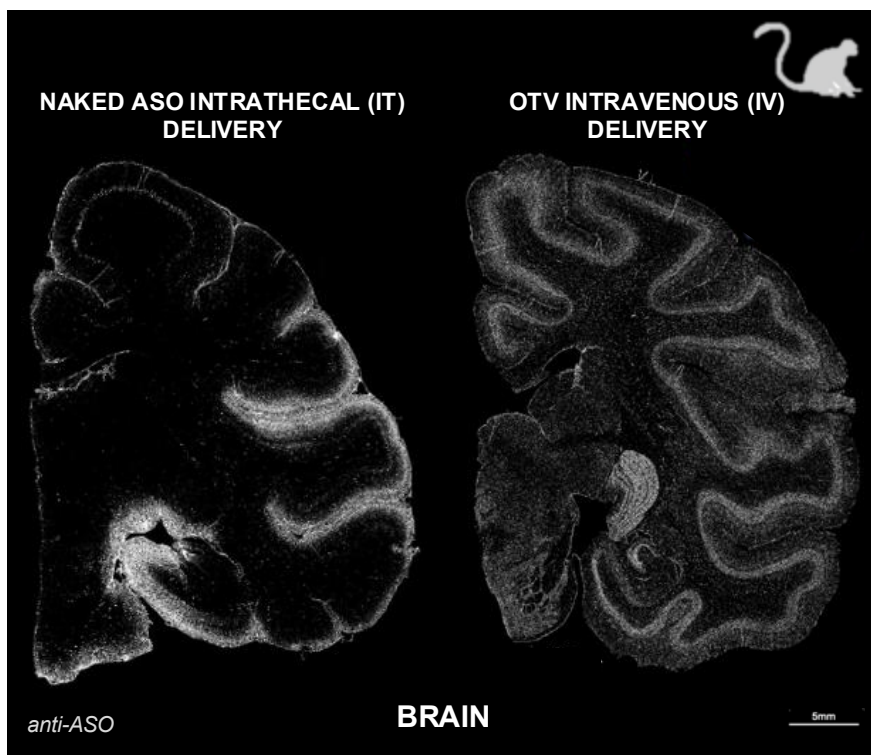
Engineered ETV:GCase may enable highly stable and potent brain-penetrant enzyme replacement therapy for Parkinson's disease and Gaucher

CAPTURING THE FULL POTENTIAL OF THE TRANSPORTVEHICLE™ (TV)

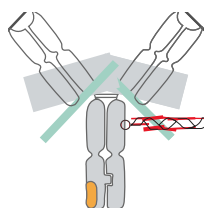


Each TV Franchise has a market potential of \$3B+
Expect to file 1-2 INDs per year over the next 3 years

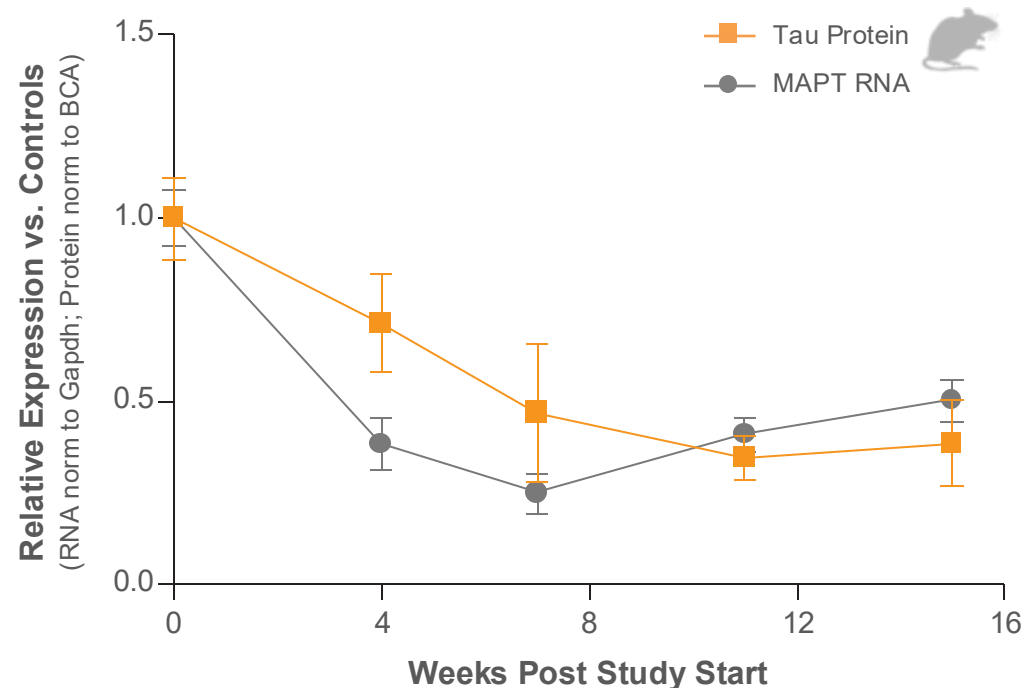
DEVELOPING A **FIRST-IN-CLASS** ANTI-TAU THERAPY WITH **OTV:MAPT**



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



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

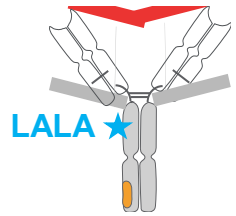


- Brain MAPT RNA and tau protein knockdown persists for >15 weeks following four IV doses of OTV:MAPT
- Extended knockdown duration of action enables less frequent maintenance dosing

Robust and sustained reduction in tau protein with OTV:MAPT

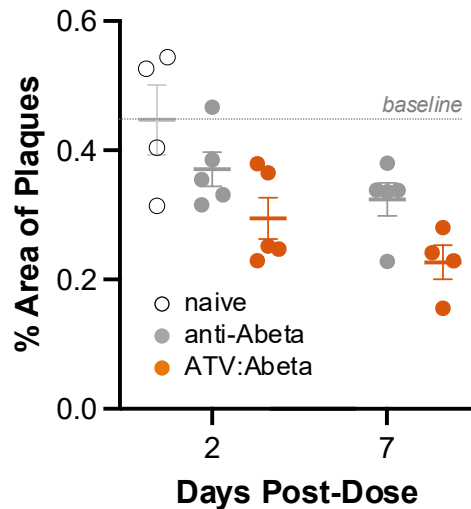
DEVELOPING A BEST-IN-CLASS ANTI-AMYLOID THERAPY WITH ATV:A β

Greater Reductions in Oligomeric A β and Plaque and Less ARIA with ATV:A β



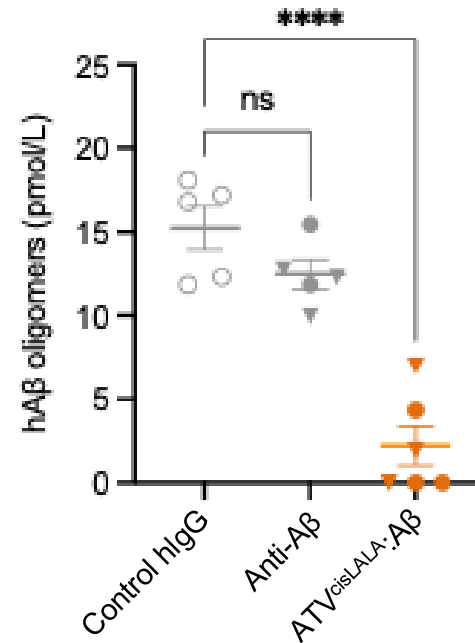
A β Plaque Load

Single, mid dose,
APP^{SAA} KI¹



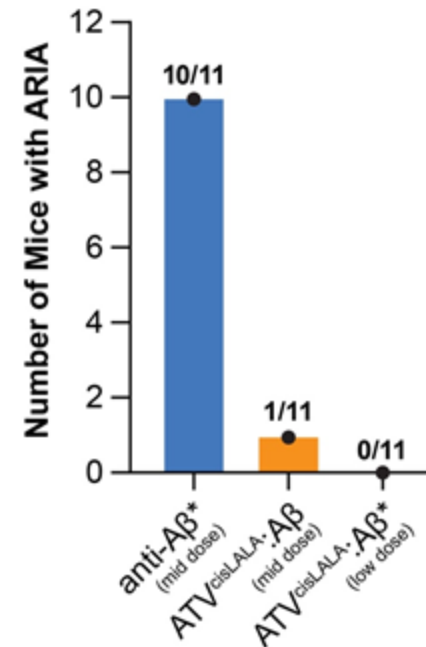
Oligomeric A β Load

Single, mid dose,
APP^{SAA} KI²



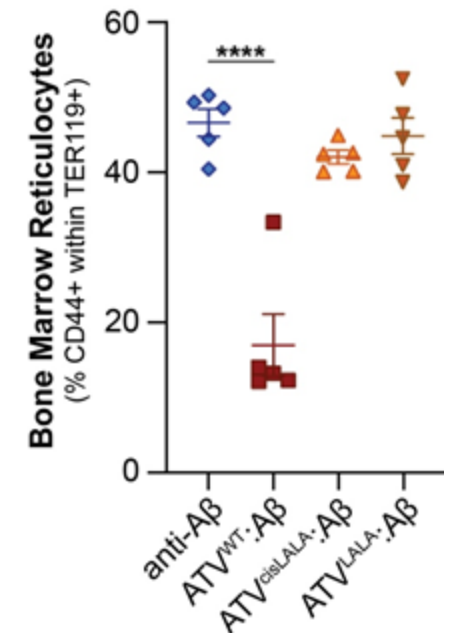
ARIA-Like MRI Events

Weekly dosing x 11 wks,
5xFAD TfR^{mu/hu} KI³



Reticulocyte Numbers

Single dose
TfR^{mu/hu} KI³



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

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:GCas) 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

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

A photograph of the Golden Gate Bridge in San Francisco, viewed from a high vantage point on a cliff. The bridge's red-orange towers and suspension cables are prominent against a backdrop of a blue sky with light clouds. The bridge spans a deep blue bay, with white-capped waves visible at the base of the cliff. The foreground shows a rugged, brownish-red cliffside with sparse green vegetation.

THANK YOU