

**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

**Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934**

Date of Report (Date of earliest event reported):

December 4, 2025

Denali Therapeutics Inc.

(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation)

001-38311
(Commission
File Number)

46-3872213
(I.R.S. Employer
Identification No.)

**161 Oyster Point Blvd.
South San Francisco, California 94080**
(Address of principal executive offices, including zip code)

(650) 866-8547
(Registrant's telephone number, including area code)

Not Applicable
(Former name or former address, if changed since last reports)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol (s)	Name of each exchange on which registered
Common Stock, par value \$0.01 per share	DNLI	Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Item 7.01 Regulation FD Disclosure.

On December 4, 2025, Denali Therapeutics Inc. ("Denali" or the "Company") hosted its 2025 Investor Day, during which members of the Company's executive management team provided updates on Denali's development programs and upcoming milestones. A copy of the presentation made available in connection with the 2025 Investor Day is furnished as Exhibit 99.1 to this Current Report on Form 8-K.

The information contained in this Item 7.01, including Exhibit 99.1, is being furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference into any filing made under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 8.01 Other Events

On December 4, 2025, Denali provided the following key updates on programs across its development pipeline at its 2025 Investor Day.

Tividenofusp Alfa (ETV:IDS) — MPS II (Hunter Syndrome)

The Biologics License Application ("BLA") for tividenofusp alfa remains under review with the U.S. Food and Drug Administration ("FDA"), with a Prescription Drug User Fee Act ("PDUFA") target action date of April 5, 2026. A Late Cycle Meeting with the FDA has been completed and labeling discussions are underway. Commercial readiness activities are progressing. Enrollment in Cohort A (neuronopathic) of the Phase 2/3 COMPASS study of tividenofusp alfa is expected to complete in December 2025.

Tividenofusp alfa received Rare Pediatric Disease Designation ("RPDD") status for the treatment of Hunter syndrome in January 2019. Denali is in ongoing dialogue with the FDA related to the eligibility of tividenofusp alfa to receive a Rare Pediatric Disease Priority Review Voucher ("PRV") upon approval¹. Because Denali submitted a filing of its intent to request a PRV after the initial BLA submission, based on discussions with the FDA, the Company may not be eligible to receive the PRV. Therefore, Denali is not including any potential future proceeds from the sale of a PRV in its financial planning. Denali continues to work with the FDA and the FDA will determine whether to award a PRV upon approval of tividenofusp alfa.

DNL126 (ETV:SGSH) — MPS IIIA (Sanfilippo Syndrome Type A)

The Phase 1/2 study of DNL126 remains on track for completion in 2026, supporting a potential accelerated approval pathway and commercial launch by the end of 2027. Denali plans to present initial Phase 1/2 data at the 2026 WORLD Symposium. Phase 3 planning is ongoing.

TAK-594/DNL593 (PTV:PGRN) — Frontotemporal Dementia (GRN Mutation)

The Phase 1/2 study of TAK-594/DNL593 is ongoing with screening closed in Cohort B. Initial FTD-GRN patient data are expected in 2026.

¹ Congress created Section 529 of the Food, Drug, & Cosmetic Act to incentivize drug development for rare diseases in children. Under Section 529, the FDA administers the RPDD and PRV programs.

DNL952 (ETV:GAA) — Pompe Disease

The Investigational New Drug ("IND") application for the Phase 1 study of DNL952 has been placed on clinical hold. The FDA requested a protocol amendment to include a lower starting dose, revised inclusion criteria, certain safety monitoring commitments, and stopping rules. These requests are related to preclinical hypersensitivity reactions observed in GAA mouse models, which are commonly observed across all GAA enzyme replacement therapies in mice. The FDA did not request additional nonclinical studies. Denali has submitted a response to the FDA, and pending FDA feedback, anticipates minimal delays in the initiation of the Phase 1 study. As part of our global development strategy for DNL952, Denali is on track to submit a Clinical Trial Application ("CTA") in Europe in the first half of 2026.

DNL628 (OTV:MAPT) — Alzheimer's Disease

A CTA for DNL628 has been submitted, and a Phase 1b study in patients with Alzheimer's disease is expected to begin in the first half of 2026.

DNL921 (ATV:Abeta) — Alzheimer's Disease

A regulatory submission for DNL921 is planned for the first half of 2026 to initiate clinical studies.

BIIB122 (LRRK2 Inhibitor, partnered with Biogen)

The Phase 2b LUMA study for BIIB122 in patients with early-stage Parkinson's disease is expected to read out in 2026. The BEACON study in patients with LRRK2-associated Parkinson's disease continues to enroll.

Eclitaserib (SAR443122, RIPK1 Inhibitor, partnered with Sanofi)

Phase 2 data in ulcerative colitis are expected in 1H 2026. Development is led solely by Sanofi.

Forward-Looking Statements

Certain of the statements made in this report are forward looking, such as those relating to: the progress, success costs and anticipated timing of our development activities, preclinical studies and clinical trials; the timing or likelihood of regulatory filings and approvals; and our ability to obtain and maintain regulatory approval of our product candidates, and any related restrictions and limitations. Actual results or developments may differ materially from those projected or implied in these forward-looking statements. More information about the risks and uncertainties faced by Denali may be found in Denali's Annual and Quarterly Reports filed on Forms 10-K and 10-Q filed with the Securities and Exchange Commission (the "SEC") on February 27, 2025, and November 6, 2025, respectively, and 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. 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.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Denali Therapeutics 2025 Investor Day Presentation
104	Cover Page Interactive Data File (formatted as Inline XBRL)

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

DENALI THERAPEUTICS INC.

Date: December 4, 2025

By: /s/ Alexander O. Schuth
Alexander O. Schuth, M.D.
Chief Operating and Financial Officer

The Denali logo is displayed in a white, sans-serif font. The letter 'A' is stylized with a diagonal slash through it. The background of the slide is a photograph of a snow-capped mountain range under a blue sky with light clouds.

/ December 4, 2025

Welcome to Denali Therapeutics 2025 Investor Day

©2025 Denali Therapeutics, Inc.

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 and manufacturing 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.



Leading a New Era of BBB-Crossing Therapeutics

/ Key Messages

Ryan Watts, Ph.D.
Chief Executive Officer

Our Purpose



**Deliver the power of biotherapeutics to the whole body, including the brain,
transforming life for people living with serious diseases**

DENALI

Key Messages for Today

Best-in-Class Blood-Brain Barrier (BBB) Platform

- ▶ TransportVehicle™ is the most validated, differentiated, and clinically proven technology enabling systemic delivery of biologics to the brain and other hard to target tissues

Ready to Capture \$1B+ Market Opportunity with Two Near-Term Launches

- ▶ Launch of tvidenofusp alfa (DNL310) in 2026 and DNL126 in 2027 lay the commercial foundation for ETV franchise and leadership in next-generation enzyme replacement therapy

Deep Pipeline Across High-Value Therapeutic Areas

- ▶ Broad clinical stage pipeline, including two potential best-in-class TfR-enabled programs for Alzheimer's disease, provides several near-term high-value milestones

Efficient Execution and Capital Allocation

- ▶ Well-capitalized and increasingly efficient capital allocation and execution timelines for long-term value creation

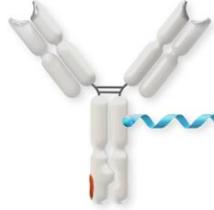
A New Class of Biotherapeutics for the Whole Body, Including the Brain

Enzyme TV (ETV)



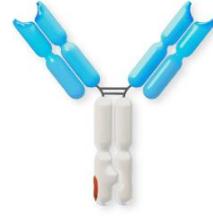
Enzyme replacement therapy
for the body and brain

Oligonucleotide TV (OTV)



Genetic medicines for the
brain, delivered systemically

Antibody TV (ATV)



Brain-penetrant immunotherapy
for a wide range of diseases

Our **TransportVehicle™ (TV) Platform** enables TfR-mediated brain biodistribution and enhanced tissue delivery of biotherapeutics throughout the body with systemic administration

TfR – Transferrin receptor

Our Broad Therapeutic Portfolio

Lysosomal Storage Disorders

Molecule	Indication	Stage
tividenofusp alfa (ETV:IDS)	MPS II	Regulatory Filing
DNL126 (ETV:SGSH)	MPS IIIA	Phase 1/2
DNL593 (PTV:PGRN)	FTD-GRN ¹	Phase 1/2
DNL952 (ETV:GAA)	Pompe	Phase 1 ^{2,3}
DNL111 (ETV:GCCase)	Gaucher	IND-Enabling
DNL622 (ETV:IDUA)	MPS I	IND-Enabling



>30,000 Patients WW⁴

\$500M-\$1B+ per Indication

Common Neurodegenerative Diseases

Molecule	Indication	Stage
BIIB122 LRRK2 Inhibitor	PD	Phase 2b
DNL628 OTV:MAPT (tau)	AD	Phase 1b ²
DNL921 ATV:Abeta	AD	IND-Enabling
DNL111 ETV:GCCase	PD	IND-Enabling
DNL422 OTV:SNCA	PD	IND-Enabling



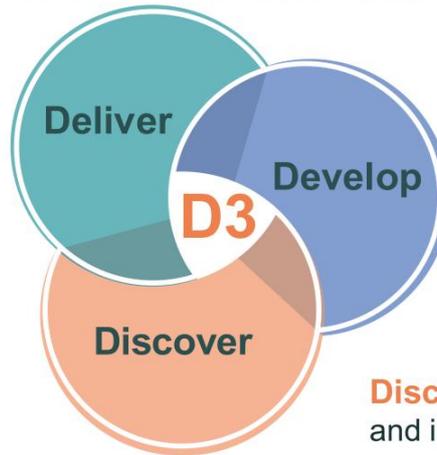
>40M Patients WW⁴

>\$5B per AD/PD Indication

1. FTD-GRN has a lysosomal phenotype and can be considered a rare lysosomal storage disease; 2. Regulatory applications filed to begin human clinical studies; 3. Protocol amended and response to FDA submitted regarding clinical hold; 4. Denali estimates of worldwide aggregate prevalence, excluding China and India for the lysosomal storage disorders; MPS – Mucopolysaccharidosis; PD – Parkinson's disease; AD – Alzheimer's disease

Our D3 Strategy for Sustainable Value Creation

Deliver the blockbuster potential of **ETV**, **ATV**, **OTV** franchises



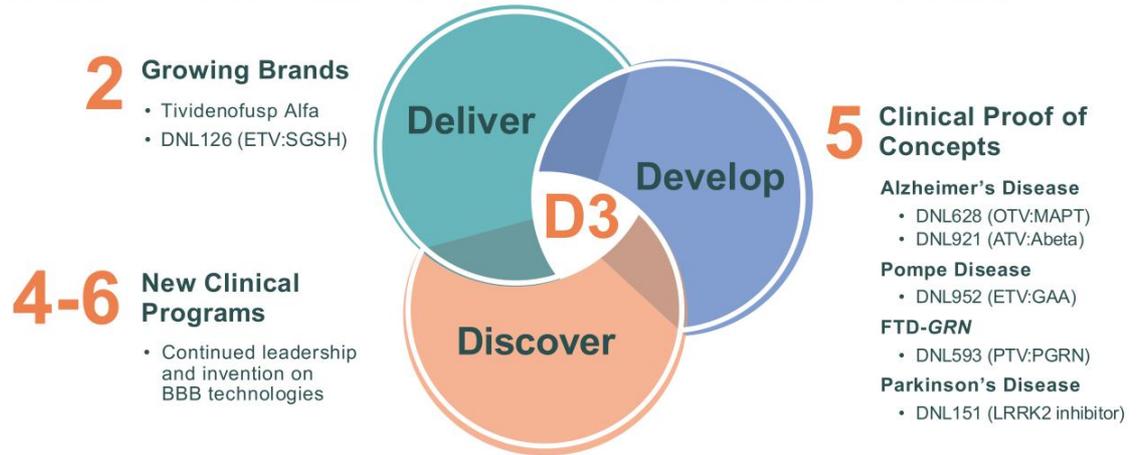
Develop first or best-in-class **TV** therapeutics

Discover new **TV** targets and indications

D3 Strategy: Discover, Develop and Deliver on the TransportVehicle™ platform opportunity

D3 – Deliver, Develop, Discover; ETV – Enzyme Transport Vehicle™; ATV – Antibody TransportVehicle™; OTV – Oligonucleotide TransportVehicle™; TV – TransportVehicle™

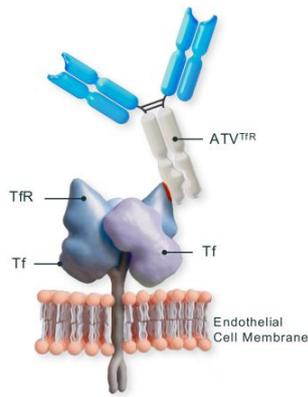
On Track to Deliver Denali’s D3X3 Goals: 3-Year Outlook



Delivering near-term value from planned product launches, advancing a robust pipeline and capturing the full potential of the TransportVehicle™

D3 – Deliver, Develop, Discover; BBB – Blood-brain barrier

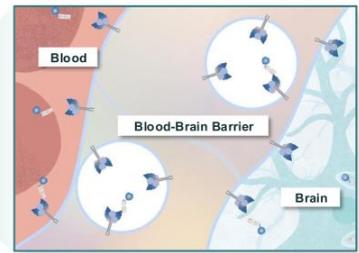
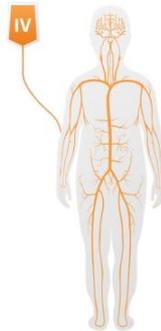
Treating the Whole Body, Including the Brain



Transferrin receptor (TfR) is highly expressed at the blood–brain barrier for natural iron transport

TfR – Transferrin receptor

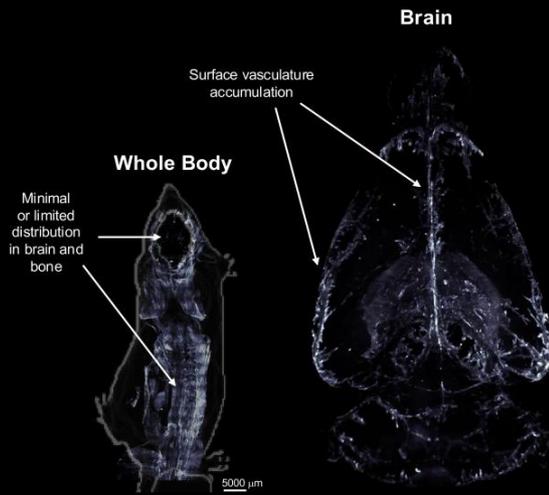
Our **TransportVehicle™** leverages TfR to enable **brain delivery** of biotherapeutics



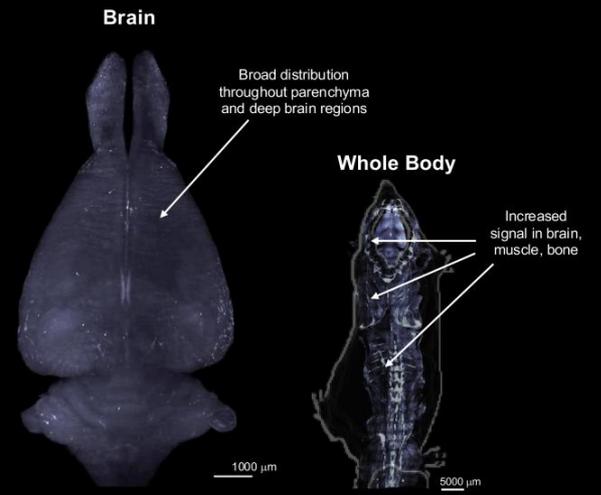
TfR may also facilitate delivery into tissues such as **bone**, **cartilage**, and the **heart**

TransportVehicle™ Distributes to Whole Body, Including Brain

Standard Antibody (IgG)



TV-enabled Antibody (TfR)

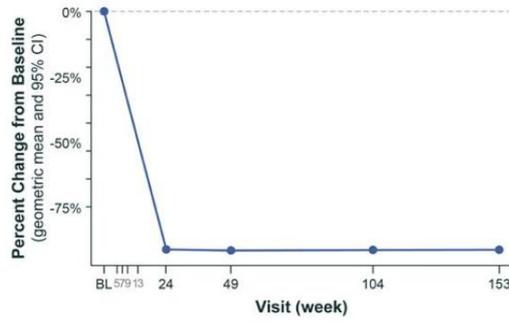


TransportVehicle™ Clinical Effects: MPS II Phase 1/2 Study



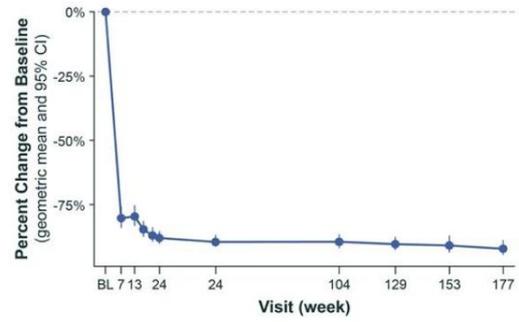
Brain

CSF Heparan Sulfate
Biomarker of CNS disease



Body

Urine Heparan Sulfate
Biomarker of peripheral disease

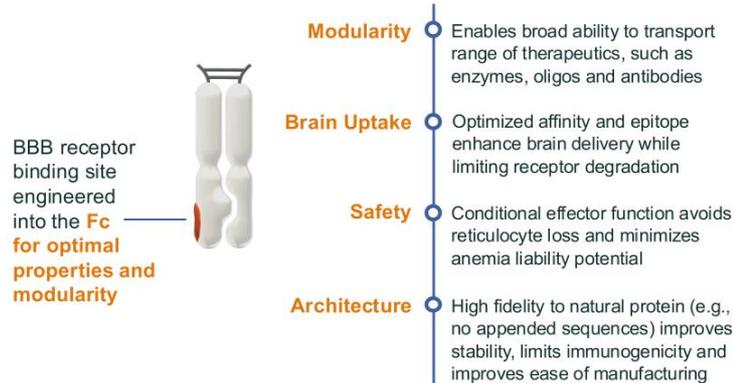


Our ETV franchise is clinically validated, derisking the broader TV platform

Source – WORLD 2025; MPS II – Mucopolysaccharidosis Type II; CSF – Cerebrospinal fluid; CNS – Central nervous system; ETV – Enzyme Transport Vehicle™

Our TransportVehicle™ Platform Sets the Bar for BBB Delivery

Our Fc-based TransportVehicle™ (TV) Is Designed & Engineered to Optimize Brain Delivery



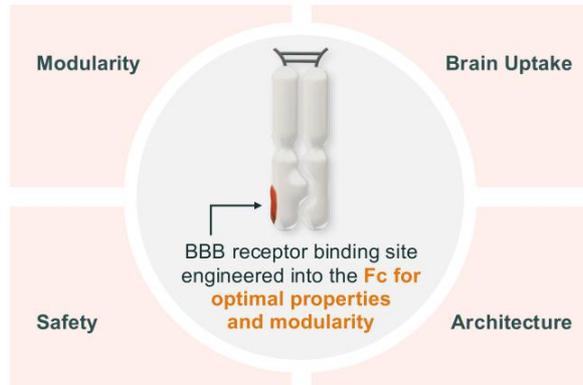
Industry Leading Platform

- 1st Potential FDA-approved TfR therapeutic to cross the BBB
- 5 Clinical programs*
- Demonstrated ability to correct neurodegeneration (e.g., NFL)
- >10 Preclinical programs
- >200 Subjects dosed
- >11,000 Doses administered
- >20 Publications in last 5 years
- >350 Patents/Applications

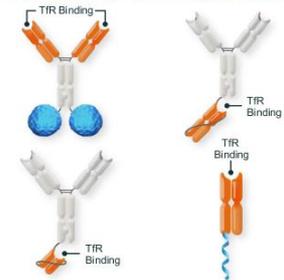
*Includes regulatory applications to begin clinical studies for DNL628 and DNL952; BBB – Blood-brain barrier; TfR– Transferrin receptor; NFL – Neurofilament light chain

TransportVehicle™ has Demonstrated Best-in-Class Properties

Our Fc-based TransportVehicle™ (TV) Is Designed & Engineered to Optimize Brain Delivery



Conventional Fab Approaches



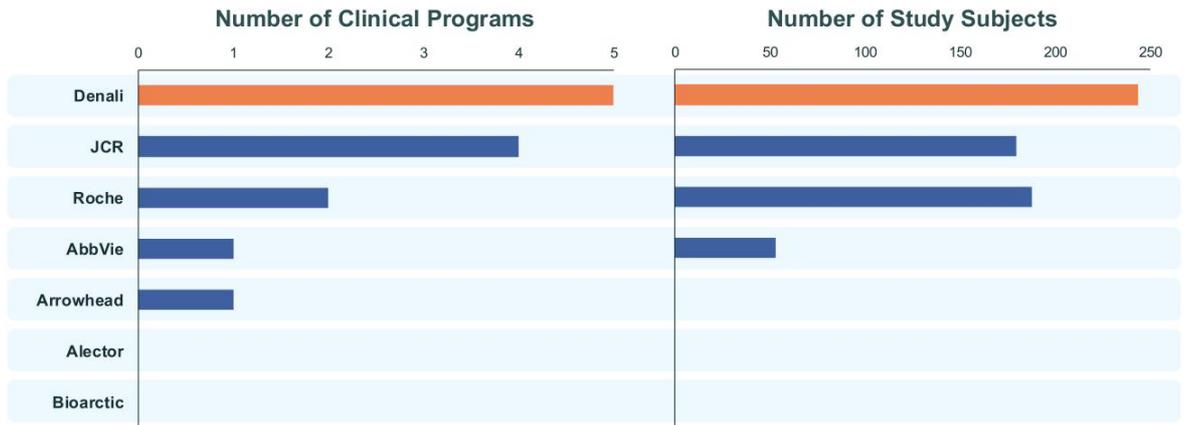
Linker chemistry adversely affects stability

Full effector function increases anemia risk

High affinity, bivalent binding leads to suboptimal brain biodistribution

Low fidelity to natural protein increases risk of immunogenicity

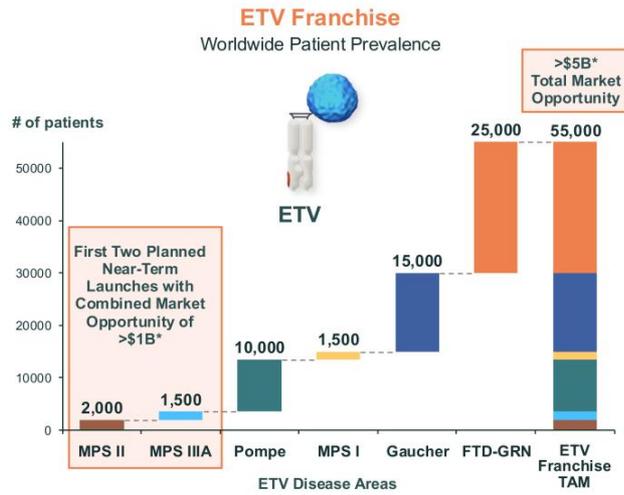
TransportVehicle™ Has Broad Clinical Experience



Denali's TV is the most clinically validated BBB technology with over 11,000 doses administered, and including patients who have been continuously dosed for more than 5 years

Includes companies with TTR-based platforms and is not a comprehensive list. Peer company estimates are based on publicly available sources, i.e., investor presentations, medical congress presentations, and actual number of participants enrolled in studies as posted on ClinicalTrials.gov as of December 3, 2025. Roche number of subjects does not include two Phase 3 studies in AD recently initiated and for which actual enrollment number is not available on ClinicalTrials.gov.

ETV: Foundational Franchise for Lysosomal Storage Disorders



Delivering Next Generation Enzyme Replacement Therapy (ERT)

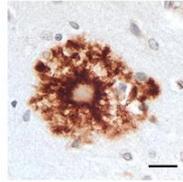
- ~30,000 people with LSDs worldwide
- Single enzyme deficiencies
- 2/3 LSDs with CNS manifestations
- 23 ERTs currently marketed; ~\$9B in sales
- ~90% historical ERT approval rate
- Traditional ERTs do not penetrate CNS
- ETVs address full spectrum of the disease

*Based on internal Denali estimates. TAM – Total Addressable Market; ETV – Enzyme Transport Vehicle™; ERT – Enzyme Replacement Therapy

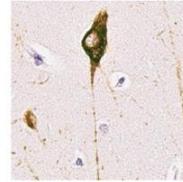
OTV & ATV: Opportunity to Set the Bar in Alzheimer’s Disease



ATV
Targeting
Abeta Plaques



OTV
Targeting
Tau Tangles



Advancing the Next Generation of Therapeutics for AD

Reducing risk of amyloid-related imaging abnormalities (ARIA)

Clearing amyloid plaque faster via better brain biodistribution

Addressing tau pathology by suppressing MAPT expression

Unmet medical need provides opportunity for BBB-enabled AD therapeutics with \$5B+ market potential

Walker L, *Free Neuropath*, 2020; Bengoa-Vergniory et al, *Acta Neurop*, 2021; ATV – Antibody TransportVehicle™; OTV – Oligonucleotide TransportVehicle™; AD – Alzheimer’s disease

Today's Agenda

Session	Topic	Speaker	Time
Leading a New Era of BBB-Crossing Therapeutics	Key Messages • Opportunity, Technology, Portfolio, 3-Year Goals	Ryan Watts, Ph.D. Chief Executive Officer	8:30am ET
Enzyme TransportVehicle™ (ETV) Franchise for Lysosomal Storage Disorders	Overview • MPS II, MPS IIIA and Pompe Disease	Barbara Burton, M.D.	8:45am ET
	MPS Diseases • Clinical Development & Regulatory Path • Market Opportunity & Commercial Launch Plans • MPS II Community Perspectives (Moderated Panel)	Peter Chin, M.D., Acting Chief Medical Officer Katie Peng, Chief Commercial Officer Dr. Burton, Jason Madison and Kim Stephens, Ph.D.	9:05am ET
	Building a Broader ETV Portfolio	Peter Chin, M.D. Acting Chief Medical Officer	10:05am ET
TransportVehicle™ Platform: Transforming Treatment for Alzheimer's Disease (AD)	Why Now Is the Time for Breakthroughs in AD	Ryan Watts, Ph.D. Chief Executive Officer	10:20am ET
	Next-Generation of TV-Enabled Therapeutics for AD	Joe Lewcock, Ph.D. Chief Scientific Officer	10:30am ET
Integrated Manufacturing	Driving Speed, Flexibility and Value	Dana Andersen, Ph.D. Chief Technical and Manufacturing Officer	10:50am ET
Evolving Our Business	Delivering the Value of the TransportVehicle™	Alexander Schuth, M.D. Chief Operating and Financial Officer	11:00am ET
Q&A	Portfolio and Strategy	Denali's Leadership Team	11:10am ET

Denali's Leadership Team



Ryan Watts, Ph.D.
Chief Executive Officer



Alexander Schuth, M.D.
Chief Operating and
Financial Officer



Peter Chin, M.D.
Acting Chief Medical Officer
and Head of Development



Katie Peng
Chief Commercial Officer



Joe Lewcock, Ph.D.
Chief Scientific Officer



Dana Andersen, Ph.D.
Chief Technical and
Manufacturing Officer



Cindy Dunkle
Chief People Officer



Chris Walsh, J.D., Ph.D.
General Counsel

Analyst Day Guest Speakers



Barbara Burton, M.D.

- Professor of Pediatrics at Northwestern University and Attending Physician in Genetics, Genomics, and Metabolism at Lurie Children's Hospital
- Board certified in Pediatrics, Clinical Genetics, and Clinical Biochemical Genetics with research focused on inborn errors of metabolism and newborn screening
- Leading researcher in metabolic and lysosomal disorders and author of 300+ peer-reviewed papers and co-editor of two textbooks



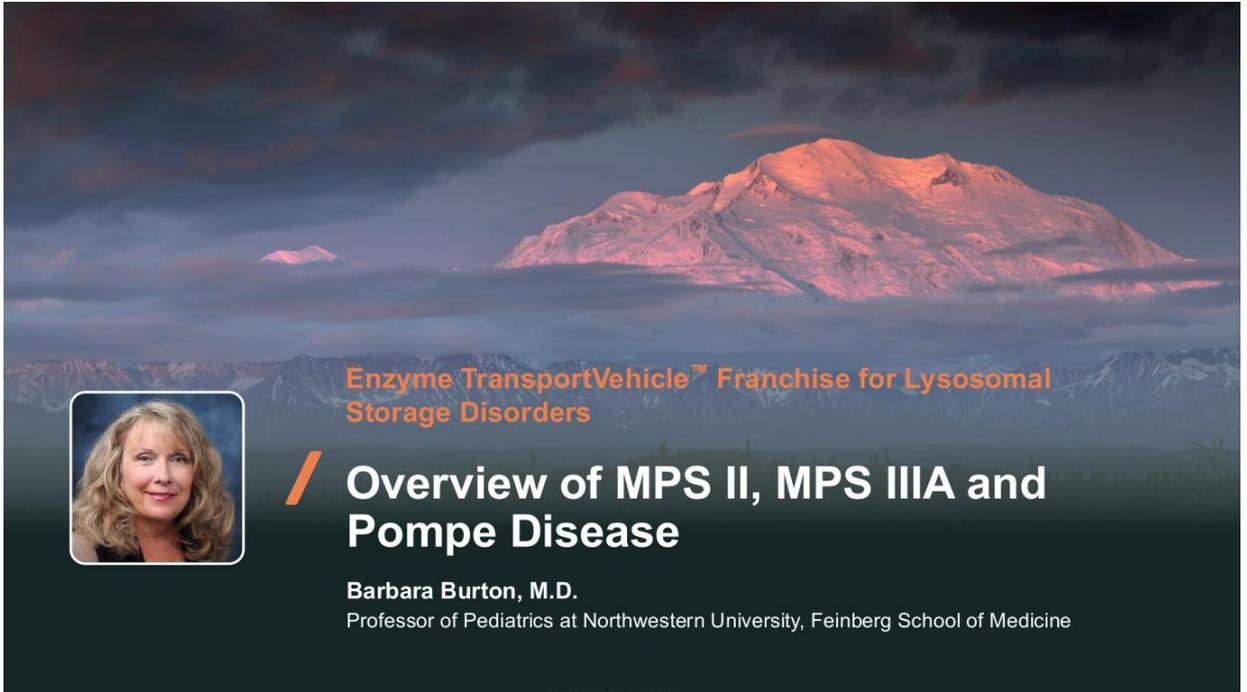
Kim Stephens, Ph.D.

- Executive Director of the Dr. Joseph Muenzer MPS Research and Treatment Center at UNC, Chapel Hill
- Mother to Cole, who was diagnosed with MPS II when he was 2 ½ and has been in a clinical trial at UNC for the past ten years
- Former co-chair of the Newborn Screening Committee for EveryLife Foundation
- Board Member Emeritus for Project Alive, a research and advocacy organization for MPS II



Jason Madison

- Longtime member of the MPS II (Hunter syndrome) community and active leader based in Allentown, Pennsylvania
 - More than 25 years of service with the National MPS Society, including Board membership and founding the Adult Resource Committee; background in graphic design and music composition
 - Dedicated patient advocate contributing to multiple research studies and a unifying voice within the adult MPS community
-



Enzyme TransportVehicle™ Franchise for Lysosomal Storage Disorders



/ Overview of MPS II, MPS IIIA and Pompe Disease

Barbara Burton, M.D.
Professor of Pediatrics at Northwestern University, Feinberg School of Medicine

What are LSDs?

- A group of over 50 disorders, each associated with deficiency of a different lysosomal enzyme or transport protein
- Inherited in an autosomal recessive or X-linked fashion
- Very heterogenous

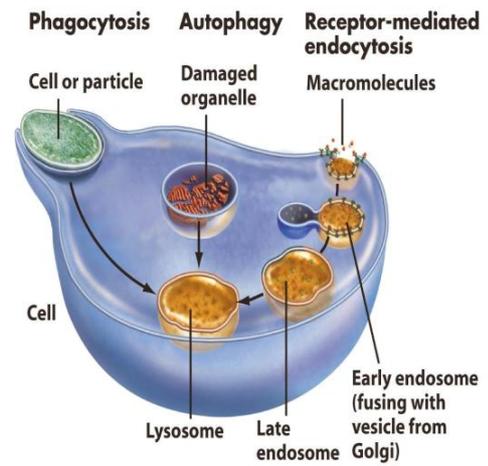


Figure 7-14, *Biological Science*, 2/e, ©2005 Pearson Prentice Hall, Inc.

/ MPS II (Hunter Syndrome)



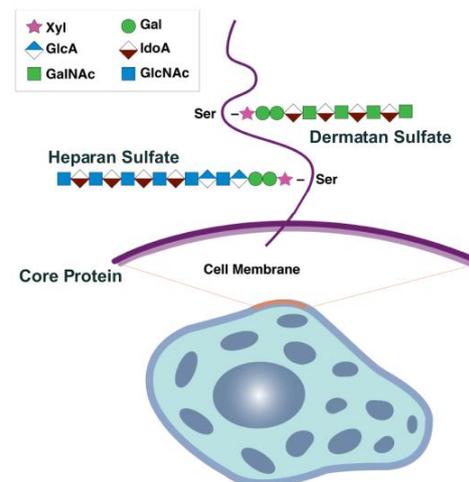
Hunter Syndrome (MPS II) is a Type of Mucopolysaccharidosis, a Subset of the Lysosomal Storage Disorders (LSDs)^{1,2}

- Mucopolysaccharidosis (MPS) conditions are rare, progressive genetic disorders that can affect nearly every organ in the body^{1,2}
- Hunter syndrome, or mucopolysaccharidosis type II (MPS II), is one of 8 distinct MPS disorders
 - It is estimated that 1 in every 25,000 infants born will have an MPS disorder⁴
 - Approximately 1 in every 100,000 infants will have Hunter syndrome. This is an X-linked disorder so almost all affected infants are male
- MPS diseases are caused by a deficiency of lysosomal enzymes, which are needed to degrade glycosaminoglycans (GAGs)
- The specific enzymatic deficient in MPS II is iduronate-2-sulfatase which is coded for by the IDS gene. Enzyme deficiency leads to progressive accumulation of the glycosaminoglycans heparan and dermatan sulfate.

1. Giugliani R et al. *Genet Mol Biol*. 2014;37(2):315-329; 2. Wang RY et al; ACMG Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases. *Genet Med*. 2011;13(5):457-484; 3. Muenzer J. *Rheumatology*. 2011;50:v4-v12; 4. NINDS, Mucopolysaccharidoses Fact Sheet, November 2019. NIH Publication No. 19-NS-5115; 5. Meikle PJ et al. *JAMA*. 1999;281(3):249-254.

What are Glycosaminoglycans (GAGs)?

- GAGs consist of a core protein plus simple carbohydrates to form a type of molecule called proteoglycans
- Proteoglycans are expressed throughout the extracellular matrix and cell surface to support cell signaling and proliferation, tissue morphogenesis, and the interaction of growth factors



Gal – Galactose; GalNAc – N-acetylgalactosamine; GlcA – Glucuronic acid; GlcNAc – N-acetylglucosamine; IdoA – Iduronic acid; Xyl – Xylose; Mizumoto S et al. *Biomed Res Int.* 2014;2014:495764. <https://doi.org/10.1155/2014/495764>. Accessed April 6, 2020.

Variability of MPS II

- MPS II occurs along a spectrum of severity but there are two major subtypes – the neuronopathic form (70% of cases) characterized by progressive neurodegeneration and cognitive decline and the non-neuronopathic or attenuated form (30%) characterized by normal or near-normal cognitive development without progressive decline
 - Within the neuronopathic subtype there is considerable variability in the pattern of decline
 - There are a small number of “intermediate” patients with stable mild to moderate cognitive impairment- 5-10% of total patients – may be classified in either neuronopathic group or attenuated group depending on definitions used
-

Real Patient Symptom Progression



Abdominal Hernia¹
Aiden's age at symptom onset: **4-10 months**

Otitis Media¹
Aiden's age at symptom onset: **4-10 months**

Enlarged Tongue and Tonsils¹
Aiden's age at symptom onset: **18 months**

Developmental Delays²
Aiden's age at symptom onset: **18 months**

Coarse Facial Features¹
Aiden's age at symptom onset: **30 months**

Stiff Joints and Claw-Like Hands¹
Aiden's age at symptom onset: **36 months**

Aiden, Age 3 **Aiden, Age 5**

1. Wraith JE et al. *Genet Med.* 2008;10(7):508-516; 2. Burlon K et al. *Eur J Pediatr.* 2012;17(2):631-639.

Later Signs/Symptoms of MPS II

- Progressive airway narrowing
 - Cardiac valve thickening and dysfunction, cardiomyopathy
 - Carpal tunnel syndrome
 - Retinal degeneration with progressive visual impairment
 - In neuronopathic patients, developmental slowing followed by progressive neurodegeneration
 - **Death in teens for most neuropathic patients; those with attenuated disease may live into their 40's, 50's or beyond**
-

Newborn Screening



- MPS II was added to RUSP in 2017; approximately 25% of US newborns are now screened but this is expected to increase rapidly
-

Current Treatment of MPS II

- Most affected individuals receive enzyme replacement therapy with Elaprase® from time of diagnosis
 - Surveillance for complications with symptomatic treatment as needed
 - Hematopoietic stem cell transplantation is used in some cases but relatively infrequently in North America. It provides somatic benefit and may provide some CNS benefit if done within first year of life but data are limited.
-

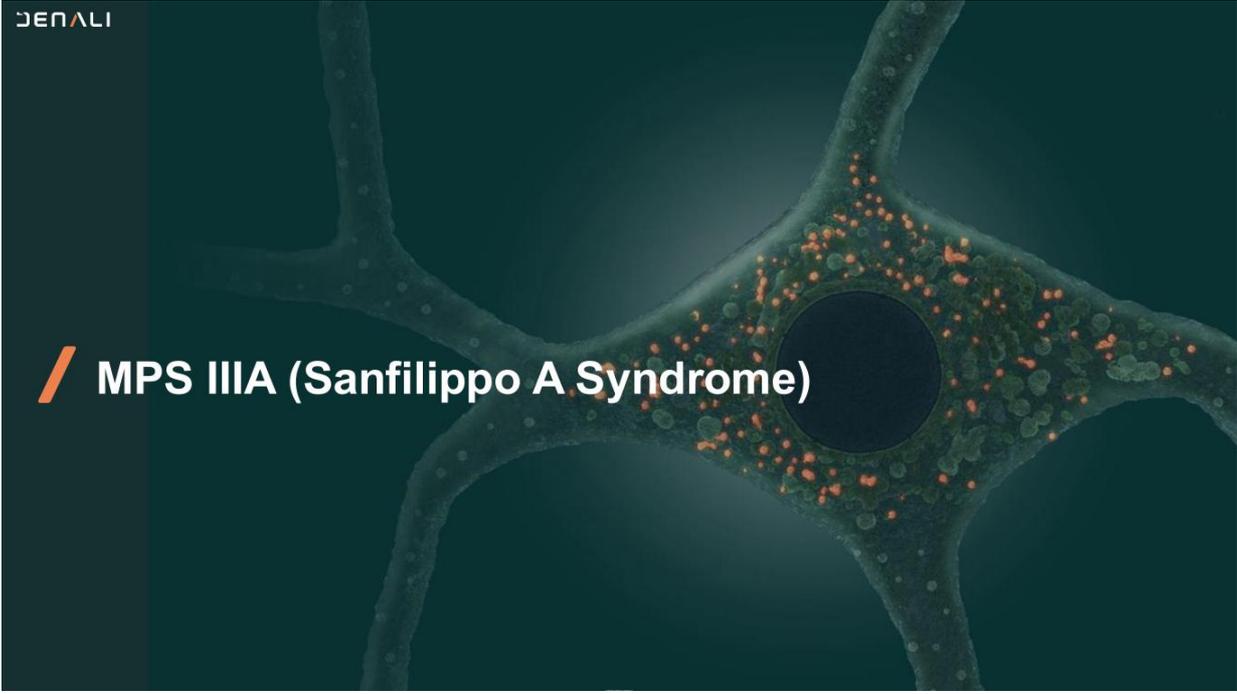
Limitations of Current ERT

- Does not cross the blood brain barrier in significant amounts so does not alter the course of neurodegeneration leading to death
 - Cardiac valve and airway issues continue to progress and are the major cause of death in attenuated patients
 - Does not prevent retinal disease
 - Does not prevent progressive hearing loss so most patients require hearing aids
-

Unmet Need in MPS II

- A treatment is needed to address the progressive neurodegeneration and cognitive decline seen in the neuronopathic form of the disease
 - Better treatment for the hard to reach peripheral tissues in which disease progression continues to occur despite current ERT
-

/ MPS IIIA (Sanfilippo A Syndrome)

A microscopic image of a cell, likely a fibroblast, showing a large nucleus and numerous small, orange, granular inclusions scattered throughout the cytoplasm. The cell is set against a dark green background. The text 'DEALI' is in the top left corner, and the title 'MPS IIIA (Sanfilippo A Syndrome)' is overlaid on the left side of the image.

MPS IIIA – Sanfilippo Syndrome, Type A

- Autosomal recessive disorder resulting from deficiency of the enzyme N-sulfoglucosamine sulfohydrolase (SGSH), also referred to as sulfamidase or heparan sulfate sulfatase. This leads to progressive accumulation of heparan sulfate.
 - **Most common of the 4 types of MPS III, accounting for about 70% of cases**
 - **Overall incidence estimated at 1 in 125,000 births**
-

MPS IIIA – Clinical Findings

- Primarily (but not exclusively) a neurologic disorder
 - Infants are normal at birth but exhibit developmental slowing at about 2 years of age with speech delay
 - Hyperactive/aggressive behavior at about age 3
 - Developmental regression becomes apparent typically by 4-5
 - Often initially misdiagnosed as ADHD, non-specific developmental delay or autism
 - Average age at clinical diagnosis 4-5 years; average age of death 10-15 years. Approximately 20 % of patients have a more attenuated course with later diagnosis and longer survival.
-

MPS IIIA – Additional Findings

- Hepatosplenomegaly
- Recurrent otitis media and other respiratory infections
- Chronic or recurrent diarrhea
- Coarse facial features- less prominent than in other MPS disorders
- Prominent GI dysmotility late in the disease
- Cardiac valve disease
- Skeletal findings such as hip dysplasia



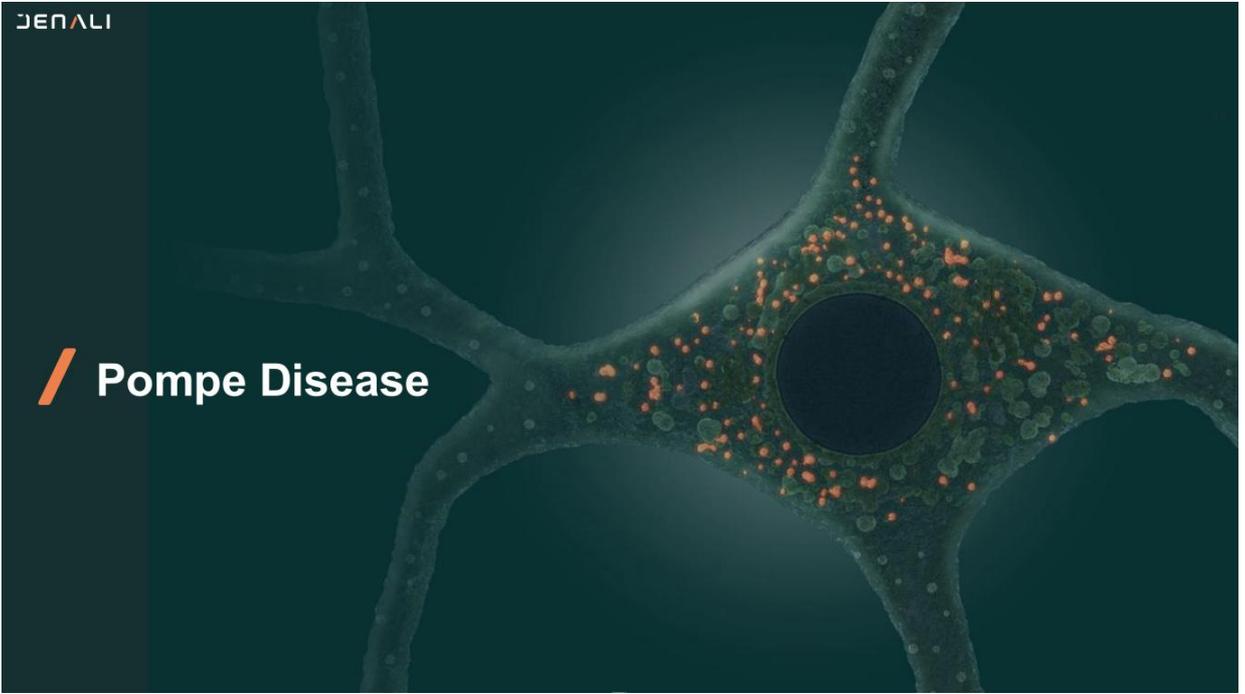
MPS IIIA – Current Treatment

- Primarily symptomatic
 - No approved disease-modifying therapy; HSCT does not alter the course of the disease
 - Many patients currently receive anakinra (Kineret®) approved for a different disorder but with some data showing benefit in MPS III
 - **Many therapeutic trials including trials of IV or intrathecal ERT and gene therapy have failed in past. The frustration in the patient community is very high.**
 - **No newborn screening underway at present but it is feasible**
-

MPS IIIA – Unmet Need

- There is a pressing need for any disease-modifying therapy to halt or slow down the relentless progression of the disease and prolong life
 - The focus is on the brain but if treatment of the brain is successful, the need for effective treatment of peripheral tissues is likely to become more pressing
-

/ Pompe Disease



Pompe Disease



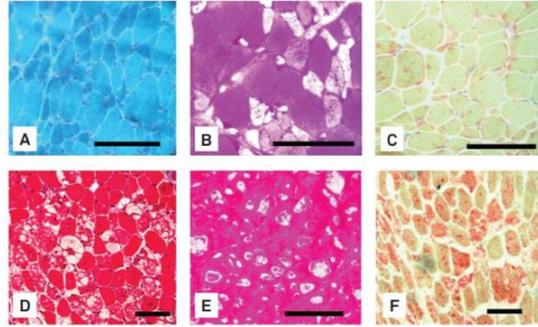
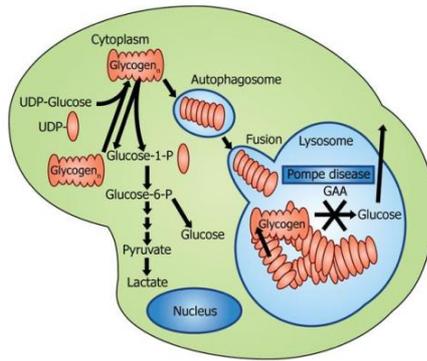
Photos courtesy of Dr. Ficioglu and Dr Herman F.M. Busch, Erasmus MC, Rotterdam, The Netherlands.

What is Pompe Disease

- It is a progressive, genetically determined disorder inherited in an autosomal recessive fashion
- Biallelic mutations in the GAA gene lead to deficiency of the lysosomal enzyme alpha-glucosidase and progressive accumulation of glycogen in lysosomes of cells
- Other names for Pompe disease used in past: acid maltase deficiency, glycogen storage disease type II

Pompe Disease: Glycogen Storage Disorder Type II and Lysosomal Storage Disorder

Incidence: 1 in 20,000; Males and Females Affected in Equal Numbers



Rabin N, et al. *Am J Med Genet C Semin Med Genet.* 2012;160:13-21; Wernke LC, et al. *Arq Neuropsiquiatr.* 2013;71(5):284-289; National Institutes of Health. Genetics Home Reference. *Pompe Disease.* 2020. <https://ghr.nlm.nih.gov/condition/pompe-disease#statistics>

Infantile-Onset Pompe Disease (IOPD)

- Poor feeding/failure to thrive
- Motor delay/muscle weakness
- Hypertrophic cardiomyopathy
- Onset within 1st few months of life
- Death within 12-18 months of life without treatment
- Emerging post-treatment phenotype includes persistent and progressive muscle weakness, hearing loss and white matter changes in the brain with progressive neurologic decline reported in a few



Late-Onset Pompe Disease (LOPD)

- Onset across the lifespan: <12 months to 7th decade
 - Includes juvenile- and adult-onset forms
- Progressive proximal and axial muscle weakness
 - Gower's sign, winging scapula
 - Common misdiagnosis: LGMD
- Respiratory dysfunction
 - Diaphragmatic weakness
 - Intercostal muscle weakness
 - Ventilatory support may be needed at night
- No apparent cardiac involvement



Leslie N, Bailey L. In: Adam MP, et al. GeneReviews. University of Washington, Seattle; 2007 [updated 2017], pp 1993-2019; Heaver C, et al. *Orthoped Trauma*. 2019;33(4)239-248; Oncohemat Key. <https://oncohematkey.com/13-pompe-disease/>.

Newborn Screening for Pompe Disease



- Added to the RUSP in 2015
 - Now on the NBS panel in all 50 states
-

Current Treatment of Pompe Disease

- 3 approved forms of ERT available in US
 - Lumizyme – approved for both IOPD and LOPD
 - Nexviazyme – approved for LOPD in children and adults
 - Pombiliti – given with Opfolda (miglustat) approved for adults not improving on their current ERT
 - Patients with IOPD are treated urgently at time of diagnosis. Patients with LOPD diagnosed clinically are offered treatment at diagnosis; those diagnosed by NBS are monitored and treated once symptoms appear
-

How Well Does Current Treatment Work

- If immunologic issues are addressed with appropriate immune modulation, it is very effective for treatment of cardiomyopathy in IOPD and is live-saving
 - It is much less effective for skeletal muscle disease. Most patients exhibit modest improvement in muscle strength, mobility and respiratory function after onset of treatment followed by variable period of stability but ultimate disease progression.
 - Long term data not available for the two newer ERT's but the improvement seen is incremental when patients are switched. Considerable unmet need still exists
-

Why is Treatment Less Effective for Skeletal Muscle?

- Sparse M6P receptors compared with other tissues
 - Inadequate dosing
 - Late diagnosis in some patients with some muscle fibers destroyed and replaced with fat
 - Lysosomal rupture leads to accumulation of cytoplasmic glycogen which is not cleared by ERT targeted to the lysosome
-

Unmet Need in Pompe Disease

- We likely need treatment of the brain in IOPD although the natural history of the brain disease has not yet been fully charted
 - Better treatment of the skeletal muscle disease is needed in both IOPD and LOPD
-



Enzyme TransportVehicle™ Franchise for Lysosomal Storage Disorders



/ Tividenofusp alfa: Clinical Development & Regulatory Path

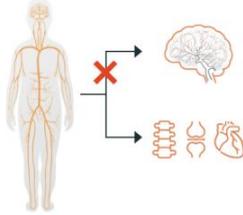
Peter Chin, M.D.
Acting Chief Medical Officer and Head of Development



ETV Franchise Opportunity in Lysosomal Storage Disorders

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



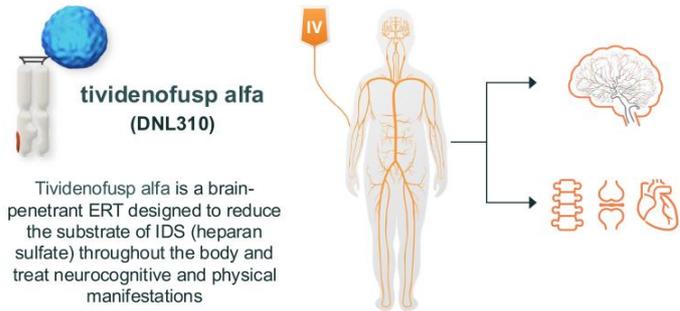
Potential to **enhance peripheral delivery**

Goal is to treat the full disease spectrum

ETV – Enzyme transport vehicle; LSDs – Lysosomal storage disorders; CNS – Central nervous system; ERTs – Enzyme replacement therapies

Brain Delivery Is Critical Unmet Need of Hunter Syndrome Therapy

Monogenic lysosomal storage disorder caused by deficient iduronate-2-sulfatase (IDS)



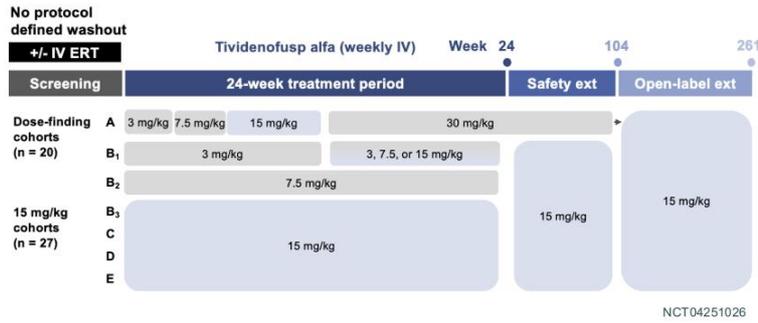
Traditional enzyme replacement therapy does not cross the blood brain barrier and only partially addresses peripheral manifestations

ERT – Enzyme replacement therapy

Tividenofusp Alfa Phase 1/2 Study Supporting US AA

Design

- **Duration:** 24-week study + 80-week safety extension + open-label extension
- **Study Design:** Open label



Study Population

- Neuronopathic and non-neuronopathic MPS II, aged ≤18 years
- ERT-naïve and treatment-experienced

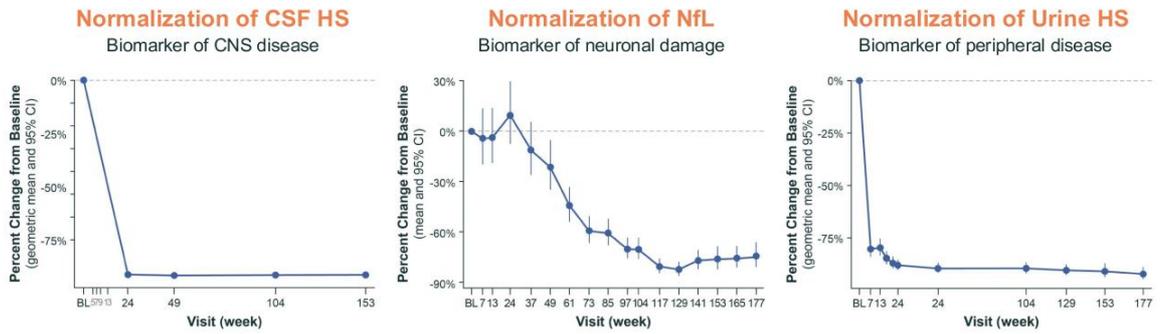
Key Endpoints

- **Primary:** Adverse events, Infusion-related reactions, other indicators of safety and tolerability
- **Secondary:** CSF HS, Urine HS, Adaptive behavior (Vineland), Liver volume
- **Exploratory:** Serum NfL, CSF biomarkers, hearing thresholds, cognition (BSID, KABC)

Substantial long-term safety and efficacy experience informs positive benefit-risk profile in MPS II

B₃ was part of the dose-finding cohorts; BSID – Bayley Scales of Infant Development; CSF – Cerebrospinal fluid; ERT – Enzyme replacement therapy; ext – Extension; HS – Heparan sulfate; IV – Intravenous; KABC – Kaufman Assessment Battery for Children; MPS II – Mucopolysaccharidosis type II; NfL – Neurofilament light chain; SOC – Standard of care; Source; WORLD 2025.

Tividenofusp Alfa Phase 1/2 in MPS II: Biomarker Effects



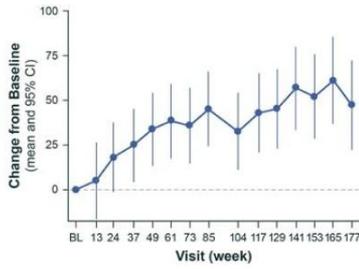
- Robust reductions from baseline in CSF heparan sulfate, serum neurofilament light, and urine heparan sulfate, with a majority in the normal range after treatment with tividenofusp alfa

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

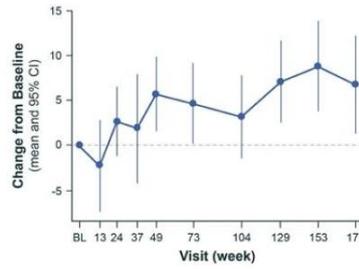
MPS II – Mucopolysaccharidoses Type II; CSF – Cerebrospinal fluid; HS – Heparan sulfate; NfL – Neurofilament light; Source: WORLD 2025.

Tividenofusp Alfa Phase 1/2 in MPS II: Clinical Outcomes

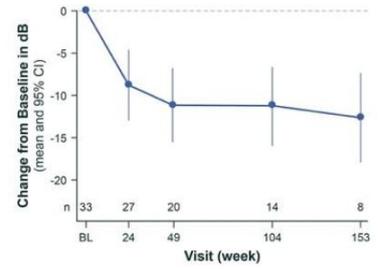
Improvement in Adaptive Behavior
Vineland-3



Improvement in Cognition
BSID-III



Improvement in Hearing
Auditory Brainstem Response (PTA)



- 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 – Mucopolysaccharidosis Type II; CI – Confidence interval; BSID-III – Bayley Scales of Infant and Toddler Development-Third Edition; PTA – Pure tone average; 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
TEAE¹, n (%)	47 (100)	47 (100)
Mild	8 (17.0)	2 (4.3)
Moderate	35 (74.5)	32 (68.1)
Severe ²	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)³; 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 IRRs³, 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

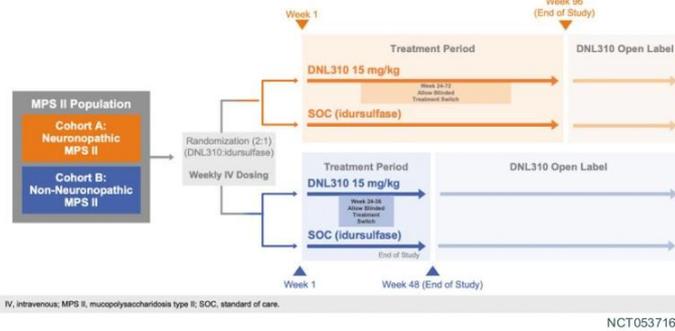
Phase 1/2 safety and clinical data supports broad indication for treatment of full spectrum of MPS II

1. TEAE by maximum severity; 2. Missing intensity was summarized as severe; 3. 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.

Tividenofusp Alfa Global Phase 2/3 Study Design

Design

- **Duration:** Cohort A: 96-week study + extension | Cohort B: 48-week study + extension
- **Study Design:** Randomized double-blinded active control



Study Population

- **Cohort A:** Neuronopathic MPS II, aged ≥ 2 to < 6 years
- **Cohort B:** Non-neuronopathic MPS II, aged ≥ 6 to < 26 years
- Receiving idursulfase for > 4 months

Key Endpoints

- **Cohort A:** CSF HS, Vineland-3, BSID-II, serum NFL
- **Cohort B:** 6MWT
- **Cohorts A & B:** Urine HS and DS, Liver and Spleen MRI volume, Patient / Caregiver Impression of Change, Safety

Rigorous design to confirm efficacy and safety and support global approvals

BSID – Bayley Scales of Infant Development; CSF – Cerebrospinal fluid; ERT – Enzyme replacement therapy; HS – Heparan sulfate; IV – Intravenous; MPS II – Mucopolysaccharidosis type II; NFL – Neurofilament light chain; SOC – Standard of care

Tividenofusp Alfa Development and Regulatory Path

PDUFA Target Action Date: April 5, 2026 Preparing for Commercial Launch

- Filed BLA for accelerated approval; granted priority review
- BLA includes data from open-label, global Phase 1/2 study (N=47)
- Up to 18 years of age
- Treatment duration up to five years
- Measuring biomarkers, safety, and exploratory clinical outcomes

47 Phase 1/2 participants

Phase 2/3 Study Ongoing Supporting Global Approvals

- Randomized, double blind, controlled study (N~63)
- Ages ≥ 2 to < 6 y.o. (Cohort A, neuronopathic)
- ≥ 6 to < 26 y.o. (Cohort B, non-neuronopathic)
- Co-primary endpoints: CSF HS and Vineland-III
- Peripheral endpoints: liver/spleen volume, 6MWT, ABR and others

63  participants

Robust data package supporting a target indication for the full MPS II phenotype spectrum

PDUFA – Prescription Drug User Fee Act; CSF – Cerebrospinal fluid; HS – Heparan sulfate; 6MWT – 6-minute walk test; ABR – Auditory brainstem response



MPS II siblings enrolled in the study: investigator perspective

- Pathogenic IDS variant (c.262C>T), absent I2S enzyme activity
- Diagnosed at 3 years 8 months and 5 months of age, respectively, and treated with weekly idursulfase (0.5 mg/kg)
- Both enrolled in the Phase 1/2 study and received weekly tvidenofusp alfa 15 mg/kg for > 4 years:
 - Older started at 6 years 4 months
 - Younger started at 2 years 6 months

VIDEOS

Informed consents were obtained for the sibling pair with MPS II to present the information and videos on this slide.

Tvidenofusp alfa (DNL310) is an investigational drug and is not approved by any Health Authority.

Tividenofusp Alfa is the Cornerstone of the ETV Franchise

	Immediate 2026	Near / Mid Term 2027 – 2028	Mid / Long Term 2028+	Clinical Value Potential
Tividenofusp alfa (MPS II) First commercial launch	 US AA PDUFA April 5, 2026	 Initial International Launches	 Full Global Potential	<ul style="list-style-type: none"> • Only therapy shown to normalize disease biomarkers in CSF and periphery
DNL126 (MPS IIIA) Path to US AA		 US AA	 Global Launch	<ul style="list-style-type: none"> • Ability to normalize CSF heparan sulfate
DNL952 (Pompe Disease) IND application filed ¹			 Global Launch	<ul style="list-style-type: none"> • TfR-enhanced delivery of GAA to muscle

The ETV franchise can deliver transformative treatments for the LSD community

¹. Protocol amended and response to FDA submitted regarding clinical hold; US AA – United States Accelerated Approval; PDUFA – Prescription Drug User Fee Act; CSF – cerebrospinal fluid; IND – investigational new drug; TfR – transferrin receptor; GAA – acid alpha-glucosidase enzyme; LSD – lysosomal storage disorders

Overview of MPS IIIA (Sanfilippo Type A)

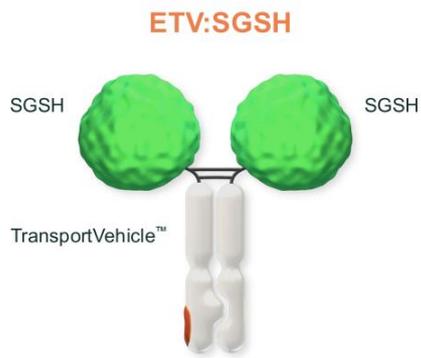
- Lysosomal storage disorder caused by deficiency in **SGSH gene encoding sulfamidase**
- Disease hallmark is accumulation of glycosaminoglycan (GAG) **heparan sulfate**, particularly in CNS
- ~**1,500+** patients worldwide¹. Life expectancy for MPS IIIA patients is 15 years².
- Almost **all patients have CNS symptoms**, including developmental delay, behavioral disturbances, seizures, and cognition and motor decline following onset (typically between ages of 2 and 6)
- **No current standard of care**, but gene and cell therapies in clinical development



Currently no disease-modifying therapies are available

1. Excluding China and India; 2. Lavery et al. 2017 *Orphanet J Rare Dis*; CNS – Central nervous system

DNL126 (ETV:SGSH) Delivers SGSH to the Brain



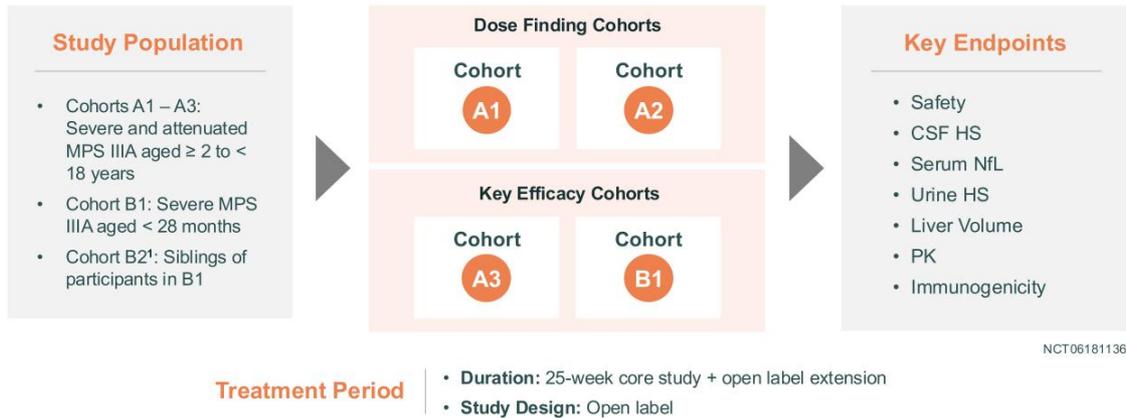
Program Status

- Achieved **biomarker proof-of-concept** in Phase 1/2
- Aligned with FDA on **accelerated approval path** in MPS IIIA
- Selected for FDA **START program**
- Phase 1/2 enrollment completed
- Phase 3 protocol under development

DNL126 aims to address the relentless neurodevelopmental disease progression in MPS IIIA

FDA – U.S. Food and Drug Administration; **START** – Support for clinical Trials Advancing Rare disease Therapeutics

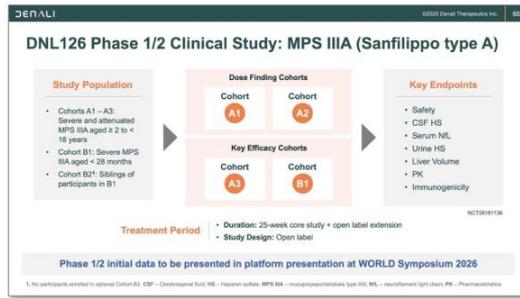
DNL126 Phase 1/2 Clinical Study: MPS IIIA (Sanfilippo type A)



Phase 1/2 initial data to be presented in platform presentation at **WORLD Symposium 2026**

¹. No participants enrolled in optional Cohort B2. CSF – Cerebrospinal fluid; HS – Heparan sulfate; MPS IIIA – Mucopolysaccharidosis type IIIA; NFL – Neurofilament light chain; PK – Pharmacokinetics

Study Data for the DNL126 Accelerated Approval



Data for BLA Submission

- At least 49 weeks of data for all participants (Cohorts A1-A3, B1; n=20)
- CSF HS reduction from baseline in key efficacy cohorts (n=12) – surrogate endpoint reasonably likely to predict clinical benefit
- Supportive data on central and peripheral biomarkers, clinical endpoints
- Long-term safety up to ~2.5 years

Expected BLA submission and approval in 2027

BLA – Biologics licensing application; AA – Accelerated approval; CSF – Cerebrospinal fluid; HS – Heparan sulfate



Enzyme TransportVehicle™ Franchise for Lysosomal Storage Disorders



/ Tividenofusp Alfa: Market Opportunity & Commercial Launch Plans

Katie Peng
Chief Commercial Officer



Living it.



We are simply amazed at his overall health and what he is capable of that we never dreamed possible when we received his diagnosis.

He has a rich vocabulary and imagination, loves listening to books, and he literally never stops talking. We are able to engage in so many family activities we enjoy together that we weren't sure we would ever be able to do as a whole family. With that said, life is not simple or easy by any means.

It is really incredible to reflect on how far he has come, while also making us wish that we could have begun treatment so much earlier ... It makes us wonder (and hope) for what could be for those children who will ... someday be able to initiate brain-targeted therapy at the earliest possible moment. **We are literally changing the future, truly creating a future that hasn't existed, for every family that comes ahead.**

– Message from current clinical study family to Denali

Waiting for it.



“60% of respondents emphasized the need for therapies that cross the BBB — underscoring the urgency for options that address cognition.”

Recent community survey in partnership with Project Alive.

Watching it.

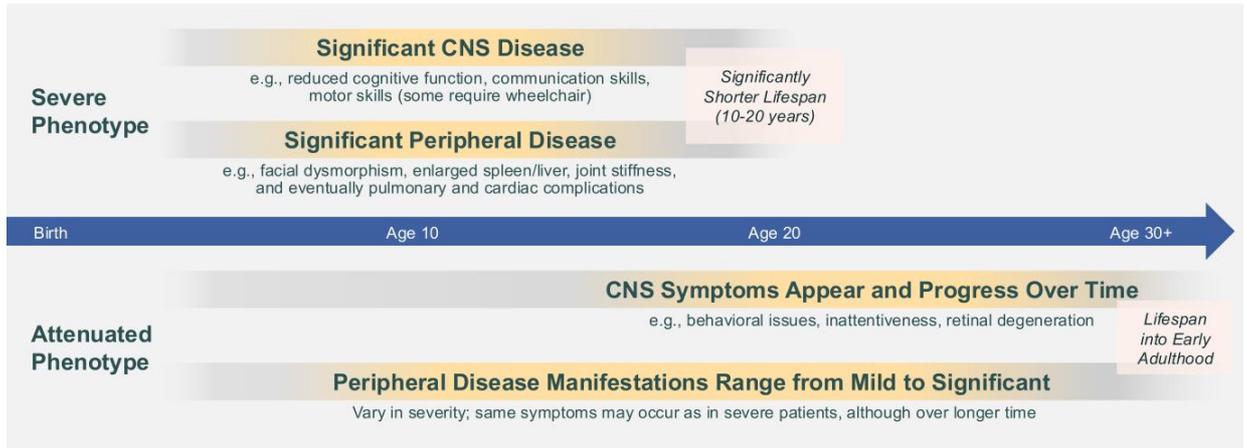
Change is not easy. As new treatments emerge, we know families are watching closely — seeking reassurance through others' experiences and outcomes.

Our goal is to make these early experiences with tivi both positive and inspiring, building confidence for families considering a future switch.

- ✓ Engagement with HCPs
- ✓ Payer and access strategy
- ✓ Working with advocacy to shape our plans
- ✓ Dedicated Patient Services Team

From lived experiences to hopeful anticipation — the Hunter community's voices guide our next chapter.

Hunter Syndrome Patients Fall on a Disease Spectrum, with CNS and Peripheral Manifestations in All



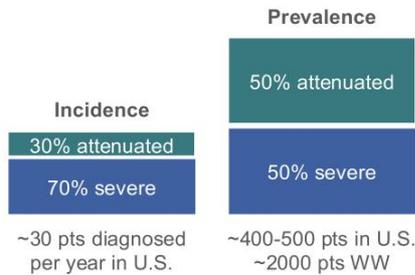
Tividenofusp alfa has the potential to address both CNS and peripheral manifestations of disease

CNS – Central nervous system

Tivi Has the Potential to Reduce the Disease Burden and Extend Survival, Leading to Growth in the MPS II Population

Current Standard Of Care Paradigm

The prevalent MPS II population reflects a higher early death rate for individuals born with severe disease



Future Tivi Treatment Paradigm

Prevalence



Larger MPS II population overall as individuals treated with tivi live longer, healthier lives



MPS II – Mucopolysaccharidosis type II; WW – worldwide

Tivi Setting a New Bar for the Treatment of MPS II



Tividenofusp alfa is an enzyme replacement therapy for **all people** with **Hunter syndrome**. It is the **first therapy to treat both the brain and body**, and the **only** therapy to **normalize GAG** levels.

Broad Indication Statement

No need to determine disease severity
(pending FDA label)

Differentiated Positioning

Only option to address all disease manifestations

Reason to Believe

GAG normalization fundamental to tivi's potential of delivering superior clinical outcomes

Our Stakeholders Are Ready and Waiting for Tivi



Physicians

- Recognize significant **unmet needs** across **brain and body**
- 90% view tivi's data as **highly motivating to prescribe**
- **No overall concerns with safety profile**



Patients & Caregivers

- Perceive significant **unmet needs**, across **brain and body**
- **80%+ are aware** of new treatments coming and **excited to try tivi**
- **Advocacy orgs and peer to peer communications most influential**



Payers

- **Robust payer engagement** underway
- **Perceive therapeutic benefit** due to ability to cross the BBB
- View tivi's **benefit/risk profile favorably**

1. HCP Insights from HCP Survey (N=68) conducted in Q1 2025 and from KOL Adboard conducted March 2025; 2. Caregiver Insights from Caregiver Survey (N=47) Conducted Q4 2024; 3. Payer Insights from AdBoard conducted April 2025 and Payer Engagements; All strategies and tactics are subject to Legal review prior to implementation.

Strategy and Path to Establish Tivi as Standard of Care

Broad Patient Reach Through Community Centered, High-Touch Engagement Model

Community & Advocacy

Strong partnership
Disease state awareness campaign

Scientific & Clinical Engagement

Medical congresses
COE engagement

Provider & Institutional Preparation

Account profiling & in-servicing
Experienced field team ready to go

Activate and maintain switch to tildenafil alfa

Seamless Access for All Patients

Patient Access & Support

Comprehensive patient support programs
Experienced distribution network

Payer & P&T Preparation

Payer education
Engaging P&T at COEs

Drive fast broad coverage

All strategies and tactics are subject to Legal review prior to implementation; COE – Centers of excellence; P&T – Pharmacy & Therapeutics committee

Strong Scientific Outreach and Community Engagement

<p>Scientific Outreach</p>	
<p>Policy Support</p>	
<p>Advocacy Partnerships & Community Council</p>	

Continued engagement with the Hunter syndrome community and HCPs

All strategies and tactics are subject to Legal review prior to implementation; HCPs – Healthcare professionals

Denali Pricing Principles



Access

Enable broad, equitable, and sustainable access for patients, the healthcare system, and society



Affordability

Address affordability by providing comprehensive support to patients and families



Fuel R&D

Ensure our ability to fuel R&D in the pursuit of meaningful and impactful treatments



Value of Our Medicines

Reflect the clinical, economic, and societal value delivered by our medicines

Expect to price tivi at a premium to standard of care, balancing access with the value to patients

All strategies and tactics are subject to Legal review prior to implementation.

Broad Reimbursement Supported by Clear Clinical Value Proposition for Tividenofusp Alfa

Value Proposition: Tividenofusp alfa could become the first FDA-approved ERT to cross the BBB to target the CNS and eliminate GAG buildup in both brain and body for all MPS II patients

Significant Disease Burden

- Progressive disease with widespread organ involvement
- Significant decline across brain and body

Current SoC Leaves Many Unmet Needs

- Current SoC ERT:
- Does not treat CNS symptoms
 - Cannot adequately penetrate hard-to-reach peripheral tissues

Low Budget Impact

- U.S. prevalence of ~400 – 500 patients
- ~1-2 MPS II patients per 1-million-member plan

Commercial & Medicaid

- ~50/50 across Commercial & Medicaid
- Longer time to coverage on Medicaid compared with commercial

Payer coverage will be achieved by communicating compelling tividenofusp alfa value proposition

All strategies and tactics are subject to Legal review prior to implementation; ERT – Enzyme replacement therapy; SoC – Standard of care; MPS II – Mucopolysaccharidosis type II; GAG – Glycosaminoglycans

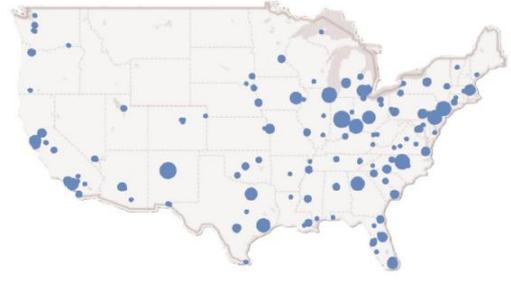
Concentrated Stakeholders Enable Us to Reach All Patients Treated Across the 80 to 100 Centers of Excellence in the U.S.

MPS II Patient Distribution



400 to 500 patients in the US on SoC ERT

MPS II Treating Physician Distribution



Most MPS II patients treated by **clinical geneticists at ~80-100 genetic centers**

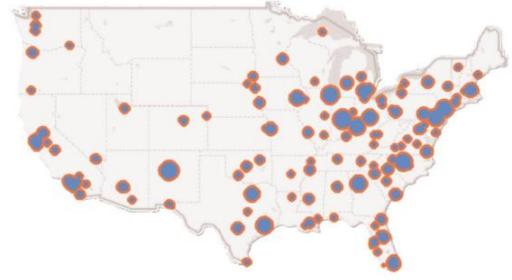
Concentrated Stakeholders Enable Us to Reach All Treaters Across the 80 to 100 Centers of Excellence in the U.S.

MPS II Patient Distribution



400 to 500 patients in the US on SoC ERT

Denali's Established Relationships



Denali has **already established relationships** with **all major** MPS II treatment centers

Built a Winning Team Ready for Launch

Leadership Team

Significant Experience Across Functions

- ✓ Product Strategy
- ✓ US and Global Marketing
- ✓ US and Ex-US Market Access
- ✓ Market Planning and Analytics
- ✓ Medical Affairs & Med Info
- ✓ Field Sales
- ✓ Field Medical
- ✓ Patient Advocacy

25+ Successful Product/Indication Launches Worldwide

Including Rare Diseases



US Field Team

Deep Industry and Disease Expertise

- ✓ 25 Years Average Biopharma Industry Experience
- ✓ 96% LSD / Rare Disease Experience
- ✓ Average Rare Disease Experience: 12 Years

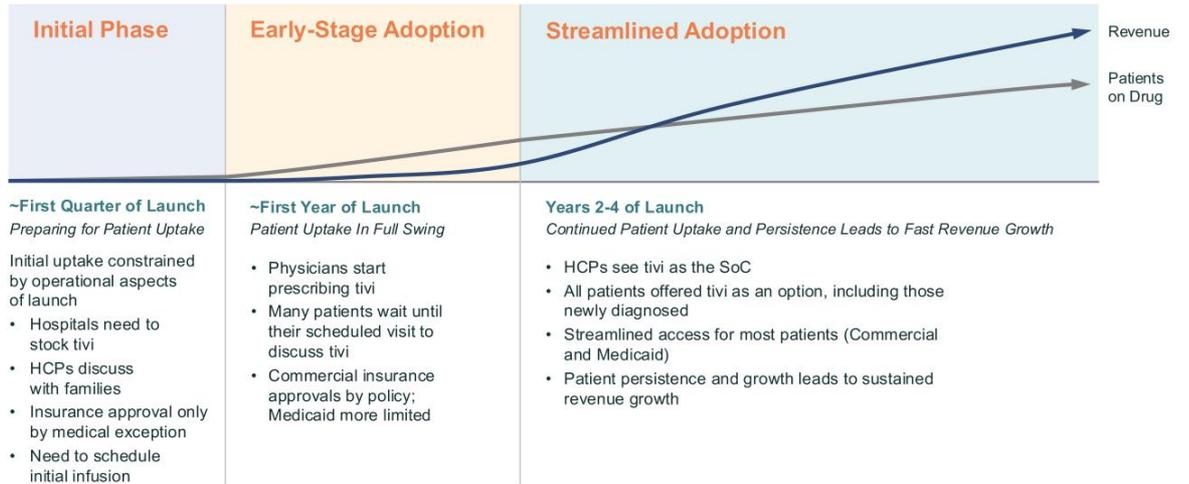
Multiple Successful Product Launches

All Rare Diseases



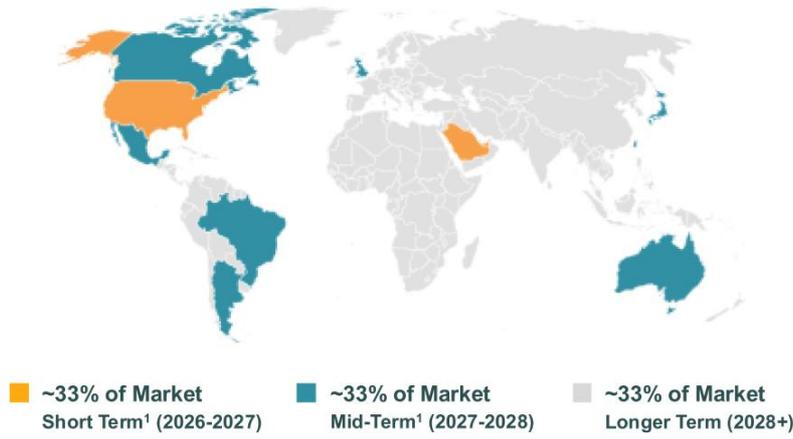
All strategies and tactics are subject to Legal review prior to implementation; LSD – Lysosomal storage disorders

Tividenofusp Alfa Launch Expected to Follow Established Rare Disease Launch Dynamics



All strategies and tactics are subject to Legal review prior to implementation; HCPs – Healthcare professionals; SoC – Standard of care

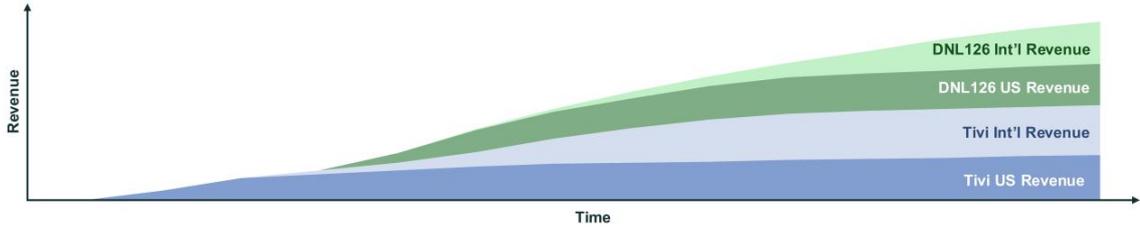
Majority of Global Market Available Based on U.S. Accelerated Approval and/or Phase 1/2 Data



- We will pursue ex-U.S. approvals via the U.S. Certificate of Pharmaceutical Product (CPP) for marketing authorization or conditional pathways, as available
- We are targeting all ~2,000 patients worldwide in commercially accessible geographies

Note: Based on estimated WW split of Elaprase annual revenues of \$650M to \$700M, assuming we launch in ~90-95% of Elaprase geographies; 1. COMPASS Phase 2/3 data not needed for regulatory filings; All strategies and tactics are subject to Legal review prior to implementation.

Building a Rare Disease Franchise: First Two Near-Term Launches Combined Opportunity of >\$1B



Successfully Launching Tividenofusp Alfa Will Be the Bedrock of a Successful Commercial Franchise



Significant Near-Term Opportunity

- Revenue starting 2026
- \$1B+ Opportunity between MPS II and MPS IIIA



Infrastructure Synergies

- Plan to leverage existing Denali infrastructure across both launches
- Ability to redeploy resources to translate into favorable margins



Established LSD Leadership

- Established relationships with key LSD stakeholders
- Ability to drive increasingly fast launches and product uptake throughout franchise

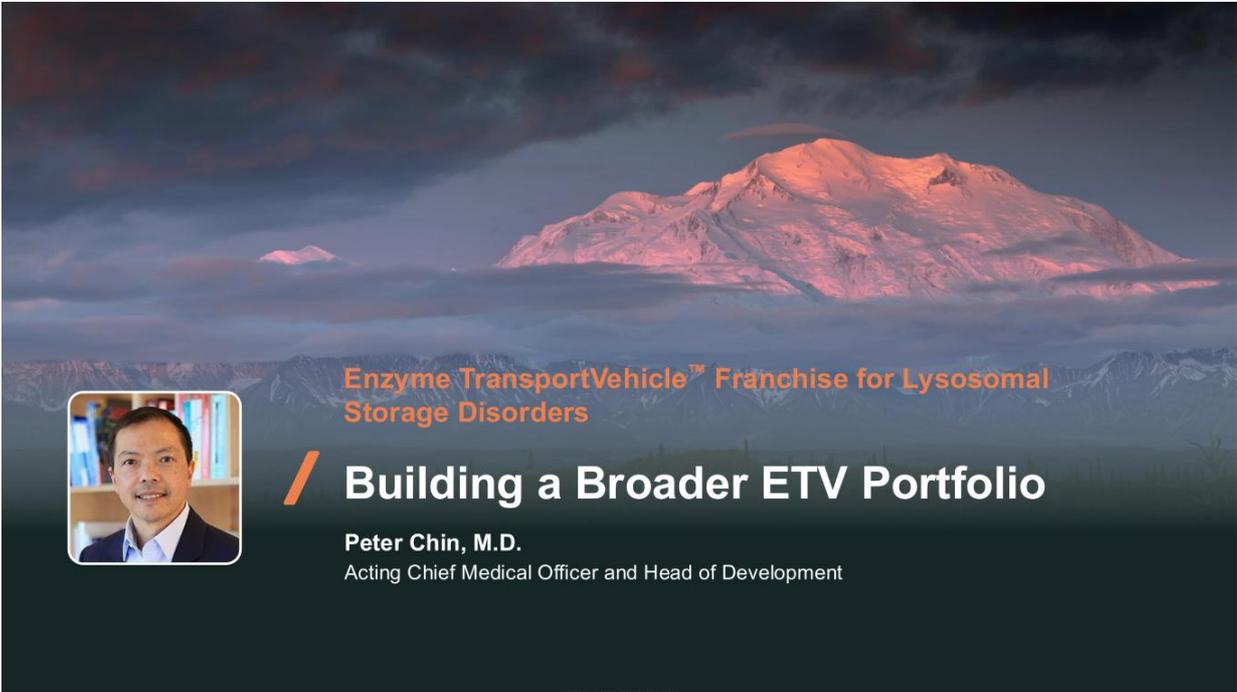
All strategies and tactics are subject to Legal review prior to implementation.



Enzyme TransportVehicle™ Franchise for Lysosomal Storage Disorders

**/ Moderated Panel:
MPS II Community Perspectives**

Barbara Burton, M.D., Kim Stephens, Ph.D., and Jason Madison



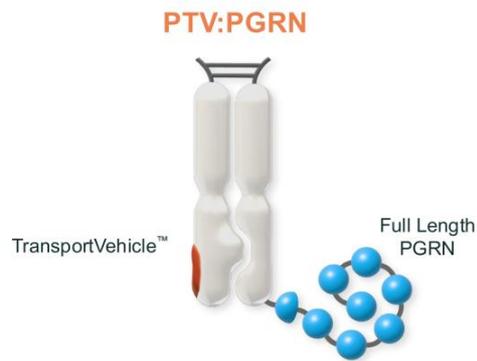
Enzyme TransportVehicle™ Franchise for Lysosomal Storage Disorders

/ Building a Broader ETV Portfolio

Peter Chin, M.D.

Acting Chief Medical Officer and Head of Development

DNL593 (PTV:PGRN) Delivers PGRN to Key Cell Types in the Brain



Program status: Phase 1/2 Study Ongoing

Key Characteristics

- Molecule delivers full length PGRN that retains binding to Sortilin receptor
- TfR tuned to maximize delivery of PGRN to the CNS and uptake into lysosomes of neurons and glial cells
- Fc domain portion of TransportVehicle™ improves manufacturability and drug-like properties

DNL593/TAK-594* approach is highly differentiated from competitor PGRN approaches

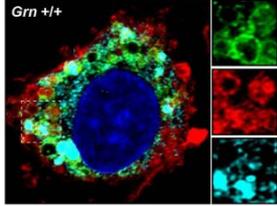
*In collaboration with Takeda

PGRN Depletion Results in Lysosomal Abnormalities Rescued by DNL593

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

Cell

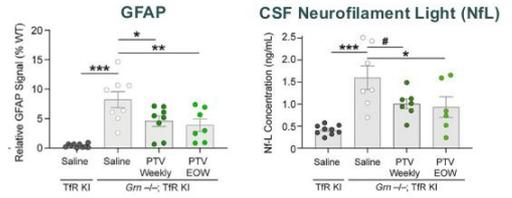
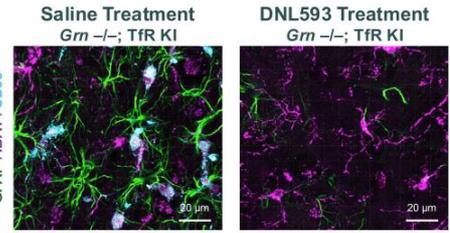
Todd Logan,^{1,6} Matthew J. Simon,^{1,6} Anil Rana,^{1,7} Gerald M. Chert,^{1,7} Ankita Srivastava,^{1,7,8} Sonnet S. Davis,¹ Ray Liah Yoon Low,¹ Chi-Lu Chiu,¹ Meng Fang,¹ Fen Huang,¹ Akhil Bhatta,¹ Coyda Llapasthica,¹ Rachel Prorok,¹ Michelle E. Pizzo,¹ Meredith E.K. Calvert,¹ Elizabeth W. Sun,¹ Jennifer Hsiao-Nakamoto,¹ Yashas Rajendra,¹ Katrina W. Lixa,¹ Devendra B. Srivastava,¹ Bettina van Lengerich,¹ Junhua Wang,¹ Yaneth Robles-Colmenares,¹ Do Jin Kim,¹ Joseph Duques,¹ Melina Lenser,¹ Timothy K. Ear,¹ Hoang Nguyen,¹ Roni Chau,¹ Buyankhishig Tsogetbaatar,¹ Pritesh Ravji,¹ Lukasz L. Skiba,¹ Hilda Solari,¹ Howard J. Rosen,¹ Bradley F. Bonves,¹ Adam L. Bozler,¹ Hilary W. Heuer,¹ Mark S. Dennis,¹ Mihaila S. Kartalis,¹ Kathryn M. Monroe,¹ Laralyne Przybylski,¹ Pascal E. Sanchez,¹ Rene Molmer,¹ Dolores Diaz,¹ Kirk R. Harris,¹ Ryan J. Watts,¹ Anastasia G. Henry,¹ Kamran Gursankaran,¹



LAMP2
Lysosome Marker

BMP
Lipid critical for lysosome activity

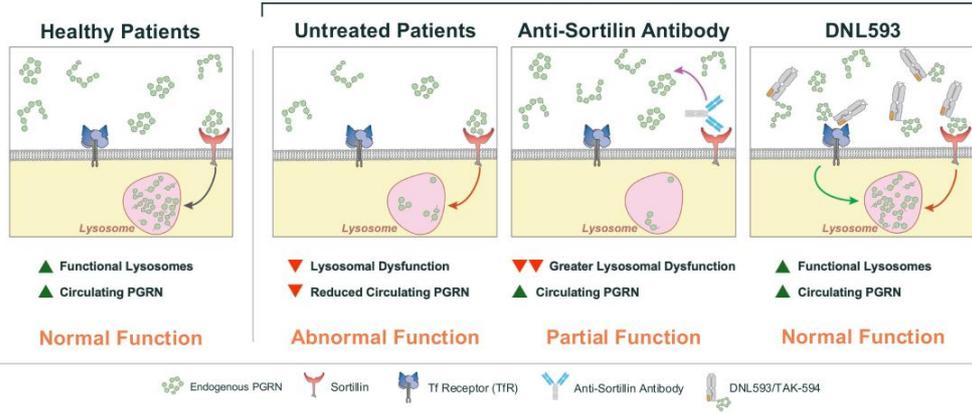
PGRN
Localized to lysosome



In preclinical models, DNL593 improves both glial activation and neurodegeneration biomarkers relevant in FTD-GRN

DNL593 Mechanism Is Distinct from Other Therapeutic Approaches

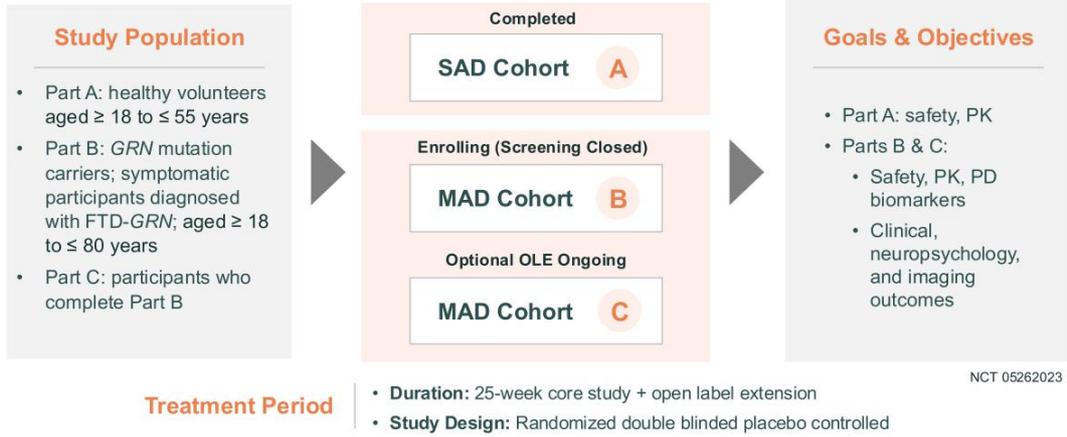
FTD-GRN



DNL593 is a protein replacement therapy designed to restore extracellular and lysosomal PGRN while Anti-Sortilin MOA boosts extracellular PGRN but leaves lysosomal deficiency unresolved

Modified from Simon et al. *TICB* 2022

DNL593 Phase 1/2 Clinical Study



Phase 2 Part B interim data in patients with FTD-*GRN* will read out in 2026

FTD – Frontotemporal dementia; *GRN* – Granulin; MAD – Multiple ascending dose; PD – Pharmacodynamics; PK – Pharmacokinetics; SAD – Single ascending dose

Accumulating ETV Clinical Experience Supports Broad Platform Potential

Franchise	Current Study	Efficacy to Date	Safety to Date
tividenofusp alfa DNL310 MPS II (Hunter syndrome)	Phase 1/2 DNLI-E-0002 Primary analysis ¹	<ul style="list-style-type: none"> >90% reduction in CSF HS Normalization of CSF and urine HS Reduction and normalization of serum NFL 	<ul style="list-style-type: none"> IRR's clinically manageable and decrease over time Anemia: early declines in hemoglobin generally returning to baseline, clinically manageable, no discontinuations due to anemia Anemia frequently observed at baseline in MPS II
ETV:SGSH DNL126 MPS IIIA (Sanfilippo syndrome)	Phase 1/2 DNLI-I-0001 Initial data ²	<ul style="list-style-type: none"> Biomarker POC achieved 	<ul style="list-style-type: none"> IRR's clinically manageable and decrease over time Anemia: mild anemia (Grade 1) in 1 participant with iron deficiency at baseline
PTV:PGRN DNL593 FTD-GRN (Frontotemporal dementia-granulin)	Phase 1/2 DNLI-H-0001 Blinded study ongoing ³	<ul style="list-style-type: none"> Dose-dependent increase in CSF progranulin in healthy volunteers 	<ul style="list-style-type: none"> IRR's appear clinically manageable with standard measures including pre-medications No anemia-related TEAEs to date

Robust CNS activity and manageable safety observed across multiple ETV programs

1. October 9, 2024 CCOD (N=47); 2. June 4, 2025 CCOD (N=14); 3. As of November 20, 2025; CCOD – clinical cut off date

DNL952 (ETV:GAA) Enhances Delivery of GAA to Muscle



Program status: Protocol amended and response to FDA submitted regarding clinical hold

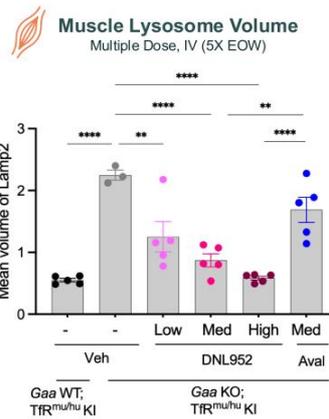
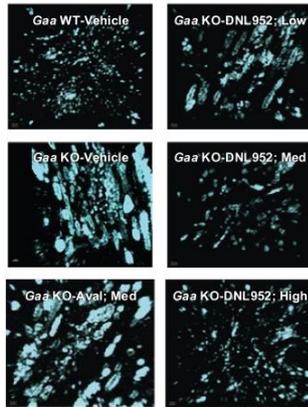
Key Characteristics

- Molecule delivers GAA to whole body, including difficult to access tissues
- TfR tuned to maximize delivery of GAA to both muscle and CNS
- Fc domain portion of TransportVehicle™ improves manufacturability and drug-like properties

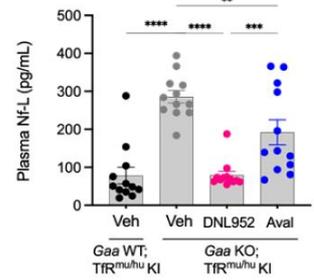
DNL952 aims to improve GAA delivery to muscle over existing therapy and deliver GAA to the brain

DNL952 (ETV:GAA) Superior to Competitor Enzyme in Both Muscle and Brain

LAMP2



Plasma Neurofilament



DNL952 improves muscle and CNS biomarkers relative to 2nd generation ERT in a preclinical model

Standard of care: Aval. – avalglucosidase alfa-ngpt

DNL952 Phase 1 Clinical Study Plan



Treatment Period

- **Duration:** 24-week core study + 24-week safety extension
- **Study Design:** Open label

Phase 1 biomarker data expected in 2027¹

1. Protocol amended and response to FDA submitted regarding clinical hold; ERT – Enzyme replacement therapy; LOPD – Late onset Pompe disease; PK – Pharmacokinetics

Building the ETV Franchise Portfolio

	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-granulin)	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 application submitted ³	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. PDUFA target action date of 4/5/26 for accelerated approval; 3. Protocol amended and response to FDA submitted regarding clinical hold



TransportVehicle™ Platform: Transforming Treatment
for Alzheimer's Disease (AD)



/ Why Now Is the Time for Breakthroughs in AD

Ryan Watts, Ph.D.
Chief Executive Officer

Opportunity is Breaking Open in Alzheimer’s Disease (AD)

Recent Advances Bring New Hope to People Living with AD

- New anti-amyloid therapies are the first disease modifying treatments
- New biomarkers and imaging tools
- New targets show promise in clinical testing, e.g., tau
- TfR-based targeting technology shows promise in clinical testing

55 Million People Live with AD and Other Forms of Dementia

Opportunity for New Therapies to Improve Efficacy and Safety

Unmet Needs Include:

- Faster plaque reduction
- Lower doses
- More convenient delivery
- Reduced risk of ARIA



Denali is Positioned to Deliver the Next Generation of AD Therapies

- Discovery programs for multiple AD targets
- Best in class opportunities to improve efficacy and safety

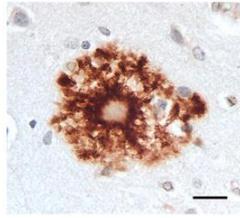


We Aim to Deliver Effective Medicines with Broad Societal Impact

TfR – Transferrin receptor; ARIA – Amyloid-related imaging abnormalities

Three Pillars of Alzheimer's Disease Pathology

1 Amyloid-Beta (Aβ) Plaques

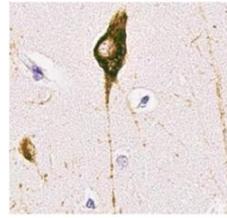


Disease Pathology Often thought to be the "trigger" that kicks-off the disease

Therapeutic Strategy Anti-Aβ clinically validated

TV Opportunity Clear path to differentiate with TfR

2 Neurofibrillary (Tau) Tangles

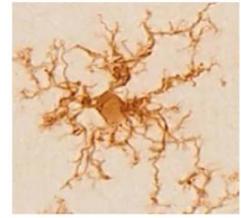


Most closely associated with cognitive decline in AD

Knockdown of Tau emerging as optimal strategy

TfR delivery enables improved BioD and peripheral dosing

3 Neuroinflammation & Hypometabolism



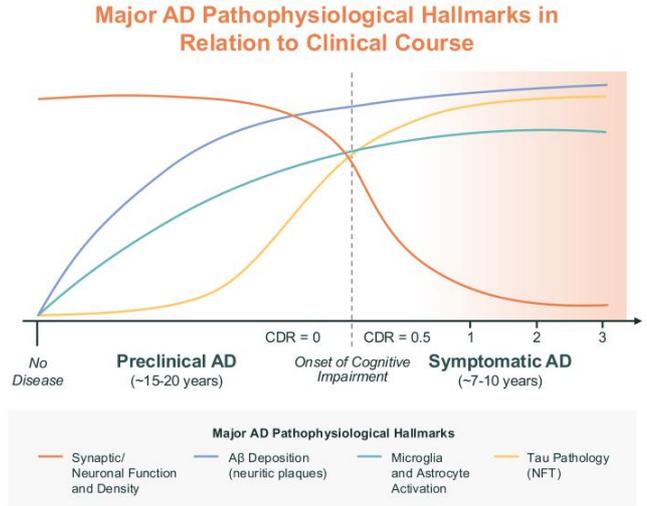
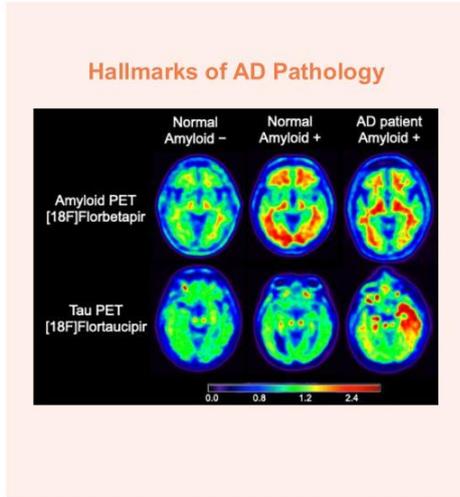
Characterized by microglial activation

Currently higher biology risk; ideal mechanism unclear

TfR delivery possible pending target validation

Walker L, *Free Neuropath*, 2020; Bengoa-Vergniory et al, *Acta Neurop*, 2021; Fernandez-Arjona et al, *Frontiers*, 2017

Alzheimer's Disease Progresses Over Decades



Left image from Carney Institute for Brain Science / Brown University (HEAD Study); Right image adapted from Long and Holtzman (2019) *Cell* Volume 179, Issue 2p312-339

Advancements in Biomarkers Enable AD Trial Optimization

Current Biomarkers in AD Clinical Studies

	Blood	PET	CSF	Advancements
Patient ID	Abeta pTau	Abeta Tau	Abeta	<ul style="list-style-type: none"> • Tests less expensive and less invasive • Accurately IDs patients for study inclusion
Patient Stratification	–	Tau	–	<ul style="list-style-type: none"> • Stratification by tau severity predicts clinical progression rate and response magnitude
Target Engagement (TE)	pTau	Abeta Tau	Tau pTau	<ul style="list-style-type: none"> • Enables assessment of magnitude and duration of tau therapy • Enables TE assessment for Abeta therapy

AD trial precision, speed and efficiency improved by recent biomarker breakthroughs

AD Treatment Landscape is Rapidly Evolving

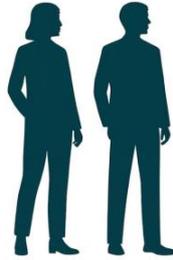
		Safety	Efficacy	Route of Administration	
	1st Gen Abeta (Abeta mAbs)	–	+	IV	Risk of ARIA; modest benefit
	Next-Gen Abeta TfR-Enabled Antibody	+	+++	IV, SC	Better brain uptake, faster plaque clearance and safer route of entry into brain
	1st Gen Tau (ASO/siRNA)	+	+	IT	Limited brain biodistribution
	Next-Gen Tau TfR-Enabled ASO/siRNA	+	++	IV	Better brain uptake and more convenient / less invasive

TransportVehicle™ is positioned to deliver best in class Next-Gen TfR-enabled therapies for AD

The Future of Alzheimer’s Disease Prevention: Treating Before Cognitive Decline Begins

Preclinical Alzheimer’s Disease

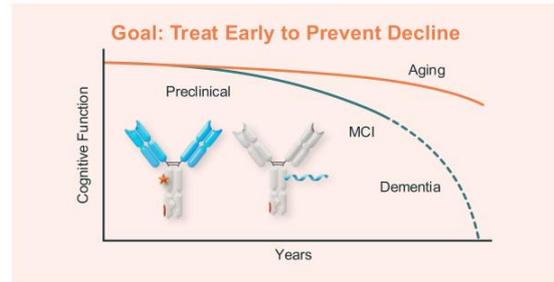
- Earliest stages of AD
- Brain changes begin
- **No signs of cognitive decline**
- Positive brain biomarkers (lesions)



- PET Amyloid / Tau
- Cognitive Decline

Future State: Early Diagnosis & Safe Treatments

- Accessible screening, simple blood tests
- Safe treatments, i.e., minimize ARIA risk
- Prevent cognitive decline



We See a Promising Future for AD with the TransportVehicle™

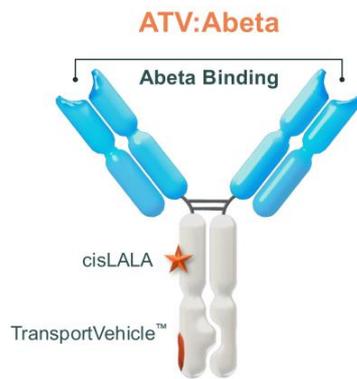


TransportVehicle™ Platform: Transforming Treatment
for Alzheimer's Disease (AD)

/ Next-Generation of TV-Enabled Therapeutics for AD

Joe Lewcock, Ph.D.
Chief Scientific Officer

DNL921(ATV:Abeta) Designed to Maximize Efficacy and Improve Safety



Program status: IND/CTA filing in 1H 2026

Key Characteristics

- TfR engagement tuned to maximize CNS biodistribution and target engagement while minimizing ARIA
- cisLALA architecture that is unique to TV allows molecule to safely retain effector function
- Designed to preferentially bind oligomeric Abeta and minimize monomer binding

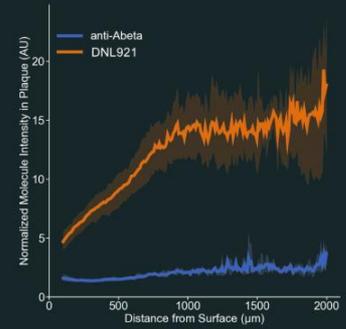
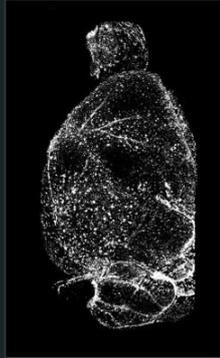
DNL921 is highly differentiated and has potential for best-in-class BBB-enabled Abeta mAb

DNL921 Exhibits Superior Target Engagement and Deeper Brain Penetration Compared to First Gen Anti-Abeta



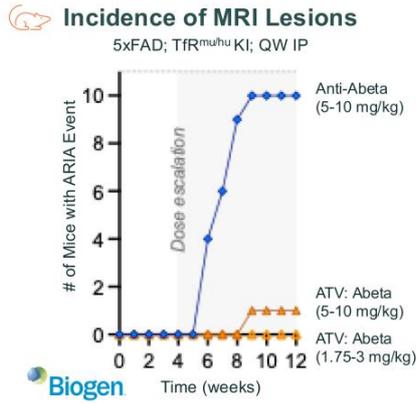
1st Generation
Anti-Abeta

DNL921

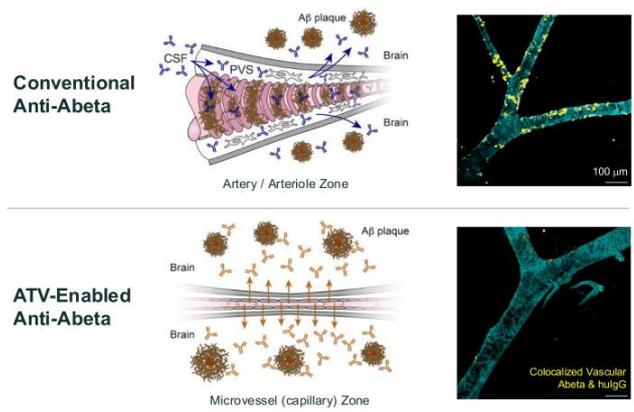


10 mg/kg, 24 hrs post-dose, iDISCO-cleared hemibrain; signal represents amyloid plaque engagement

ATV:Abeta Displays Reduced ARIA Due to TfR-Mediated Brain Uptake



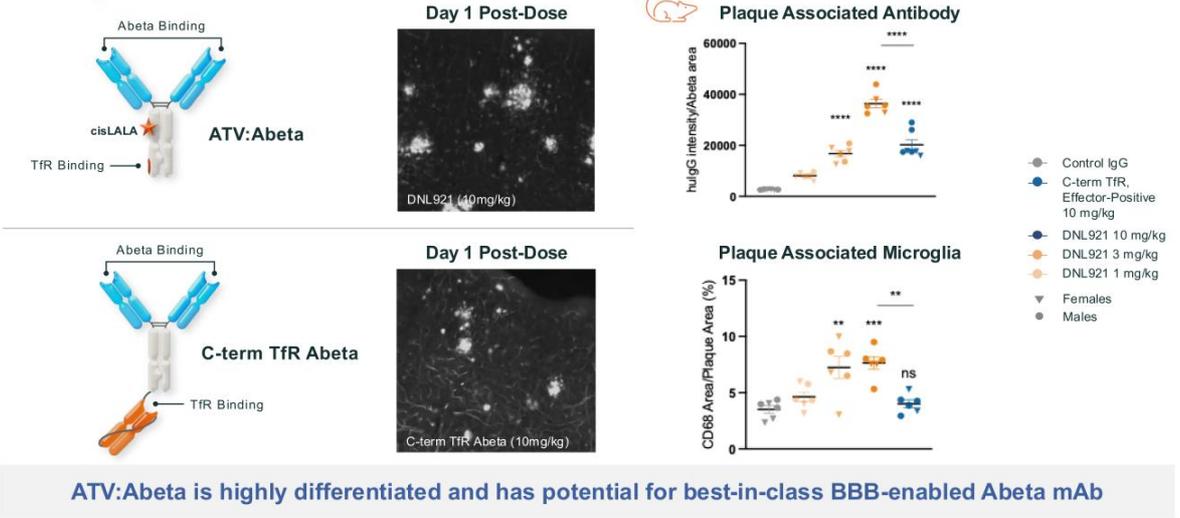
Route of Entry into Brain



Bypassing vascular plaque via TfR-mediated entry into the brain through capillaries and venules improves ARIA safety

Pizzo et al., Science, 2025

DNL921 Displays Greater Amyloid Plaque Engagement than Competitor TfR Architectures



Engineering a Better Amyloid Beta Targeting Therapeutic

Approved Amyloid Beta Immunotherapies

Modest clinical benefit with significant risk of ARIA and slow plaque reduction



Opportunity for next-generation therapies to improve safety and efficacy

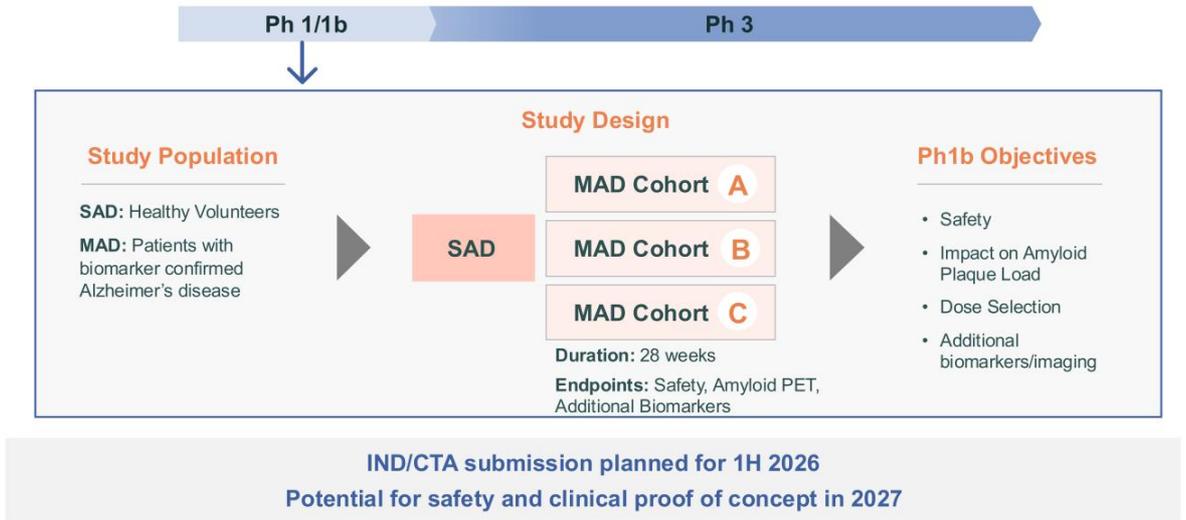
All TfR-Based Anti-Amyloid Beta Therapeutics are Not Engineered Equal

Desired Feature	ABBV-1758	Trontinemab	DNL921 ²
Properties			
Optimized TfR Binding	+	+	++
Effector Function	None	Full	Conditional
Efficacy			
Better Brain Uptake	++	++	+++
Improved Plaque Clearance	- ¹	++	+++
Safety			
Avoid ARIA	++	+	+++
Avoid Anemia	+++	+	+++
Avoid Immunogenicity	-	-	++

DNL921 (ATV:Abeta) has the potential to be the best-in-class anti-amyloid immunotherapy

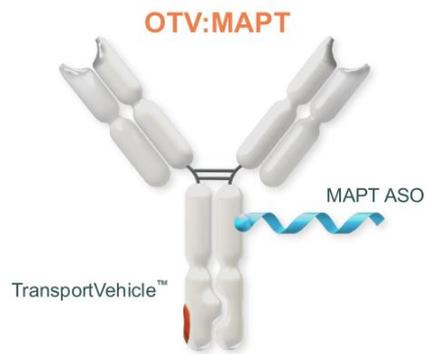
1. Denali internal results and published data demonstrates effector function is required for maximal plaque clearance. 2. Assessment based on Denali's preclinical data

DNL921 Clinical Study Design Enables Rapid Proof of Concept



SAD – Single Ascending Dose; MAD – Multiple Ascending Dose

DNL628 (OTV:MAPT) Enables Tau Knockdown Throughout CNS Following Peripheral Administration



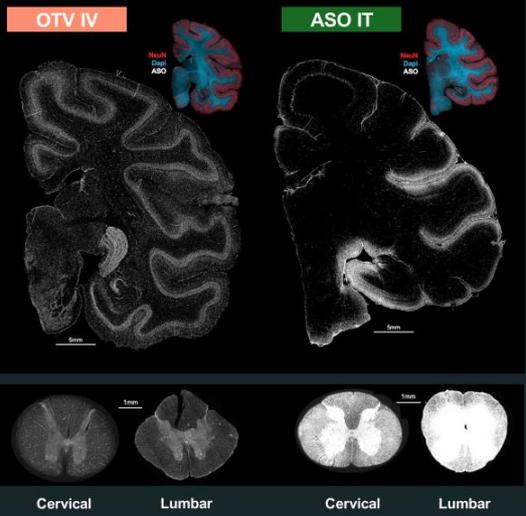
Program status: CTA Filed October 2025

Key Characteristics

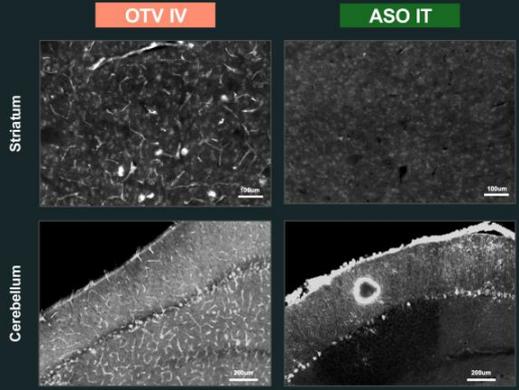
- TfR engagement optimized to maximize CNS uptake & biodistribution of oligo
- Biologic and oligo portion of molecule are engineered to improve exposure and safety
- Design principles can be readily applied to additional OTV programs

DNL628 has best in class potential based on improved brain biodistribution via peripheral administration

OTV Eliminates Sharp ASO Gradient that Results from IT Dosing



Enhanced ASO Deposition in Brain Regions that are Challenging to Target

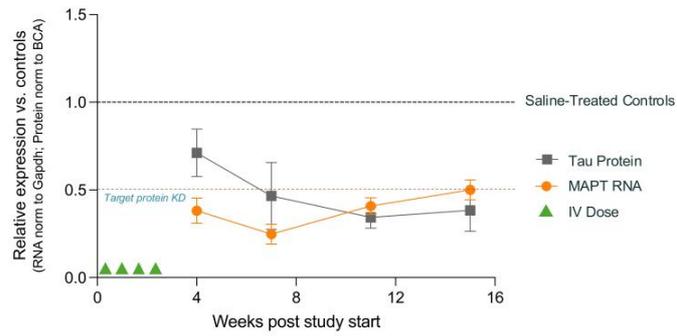


Barker et al., STM, 2024

DNL628 Displays Robust and Sustained Knockdown in Mice Expressing Human Tau



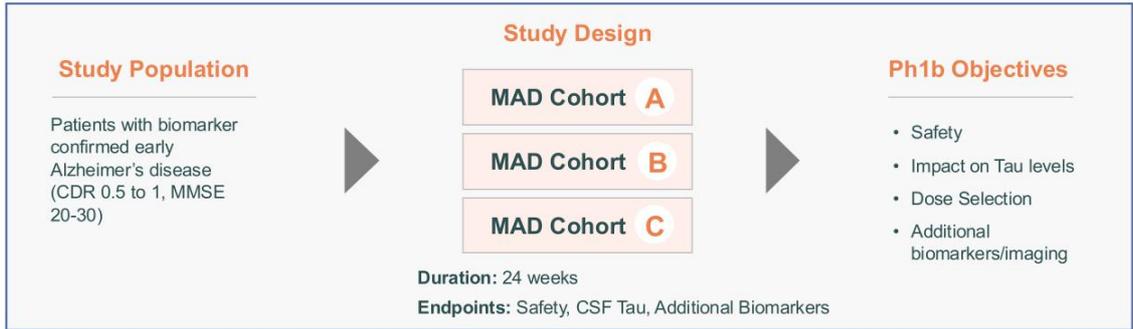
Brain MAPT RNA and Tau Protein Knockdown (KD) Persists for >12 Weeks After Dosing



Robust and sustained reduction in tau protein with DNL628

Triangles indicate individual doses over two week time period

DNL628 Clinical Plan Designed to Quickly Determine Tau Knockdown in Brain



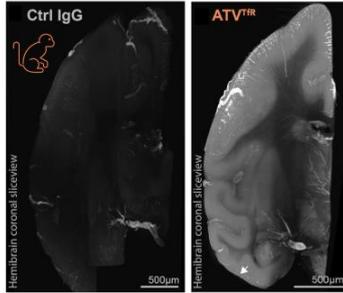
CTA submitted October 2025
Clinical biomarker data expected by 1H 2027

Our TransportVehicle™ Platform Sets the Bar for BBB Delivery

Our Fc-based TransportVehicle™ (TV) Is Designed & Engineered to Optimize Brain Delivery



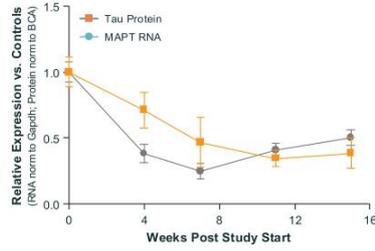
1 Modularity: TransportVehicle™ Can Deliver Diverse Therapeutic Modalities



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



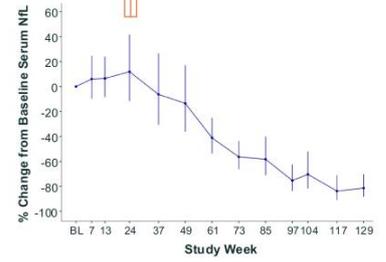
Tau Knockdown



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



NFL Correction



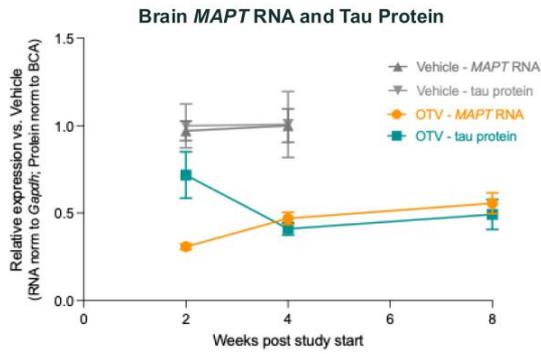
TV enables ETV:IDS to reduce serum NFL by >80%, achieving normal levels

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

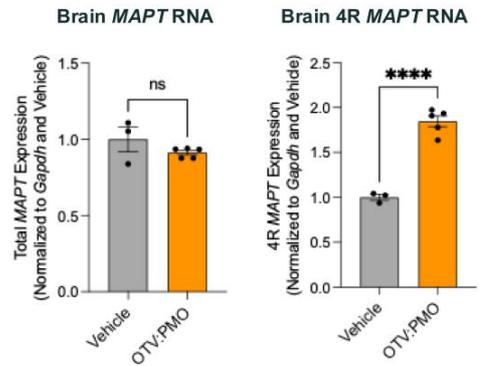
Khoury et al. *Nature Communications* (in press); NFL – Neurofilament light, a marker of neurodegeneration; Source: tau – Denali data on file, NFL – Adapted from SSIEM 2024

1 Modularity: TransportVehicle™ Is Compatible with Multiple Oligonucleotide-based Therapeutics

OTV:siRNA¹
Achieves Target
Knockdown via RISC



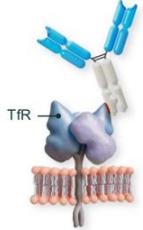
OTV:PMO¹ Achieves
Isoform Modulation via
Splicing Interference



1. OTV:siRNA and OTV:PMO generated using publicly available oligo sequences as tools for platform proof of concept

1 Modularity: TransportVehicle™ Is Capable of Leveraging Additional BBB Transporters

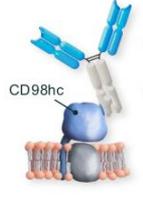
TfR TV Platform



- Highly expressed on brain endothelium
- Undergoes constitutive endocytosis and recycling = **high transport capacity**

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE | May 2020
BLOOD-BRAIN BARRIER
 Brain delivery of therapeutic proteins using an Fc fragment blood-brain barrier transport vehicle in mice and monkeys

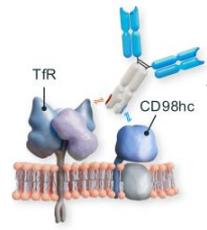
CD98hc TV Platform



- Highly expressed on brain endothelial cells
- Capacity and kinetics **distinct from TfR**; opportunity for distinct target classes

nature communications
 Article
CD98hc is a target for brain delivery of biotherapeutics

Dual TV Platform Binds Both TfR and CD98hc

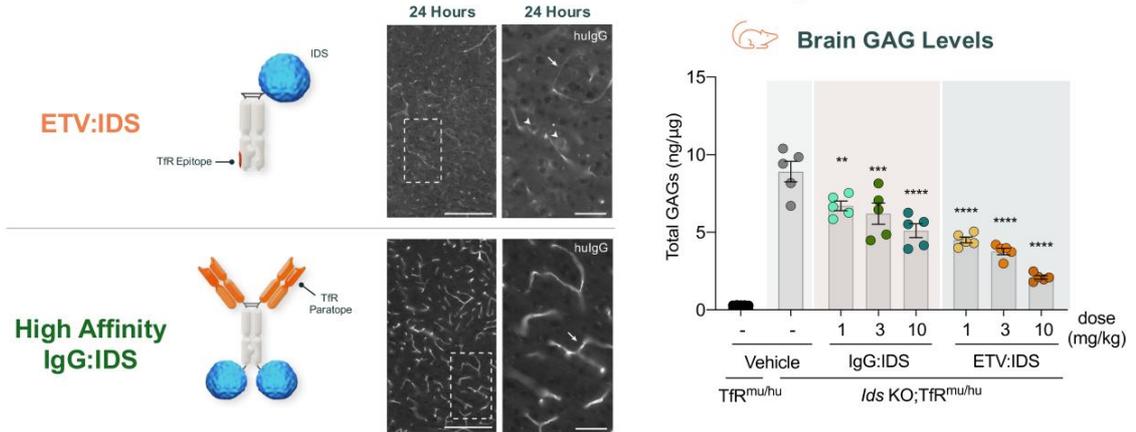


- Leveraging capacity of **two transporters** enables maximal brain uptake

Cell Reports
 Article
Dual targeting of transferrin receptor and CD98hc enhances brain exposure of large molecules

**We continue to invent and lead the BBB field
 TfR remains most validated transporter with demonstrated high capacity in humans**

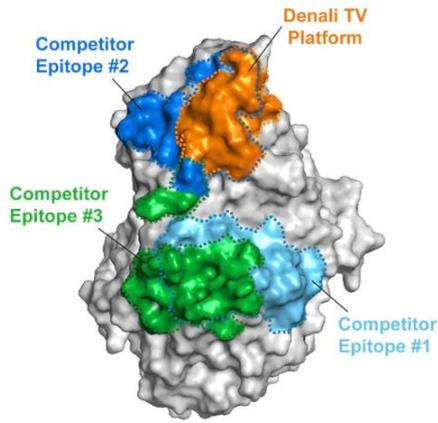
2 Brain Uptake: Optimized Affinity of Transport Vehicle™ Drives Brain Biodistribution and Efficacy



ETV:IDS shows broader biodistribution and greater GAG reduction than high affinity TfR in MPS II mouse model; results are consistent with clinical data from both architectures

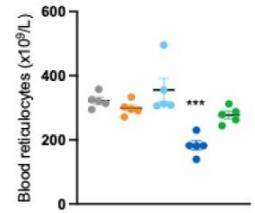
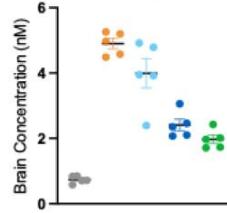
Arguello et al., JEM, 2022

3 Safety: TransportVehicle™ Engineering Enables Robust Brain Delivery Without Impacting Reticulocytes



Brain Concentration
Single Dose, IV 10 mg/kg (molar-matched)

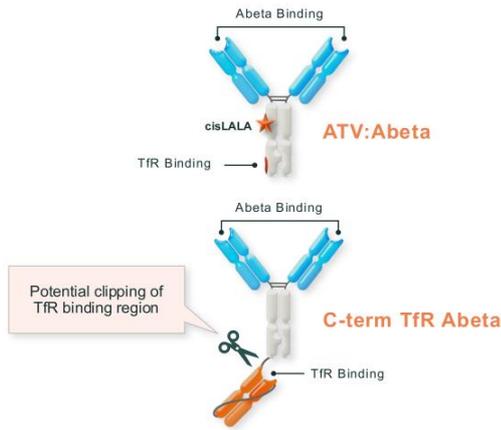
Immature Reticulocytes
Single Dose, IV 10 mg/kg (molar-matched)



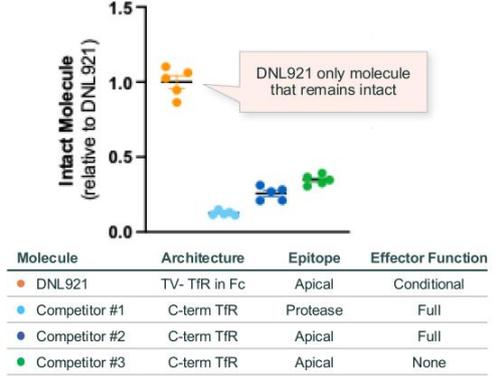
Molecule	Architecture	Epitope	Effector Function
Control	Control IgG	N/A	Full
DNL921	TV- TfR in Fc	Apical	Conditional
Competitor #1	C-term TfR	Protease	Full
Competitor #2	C-term TfR	Apical	Full
Competitor #3	C-term TfR	Apical	None

Competitor Molecules generated at Denali based on publicly available information on TfR-binding anti-Abeta antibodies currently under development

4 Architecture: Engineering of TfR Binding into Fc Domain in TransportVehicle™ Improves Stability



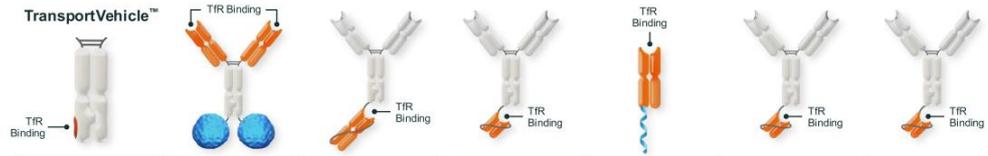
Intact Molecule
 hlgG Capture vs. TfR Capture ELISA, Single Dose IV 10 mg/kg



Appended TfR binding regions on competitor molecules are clipped *in vivo*; may limit brain uptake

Competitor Molecules generated at Denali based on publicly available information on TfR-binding anti-Abeta antibodies currently under development

TV Is Differentiated Relative to Other BBB Approaches



	DENALI	JCR Pharma	Roche	Aliada/Abbvie	Arrowhead	BioArctic	Alector
TfR Binding Format	Engineered into Fc	High affinity antibody fusion	Fab fusion	Single-chain variable fragment fusion	High affinity single-chain Fab	Single-chain variable fragment fusion	Single-chain variable fragment fusion
TfR Binding Domain	Apical	Apical	Apical	Protease-like	Apical	Protease-like	Apical
1 Modularity	Enzymes, Abs, oligos, proteins	Enzymes, gene therapy	Abs	Abs	Oligos	Abs	Claimed but limited data
2 Brain Uptake	Optimized for each program	High affinity limits uptake	Inferior compared H2H with TV	Inferior compared H2H with TV	No H2H data vs TV platform	Inferior compared H2H with TV	No H2H data vs TV platform
3 Safety	Conditional effector function	Safety caps at low doses	Some anemia	Safety strategy may limit efficacy	No data reported	Preclinical data only	Retic loss in monkey reported
4 Architecture	No appended sequences	Dose limited	Immunogenicity/stability concern	Immunogenicity/stability concern	Rapid clearance predicted	Immunogenicity/stability concern	Immunogenicity/stability concern

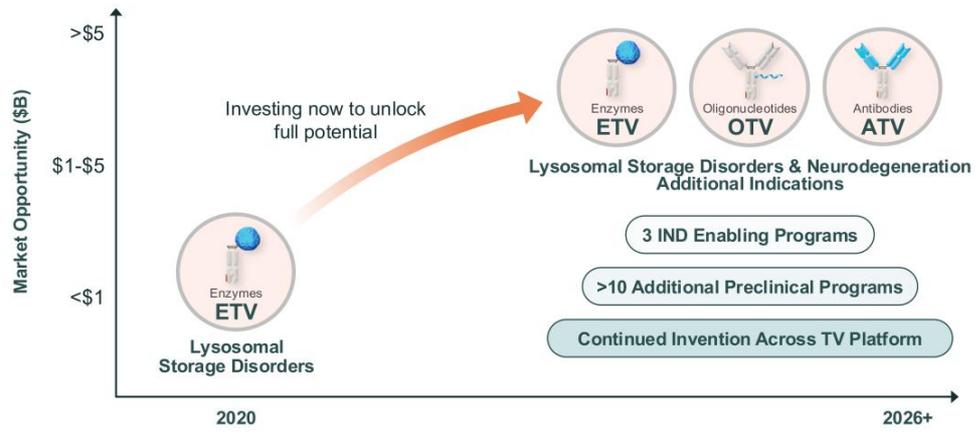
Clinical data reported

Clinical stage; No data reported

Preclinical

Heatmap based on publicly disclosures and head to head (H2H) data generated at Denali in preclinical models for any direct comparisons

Expanding the TV Franchise



We aim to recognize the full value of the TransportVehicle™ platform
Each TV Franchise has a market potential of \$5B+



Integrated Manufacturing

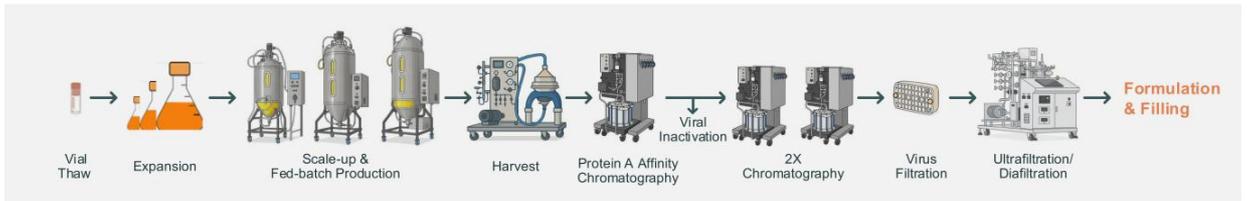
/ Driving Speed, Flexibility and Value

Dana Andersen, Ph.D.

Chief Technical and Manufacturing Officer

Denali Platform Enables Efficient Manufacturing

TransportVehicle™ (TV) architecture uses antibody-like manufacturing processes



Platform Efficiency

- Architecture enables 3-column antibody-like purification process
- Fits seamlessly within global antibody manufacturing capacity
- Royalty-free cell line and vector



Cost Impact

- Efficient processes enable projected COGS <20% of revenue
- Reduces cost and time to IND
- High productivity TV processes will support large markets



Strategic Use of Partners

- Leverage CDMOs for large-scale manufacturing to manage capacity and efficiency
- Drug product and oligonucleotide manufacturing outsourced until internalization is beneficial

Denali Has Built Internal Manufacturing Capability

GMP Manufacturing Facility Completed and Operational (Q1 2025)



- Purpose-built to support clinical production across the TransportVehicle™ platform

Strategic Benefits

Speed & Flexibility

- Enables rapid scale-up and response to evolving program needs
- Can nimbly reprioritize schedule when data supports moving quickly

Cost Efficiency

- Integrated development & manufacturing has reduced cost to IND
- Eliminates reservation fees at CDMOs

Risk Reduction

- Increases control over supply chain and product quality
- Mitigates tariff exposure

Integrated Platform Advantage

- Supports broad application of TransportVehicle™ technology
- Learnings leveraged across portfolio to increase efficiency



State-of-the-art Salt Lake City facility built for efficiency, flexibility, and speed to clinic

Manufacturing Highlights



Denali's Manufacturing Facility

- ~70,000 sq. ft. GMP facility constructed for < \$80M in Salt Lake City, UT
- 2 × 2000-L fermenters with purification train
- Designed for single-use technology and modular expansion

Flexible, Efficient Operations

- Up to 40 batches per year with staff expansion
- Single-use design enables rapid changeover between programs
- Supports both early clinical and commercial manufacturing

2025

- 8 GMP & GLP batches
- Successful GMP audit enabling EU clinical supply

All future early clinical products and commercial launch of DNL126 planned from this facility

Integrated Manufacturing Drives Speed, Flexibility & Value



Acceleration Through Integration

- Enables parallel risk-taking and quickly responding to data
- Avoids restrictions from CDMO capacity constraints
- Accelerating IND timelines by ~1 quarter for first 2 programs

Strategic Control & Risk Reduction

- Reshored DNL126 manufacturing for BLA filing and commercial launch
- Reduces at-risk manufacturing by enabling rapid response to demand signals

Economic & Strategic Advantages

- Optimized DNL126 production scale reduced COGS by ~50%
- Increased process understanding and proprietary manufacturing IP

End-to-end capabilities accelerate development, reduce risk, and strengthen long-term economics

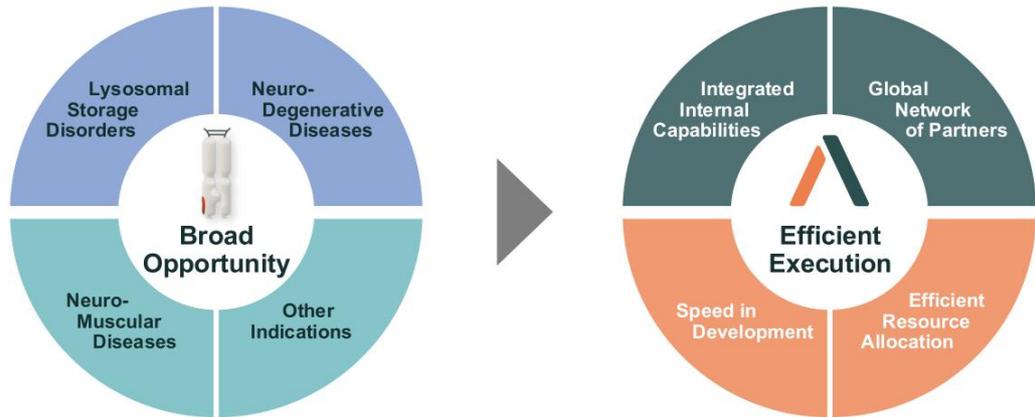


Evolving Our Business

**/ Delivering the Value of the
TransportVehicle™**

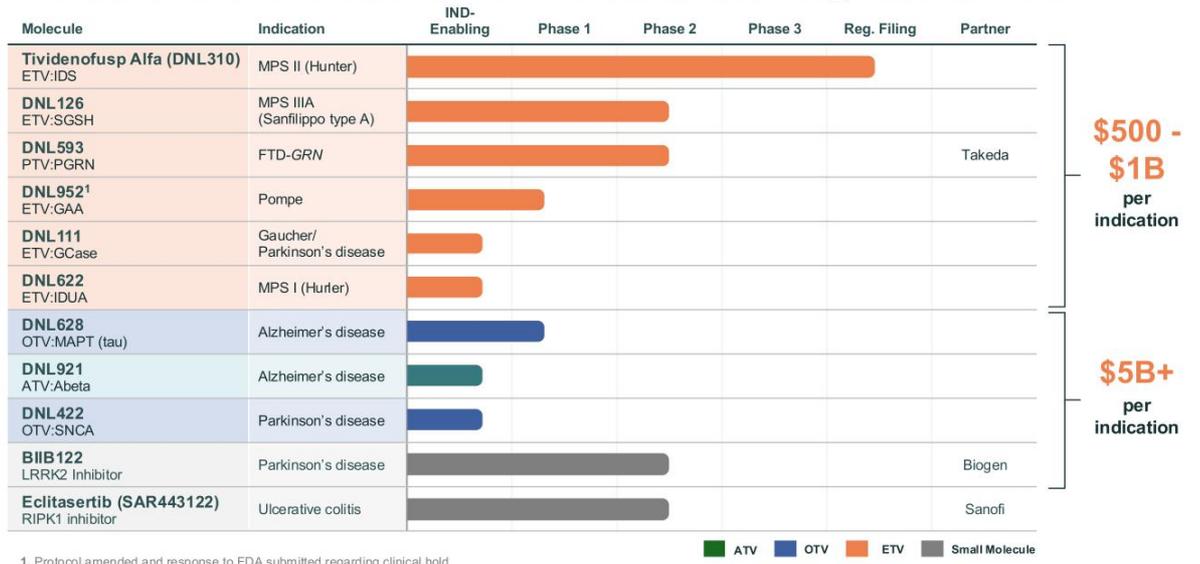
Alexander Schuth, M.D.
Chief Operating and Financial Officer

Growing and Executing the Leading Portfolio of BBB-Enabled Programs



Leading a new class of biologic therapeutics that can reach the whole body, including the brain

Broad Portfolio to Create Near-Term and Long-Term Value



Integrated Capabilities to Execute for Long Term Value

Scale and Infrastructure

- **Scale** to successfully discover, develop, manufacture and commercialize
- **Integrated infrastructure** with ~520 full time employees in South San Francisco, Salt Lake City and Zürich



South San Francisco, California

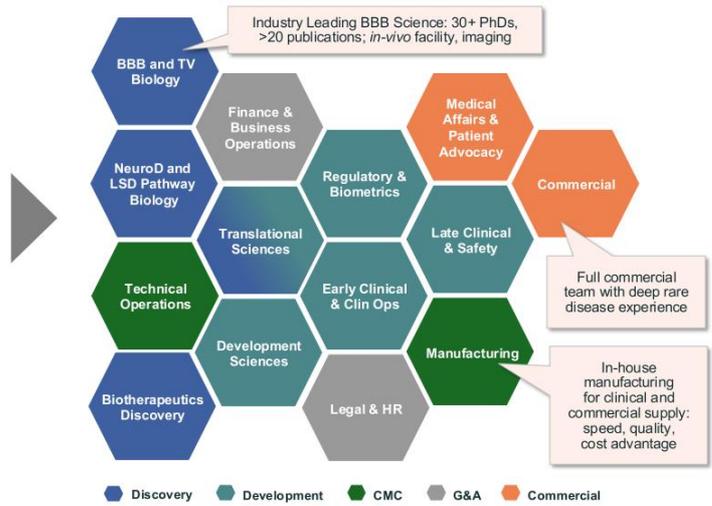


Salt Lake City, Utah



Zürich, Switzerland

Established Capabilities



Capital to Execute

Key Capital Allocation Priorities

- Invest Strategically**
 - Successful launches of tivozenofusp alfa and DNL126
 - Focused R&D investments to accelerate and expand pipeline
- Drive Capital Efficiency**
 - Apply learnings from tivozenofusp alfa to develop next programs faster and at lower cost
- Maintain Capital Optionality**
 - Partnerships remain core to strategy
 - Diversifying sources of capital

Strong Financial Foundation

\$873M + \$275M

Cash and investments as of Q3 2025 plus new royalty financing¹

2 Commercial Launches

Potential revenues from tivo and DNL126

3 Partnerships

Cost share and potential milestone income

1. Royalty financing will contribute \$200M upon approval of DNL310 by June 30, 2026 and an additional \$75M upon EMA approval by December 31, 2029

Royalty Financing Agreement with Royalty Pharma (12/4/25)

DENALI **ROYALTY PHARMA**

Denali Therapeutics and Royalty Pharma Announce \$275 Million Royalty Funding Agreement

SOUTH SAN FRANCISCO, Calif. and NEW YORK, N.Y. — December 4, 2025 — Denali Therapeutics Inc. (Nasdaq: DNLJ) and Royalty Pharma plc (Nasdaq: RPRX) today announced a \$275 million synthetic royalty funding agreement based on future net sales of tvidenofusp alfa.

Tvidenofusp alfa is Denali's lead investigational TransportVehicle™-enabled enzyme replacement therapy for the treatment of mucopolysaccharidosis type II (MPS II, or Hunter syndrome). A Biologics License Application (BLA) for accelerated approval of tvidenofusp alfa is under review by the U.S. Food and Drug Administration (FDA) with a Prescription Drug User Fee Act (PDUFA) target date of April 5, 2026.

"We are pleased to partner with Royalty Pharma, whose investment recognizes the value and potential of tvidenofusp alfa for the Hunter community and supports our ability more broadly to realize the promise of the TransportVehicle platform," said Ryan Watts, Ph.D., Chief Executive Officer of Denali Therapeutics. "With these additional funds, we are well positioned to advance our development programs as we prepare for the launch of tvidenofusp alfa, unlocking broad opportunities across serious diseases."

"We are delighted to partner with Denali and acquire a royalty on tvidenofusp alfa, an innovative therapy that addresses a significant unmet need in the cognitive and physical manifestations of Hunter syndrome," said Pablo Legorreta, Chief Executive Officer and Chairman of the Board of Royalty Pharma. "Denali's technology platform delivers therapeutics across the blood-brain barrier and is a promising new approach to brain diseases. We are thrilled to establish a relationship with Denali and believe tvidenofusp alfa is a potential practice-changing therapy that could transform the lives of patients with Hunter syndrome."

\$275M potential total funding¹:
\$200M at US approval and
\$75M at EMA approval

9.25% royalty payable on worldwide
 net sales of tvidenofusp alfa

Royalty payments capped at **2.5x**
 by Q1 2039 and **3x** thereafter

Investment to support successful commercial launch and portfolio execution

1. \$200M funded upon U.S. approval by June 30, 2026, and \$75M upon EMA approval by Dec 31, 2029

Efficient Capital Allocation and Acceleration in Execution

Applying Learnings, Leveraging Networks and Capturing Operational Synergies

- Streamlined clinical studies and validated biomarkers
- Established relationships with stakeholders (health authorities, KOLs, patient groups, policy makers)
- Preferred partnerships with clinical sites and CROs
- In-house manufacturing for all future TV programs
- Commercial infrastructure to support future launches



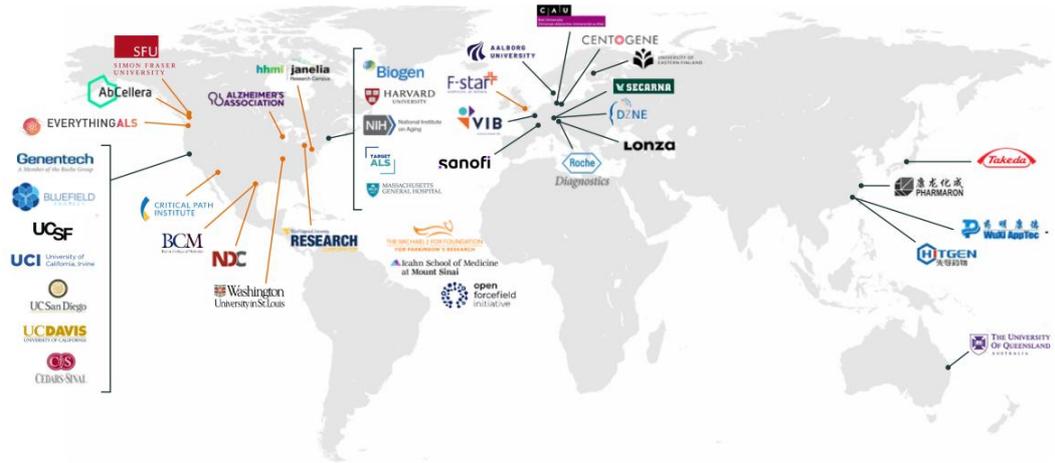
Case Study: DNL126 vs. DNL310

	Potential 1 st Launch DNL310 ¹	Potential 2 nd Launch DNL126 ²	Acceleration / Cost Saving
Number of Patients to Enable Accelerated Approval	47	20	55%
Total Manufacturing Costs	\$280M	\$100M	65%
Time from FIH to Potential US Approval	5 yrs 8 months	4 yrs	30%
Total Expected Development Costs to Approval	\$700M	\$340M	50%

Develop next programs with significantly increased speed and cost efficiency

1) PDUFA date April 5, 2026 for DNL310; 2) Potential AA in Q4 2027

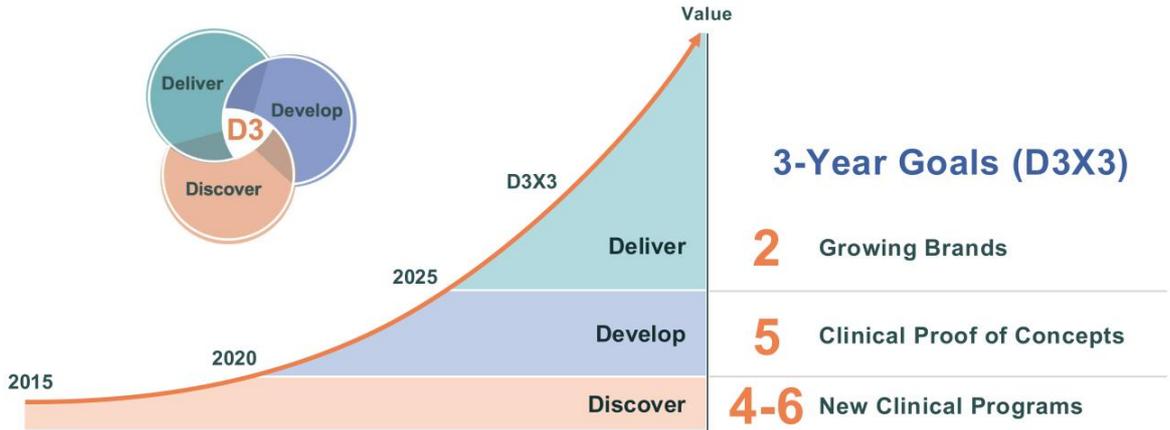
Collaborations Are Central to Our Execution Strategy



Network in academia and industry strengthens depth in science and global reach in execution

Note: Includes current and former partners

Entering a New Phase on the Path to the Summit



Pioneering a new class of biotherapeutics and capturing the full potential of the TransportVehicle™

2026-2027 Expected Milestones

◇ Trial Initiation ◆ Data ★ Submission/Approval



1. Protocol amended and response to FDA submitted regarding clinical hold

Our Purpose



**Deliver the power of biotherapeutics to the whole body, including the brain,
transforming life for people living with serious diseases**

DENALI



/ Q&A

Denali's Leadership Team

DENALI

 **Thank You**



