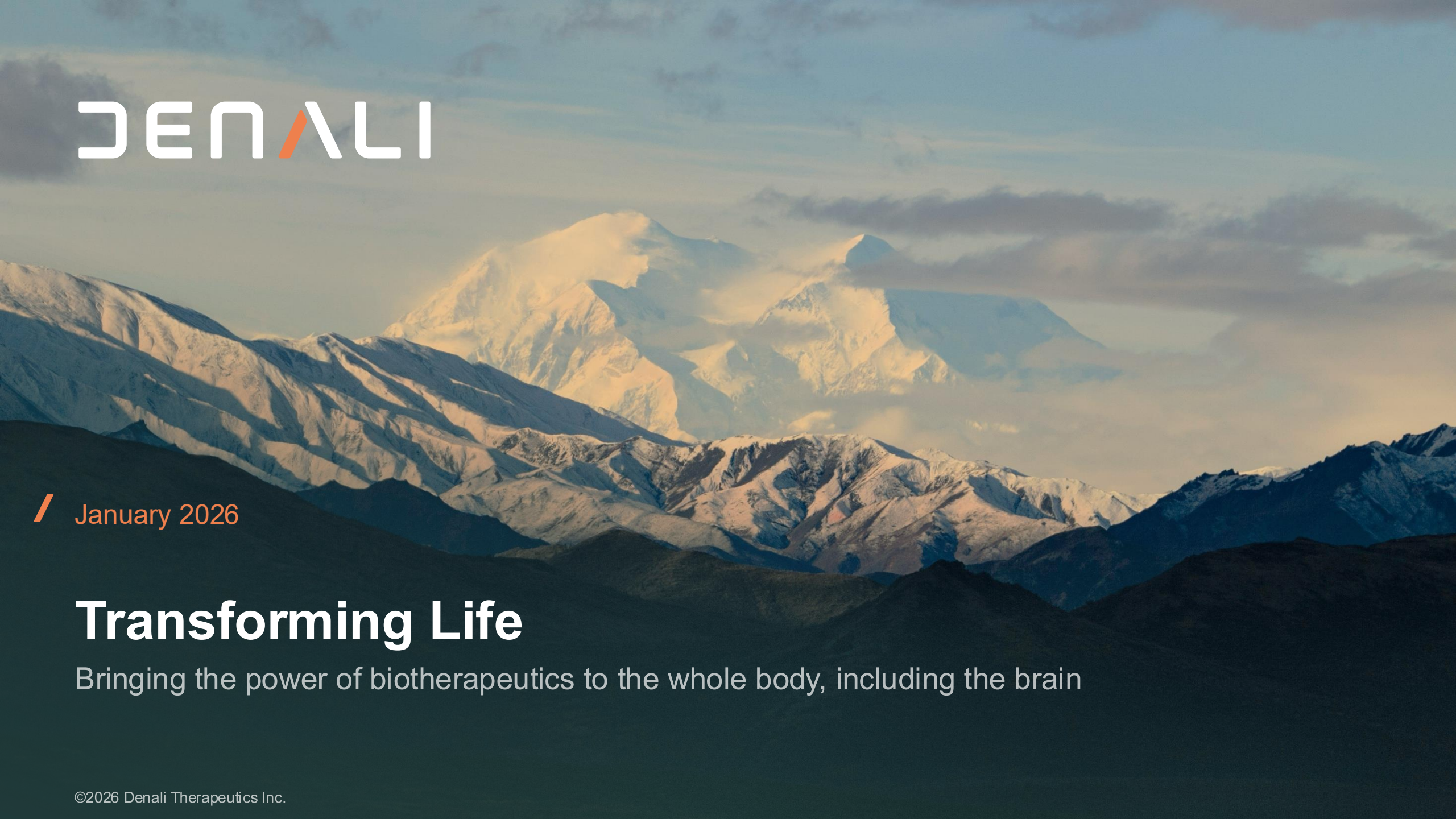


January 2026

Transforming Life

Bringing the power of biotherapeutics to the whole body, including the brain

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 2026 and beyond; Denali’s ability to execute on its tailored manufacturing and 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, its therapeutic and commercial opportunities, and the potential of TV-supported programs to be best-in-class; plans, timelines, and expectations related to the ETV franchise 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 (ETV:IDS), including the Phase 2/3 COMPASS study and its ability to support global approvals, and the timing, likelihood, and scope of regulatory approvals and commercial launch; plans, timelines, and expectations related to DNL126 (ETV:SGSH), 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 DNL628 (OTV:MAPT) and OTV:SNCA, their therapeutic and commercial potential, the timing of study initiation and the availability of data, and the timing and likelihood of planned regulatory filings; plans, timelines, and expectations relating to DNL921 (ATV:Abeta), including its therapeutic potential, the timing and likelihood of clinical proof of concept, and the timing of planned regulatory filings; plans, timelines, and expectations relating to DNL151; plans and expectations regarding DNL593 (PTV:PGRN), the ongoing Ph1/2 study, and the timing and availability of data; plans, timelines, and expectations related to DNL952 (ETV:GAA), including the timing and availability of data; plans and expectations regarding Denali's global organization and clinical and manufacturing operations, its projected cash runway and likelihood of receipt of milestone payments, and its likelihood of achieving operational efficiencies; the expected timing and likelihood of success of Denali's commercial growth; and the potential market opportunities for each 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 ability to manufacture and supply product candidates at clinical and commercial scale, including through its internal manufacturing capabilities and its reliance on third parties for the manufacture and supply of its product candidates; 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 extent to which preclinical and early clinical results (including safety-related findings) predict later-stage outcomes; 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; Denali’s ability to realize anticipated financial resources, including receipt of contingent royalty financing and milestone payments; 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 presentation are inherently uncertain and may not occur, and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements. Accordingly, you should not rely upon forward-looking statements as predictions of future events. Information regarding additional risks and uncertainties may be found in Denali’s most recent quarterly and annual reports filed with the Securities and Exchange Commission on Forms 10-Q and 10-K, respectively, as well as Denali’s future reports to be filed with the SEC. Denali does not undertake any obligation to update or revise any forward-looking statements, to conform these statements to actual results or to make changes in Denali’s expectations, except as required by law.

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

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

Our Purpose

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

Key Messages

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 tividenofusp alfa (DNL310) in 2026 and DNL126 in 2027 lay the commercial foundation for Enzyme TransportVehicle™ (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, provides several near-term milestones

Efficient Execution and Capital Allocation

- Leveraging learnings and organizational scale to accelerate timelines and reduce cost for long-term value creation

1H 2026 Expected Milestones

- Tividenofusp alfa approval decision, ETV:SGSH Phase 1/2 data at WORLD, and additional milestones (e.g., LRRK2 Phase 2b LUMA data and OTV:MAPT, ATV:Abeta, ETV:GAA Phase 1 study initiations)

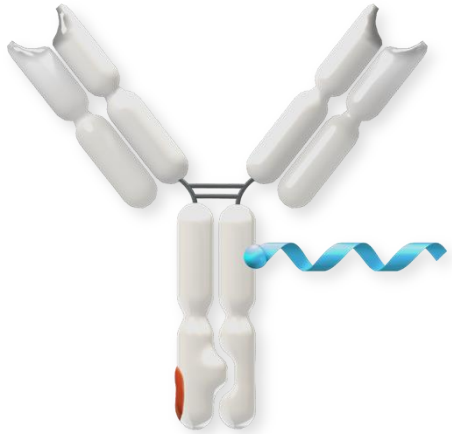
TfR – Transferrin receptor

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

Enzyme TV
(ETV)

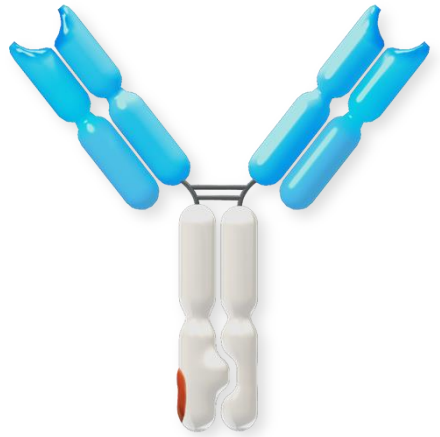
Enzyme replacement therapy for the body and brain

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

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

2 Growing Brands

- Tividenofusp Alfa
- DNL126 (ETV:SGSH)

4-6 New Clinical Programs

- Continued leadership and invention on BBB technologies

5 Clinical Proof of Concepts

Alzheimer's Disease

- DNL628 (OTV:MAPT)
- DNL921 (ATV:Abeta)

Pompe Disease

- DNL952 (ETV:GAA)

FTD-*GRN*

- DNL593 (PTV:PGRN)

Parkinson's Disease

- DNL151 (LRRK2 inhibitor)

Aiming to deliver 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

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
DNL111 (ETV:GCase)	Gaucher	IND-Enabling
DNL622 (ETV:IDUA)	MPS I	IND-Enabling

>30,000 Patients WW[2]

$500M-$1B+ per Indication[3]

Common Neurodegenerative Diseases

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

>40M Patients WW[2]

>$5B per AD/PD Indication[4,5]

1. FTD-*GRN* has a lysosomal phenotype and can be considered a rare lysosomal storage disease; **2.** Denali estimates of worldwide aggregate prevalence, excluding China and India for the lysosomal storage disorders; **3.** Lysosomal Storage Disorders Indication market based on Denali internal assessment as of Nov '25 and other syndicated data (Evaluate Pharma, Historic Annual WW Product Sales 2024, downloaded Dec 1 2025); **4.** Alzheimer's disease market opportunity based on Denali internal assessment as of Nov '25 and Evaluate Pharma Analyst Consensus Forecasts 2024 to 2034, Oct '25; **5.** Parkinson's disease market opportunity based on Denali internal assessment as of Nov '25 and other syndicated data (e.g., Herantis Pharma Plc Annual Report 2024; Herantis Pharma PLC (published March 31, 2025), Parkinson's Diseases Treatment Market 2025 to 2030, Gran View Research, https://www.grandviewresearch.com/industry-analysis/parkinsons-disease-treatment-market).
MPS – Mucopolysaccharidosis; **PD –** Parkinson's disease; **AD** – Alzheimer's disease

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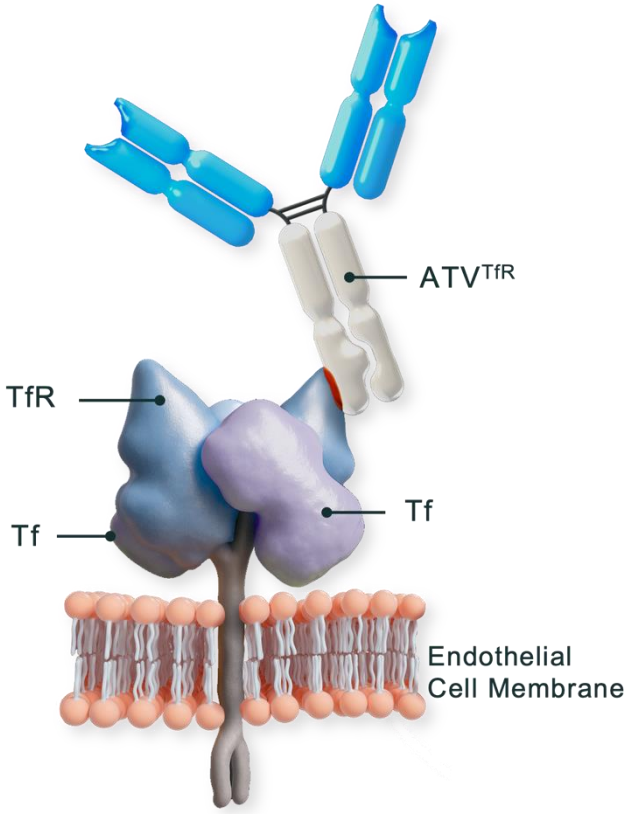
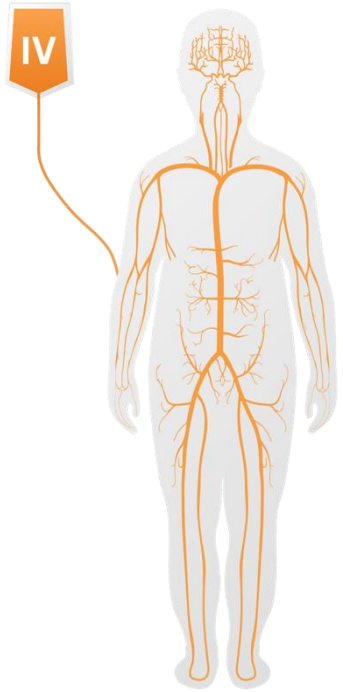
TransportVehicle™ Platform

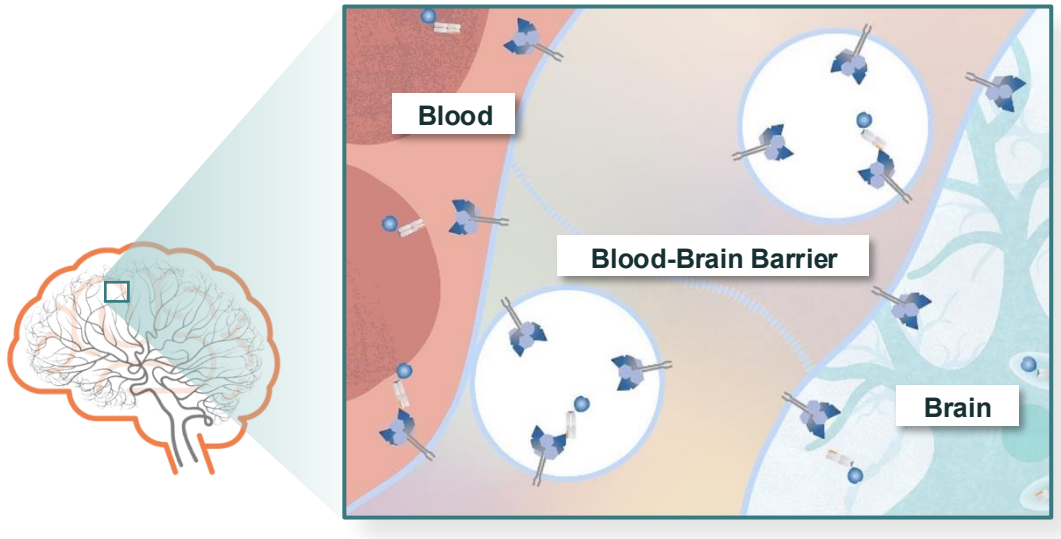
Treating the Whole Body, Including the Brain

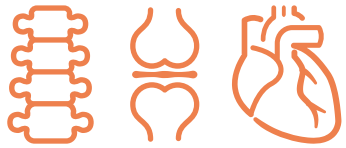


Transferrin receptor (TfR) is highly expressed at the blood–brain barrier for natural iron transport

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



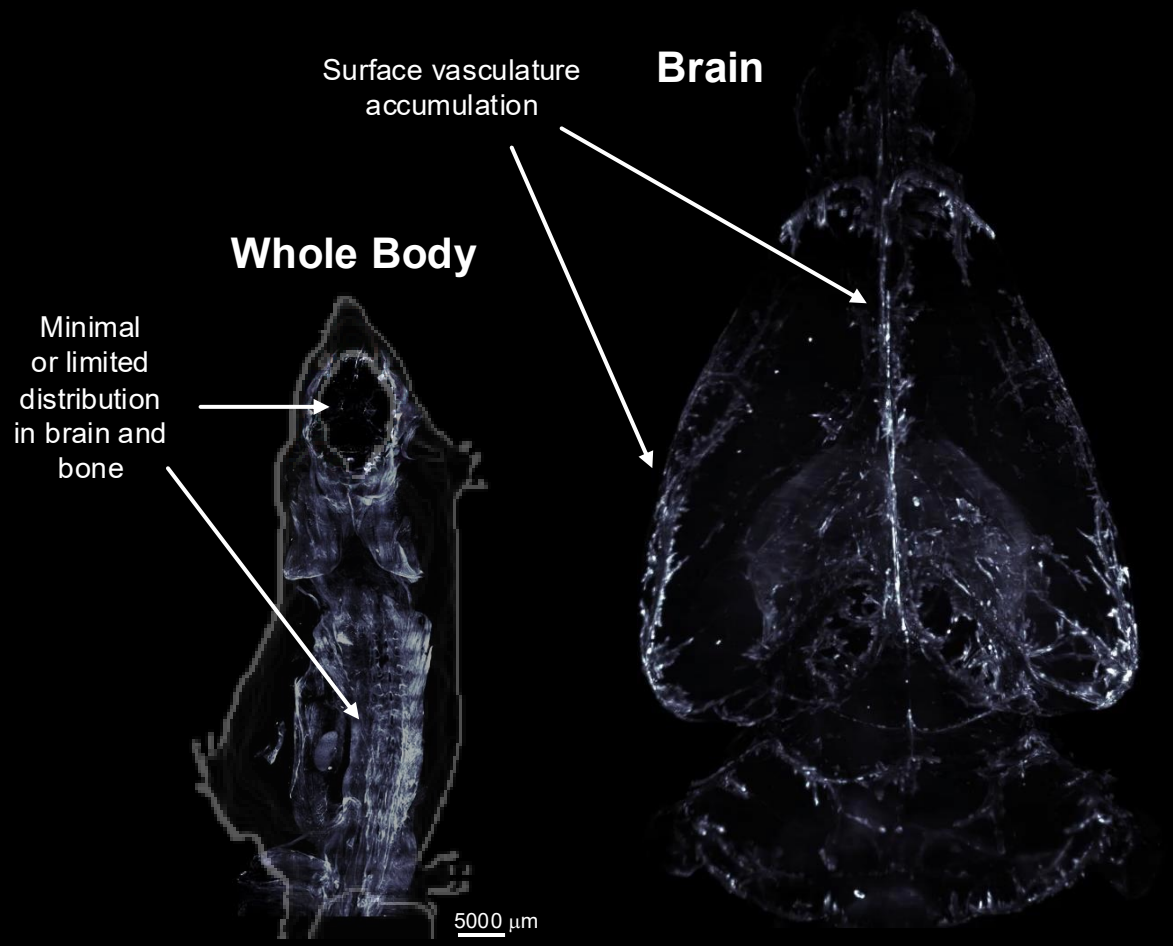




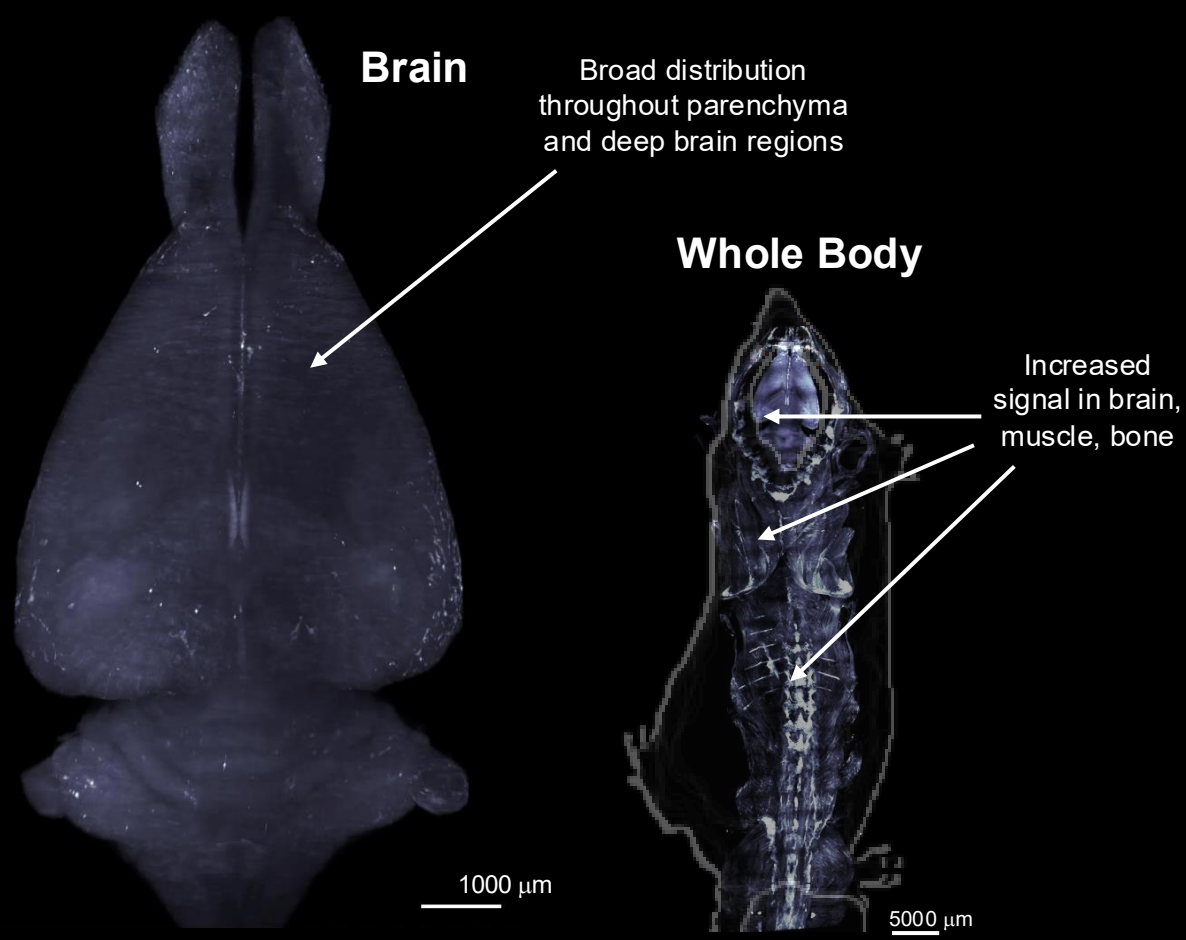
TfR may also facilitate delivery into tissues such as **bone**, **cartilage**, and the **heart**

TransportVehicle™ Distributes to Whole Body, Including Brain

Standard Antibody (IgG)



TV-enabled Antibody (TfR)



All images generated by Denali

TransportVehicle™ Has Demonstrated Best-in-Class Properties

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

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

Modularity — Enables broad ability to transport range of therapeutics, such as enzymes, oligos and antibodies

Brain Uptake — Optimized affinity and epitope enhance brain delivery while limiting receptor degradation

Safety — Conditional effector function avoids reticulocyte loss and minimizes anemia liability potential

Architecture — High fidelity to natural protein (e.g., no appended sequences) improves stability, limits immunogenicity and improves ease of manufacturing

Industry Leading Platform

- 1st Potential FDA-approved TfR therapeutic to cross the BBB
- 5 Clinical programs[1,2]
- Demonstrated ability to correct neurodegeneration (e.g., NfL)
- >10 Preclinical programs[2]
- >200 Subjects dosed[3]
- >11,000 Doses administered[3]
- >20 Publications in last 5 years[4]
- >350 Patents/Applications[4]

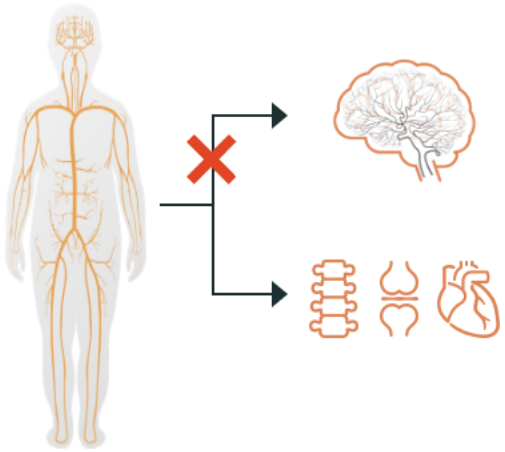
1. Includes regulatory applications to begin clinical studies for DNL628 and DNL952; **2.** As of Oct 27, 2025; **3.** As of Nov 3, 2025; **4.** As of Dec 5, 2025. **BBB –** Blood-brain barrier; **Fc –** fragment crystallizable; **TfR**– Transferrin receptor; **NfL –** Neurofilament light chain

ETV Franchise Opportunity

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**

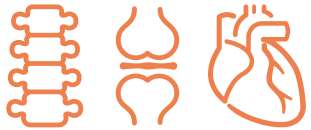


Traditional ERTs partially address somatic but not CNS symptoms

~80% historical ERT approval rate[1]

Targeting Brain & Body with ETV

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



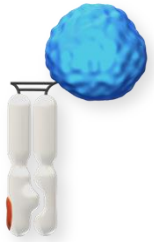
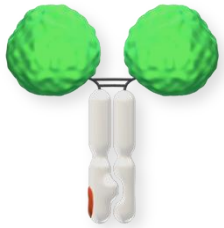
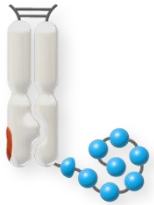
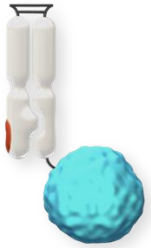
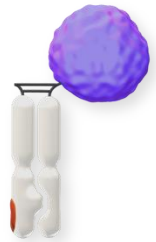
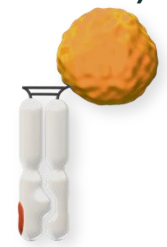
Potential to **enhance peripheral delivery**

Goal is to treat the full disease spectrum

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

1. Based on Denali internal assessment of ERTs that launched in any major market as a ratio of ERTs that have entered clinical development.

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 WW[1]	**~2,000**	**~1,500+**	**~25,000+**	**~5,000 – 10,000**	**~300,000+ (GBA-PD) ~10,000 – 15,000 (GD)**	**~1,500+**
Status	Phase 2/3 BLA filing[2]	Phase 1/2	Phase 1/2	Phase 1	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; **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

Building the ETV Franchise Portfolio

Focus for Today: Clinical-Stage Programs

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	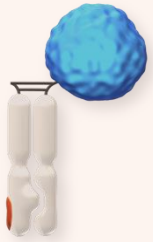	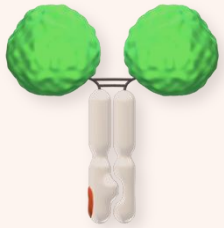	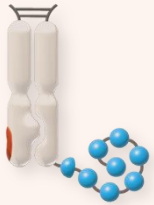	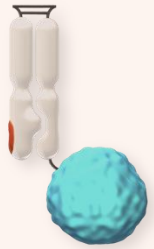	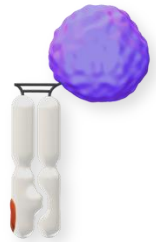	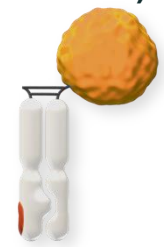
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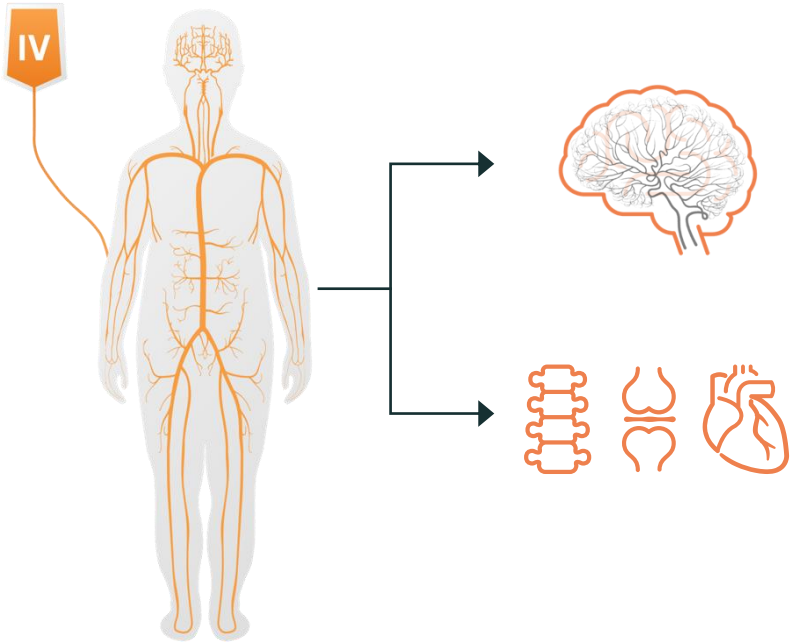
Brain Delivery Is Critical Unmet Need of Hunter Syndrome Therapy

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

tividenofusp alfa
(DNL310)

Tividenofusp alfa is a brain-penetrant enzyme replacement therapy designed to reduce the substrate of IDS (heparan sulfate) throughout the body and treat neurocognitive and physical manifestations



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

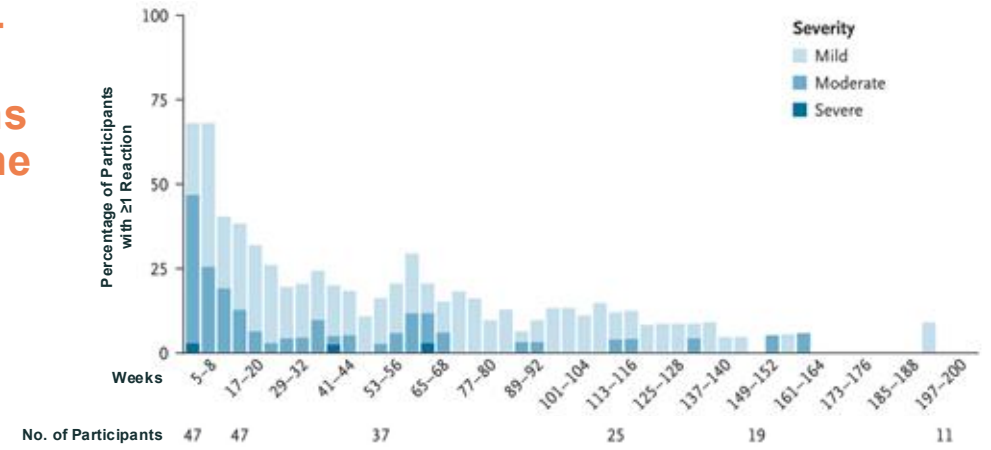
Tividenofusp Alfa Phase 1/2 in MPS II Published in *NEJM*

Summary of Adverse Events

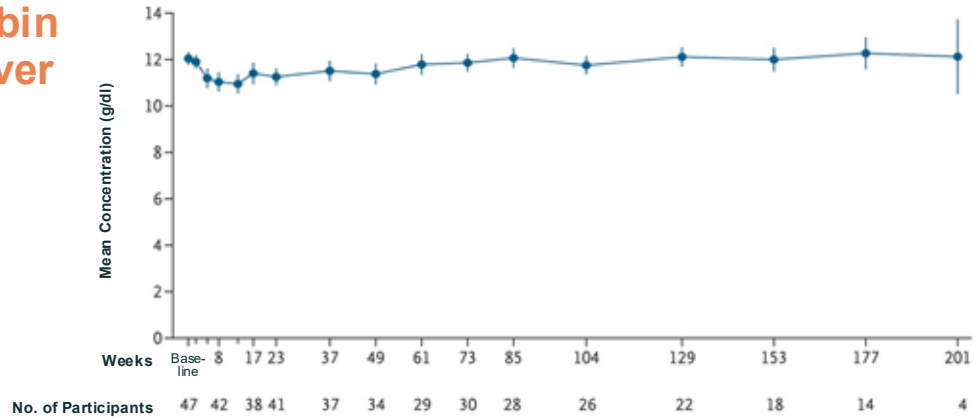
(Safety Analysis Population)

Event	Part 1: 24-Week Treatment Period (N=47)	Part 2: 80-Week Safety Extension (N=46)	Part 3: 157-Week Open-Label Extension (N=27)	All Periods (N=47)
	number of participants (percent)			
Adverse event†	47 (100)	41 (89)	25 (93)	47 (100)
Mild	8 (17)	3 (7)	8 (30)	2 (4)
Moderate	35 (74)	30 (65)	15 (56)	32 (68)
Severe	4 (9)	8 (17)	2 (7)	13 (28)
Serious adverse event‡	6 (13)	11 (24)	4 (15)	18 (38)
Treatment-related serious adverse event§	3 (6)	0	0	3 (6)
Adverse events of special interest¶				
Infusion-related reaction	27 (57)	15 (33)	4 (15)	29 (62)
Anemia	11 (23)	2 (4)	1 (4)	11 (23)
Adverse event leading to discontinuation of study participation	1 (2)	0	0	1 (2)
Adverse event leading to dose reduction	22 (47)	11 (24)	4 (15)	27 (57)
Adverse event leading to dose interruption	34 (72)	37 (80)	15 (56)	43 (91)
Most frequent adverse events				
Infusion-related reaction	39 (83)	26 (57)	11 (41)	41 (87)
Upper respiratory tract infection	11 (23)	20 (43)	8 (30)	28 (60)
Pyrexia	11 (23)	17 (37)	6 (22)	26 (55)
Cough	8 (17)	14 (30)	6 (22)	22 (47)
Vomiting	14 (30)	10 (22)	6 (22)	20 (43)
Diarrhea	9 (19)	10 (22)	4 (15)	19 (40)
Rash	10 (21)	8 (17)	6 (22)	19 (40)
Anemia	18 (38)	3 (7)	2 (7)	18 (38)
Covid-19	6 (13)	13 (28)	2 (7)	18 (38)
Rhinorrhea	9 (19)	8 (17)	4 (15)	18 (38)

Infusion-Related Reactions Over Time



Hemoglobin Levels Over Time



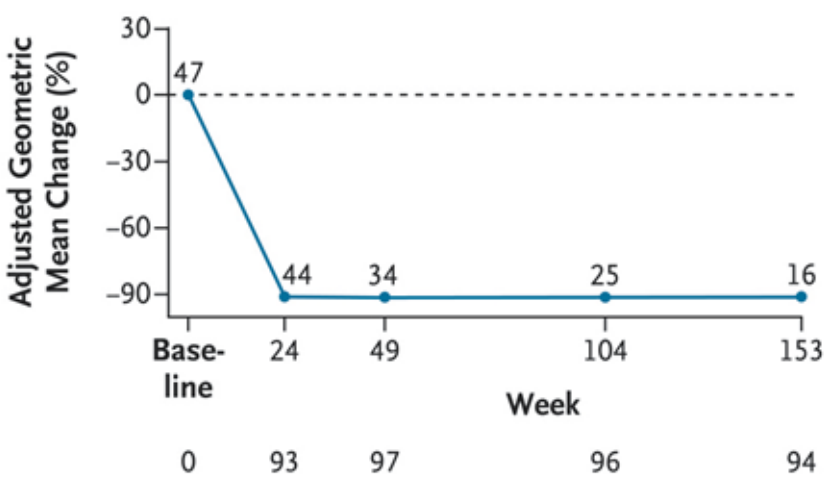
Infusion-related reactions, a known risk of ERTs, were the most common adverse event, decreasing in incidence and severity over time

Source: Muenzer et al. 2026 *NEJM*

Tividenofusp Alfa Phase 1/2 in MPS II Published in *NEJM*

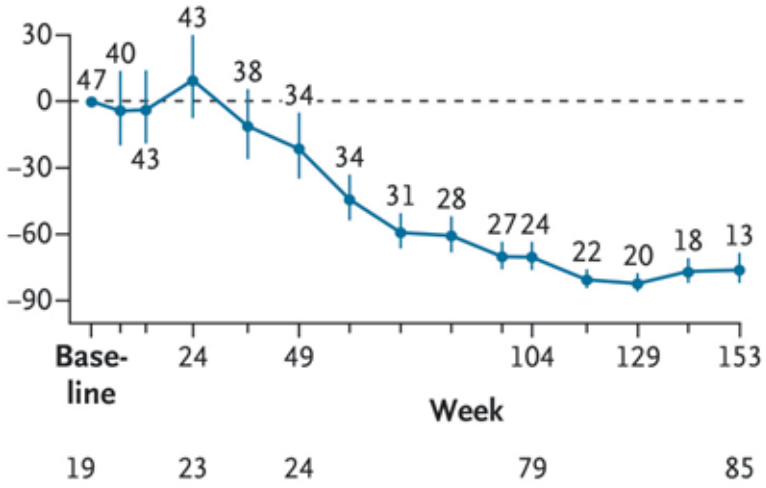
Normalization of CSF HS

Biomarker of CNS disease



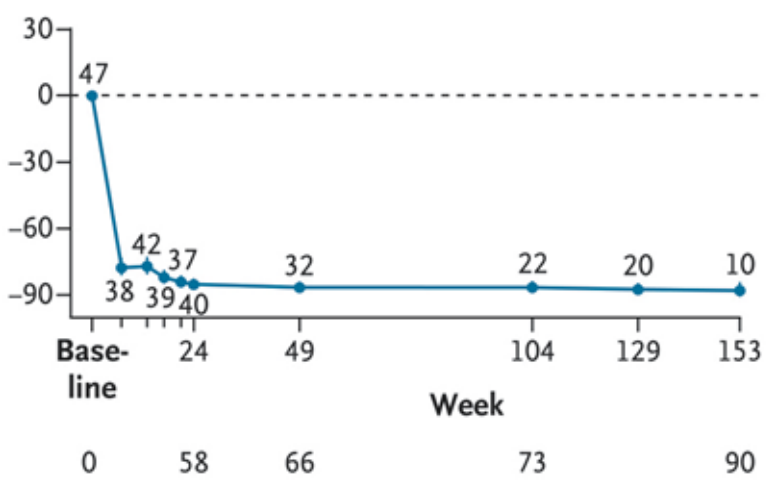
Normalization of NfL

Biomarker of neuronal damage



Normalization of Urine HS

Biomarker of peripheral disease



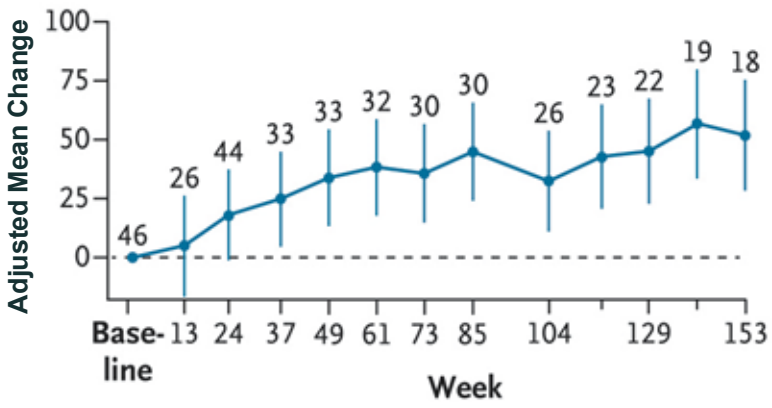
Treatment with tividenofusp alfa over a median duration of 2 years was associated with reductions in CNS and peripheral biomarkers of substrate accumulation and neuronal injury to levels within the range of unaffected children

MPS II – Mucopolysaccharidoses Type II; **CSF** – Cerebrospinal fluid; **HS** – Heparan sulfate; **NfL** – Neurofilament light; Source: Muenzer et al. 2026 *NEJM*

Tividenofusp Alfa Phase 1/2 in MPS II Published in *NEJM*

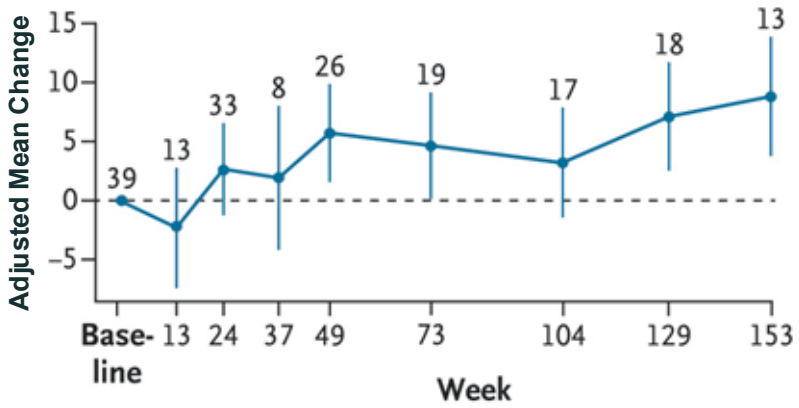
Improvement in Adaptive Behavior

Vineland-3



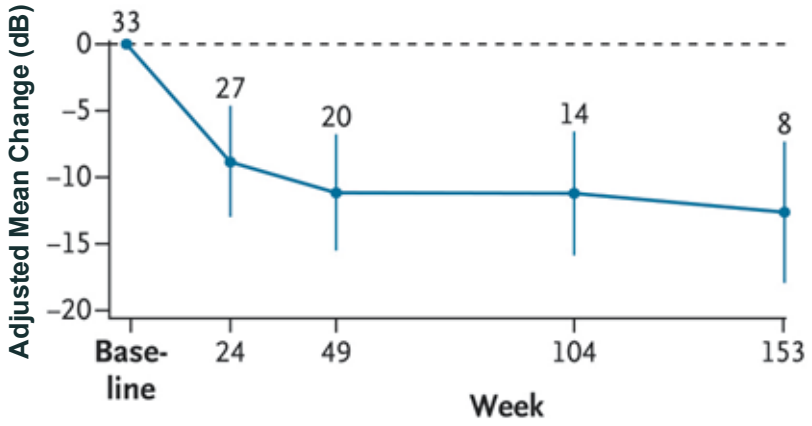
Improvement in Cognition

BSID-III



Improvement in Hearing

Auditory Brainstem Response (PTA)



While on tividenofusp alfa, clinical outcomes showed skill gains relative to baseline on measures of adaptive behavior, cognition and hearing threshold improvement

MPS II – Mucopolysaccharidoses Type II; **CI** – Confidence interval; **BSID-III** – Bayley Scales of Infant and Toddler Development-Third Edition; **PTA** – Pure tone average. Source: Muenzer et al. 2026 *NEJM*

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  COMPASS **participants**

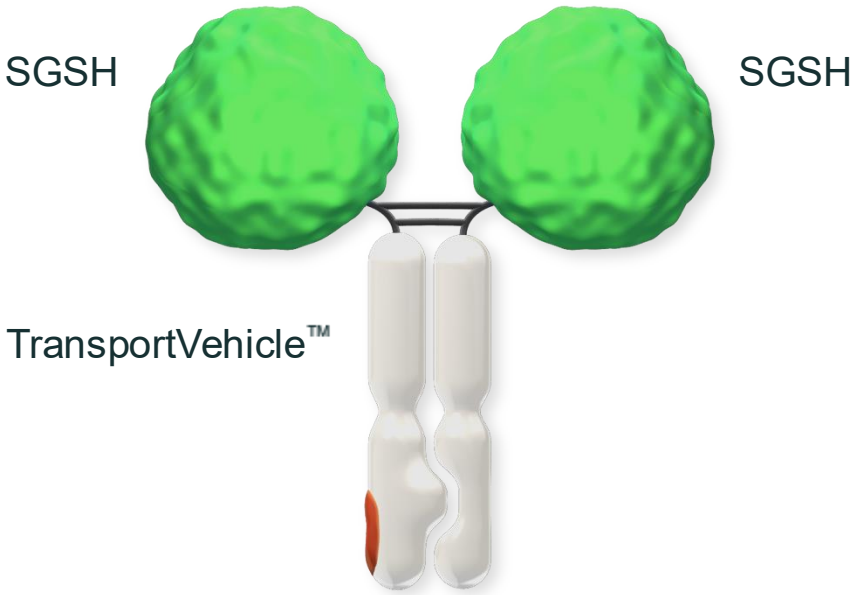
> *To summarize, tividenofusp alfa offers systemic therapy to address both the neurologic and somatic facets of MPS II, on the basis of compelling biomarker and clinical evidence. The results of this study mark a critical turning point and bring the field one step closer to the elusive goal of comprehensive disease modification.*
>
> – Can Ficicioglu, M.D., Ph.D.,[1,2] from "Breaking Barriers in Mucopolysaccharidosis Type II", *NEJM* editorial 2026

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

1. Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia; **2.** Division of Human Genetics and Metabolism, Children's Hospital of Philadelphia, Philadelphia.

DNL126 (ETV:SGSH): Designed to Deliver SGSH to the Brain

ETV:SGSH



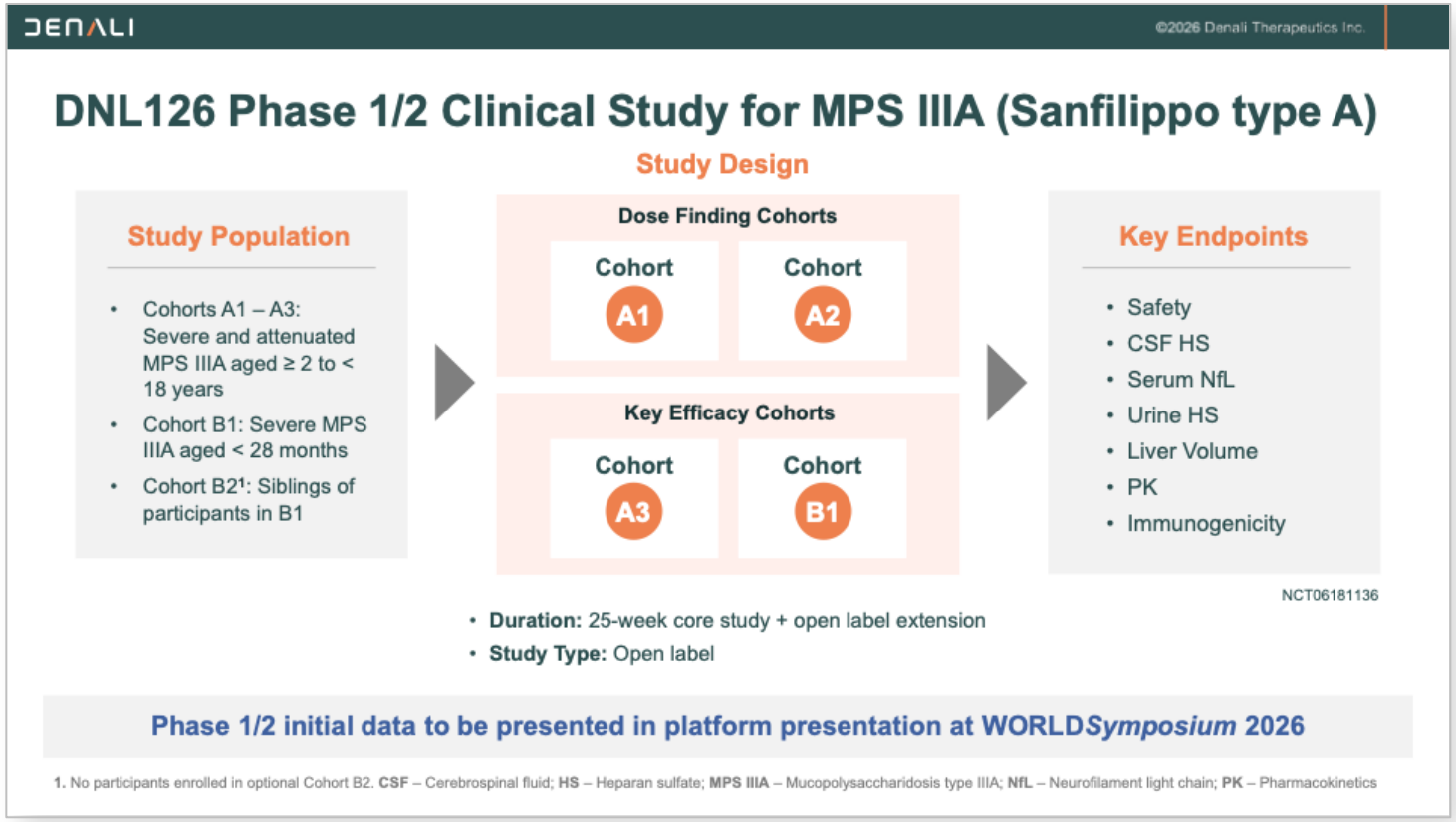
Program Status

- Selected for FDA START program
- Phase 1/2 study in MPS IIIA
  - Achieved biomarker proof-of-concept
  - Enrollment completed (n=20)
  - Data at WORLD*Symposium* (Feb 2026)
- Aligned with FDA on accelerated approval path in MPS IIIA
- Phase 3 protocol under development

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

ETV – Enzyme TransportVehicle™; **SGSH –** N-sulfoglucosamine sulfohydrolase; **FDA** – U.S. Food and Drug Administration; **START** – Support for clinical Trials Advancing Rare disease Therapeutics

DNL126: Study Data for Accelerated Approval



Data for BLA Submission

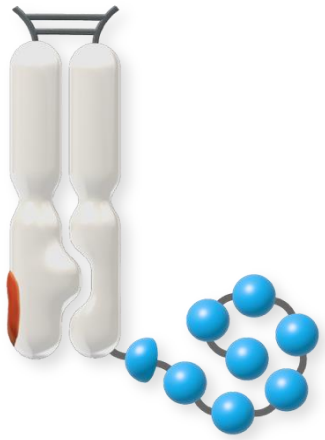
- At least 49 weeks of data for all participants (Cohorts A1-A3, B1; n=20)
- CSF HS reduction from baseline in key efficacy cohorts (n=12) – surrogate endpoint reasonably likely to predict clinical benefit
- Supportive data on central and peripheral biomarkers, clinical endpoints
- Long-term safety up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

Expected BLA submission and approval in 2027

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

DNL593 Phase 1/2 Clinical Study for FTD-*GRN*

DNL593
(PTV:PGRN)



Study Population

- Part A: healthy volunteers aged ≥ 18 to ≤ 55 years
- Part B: *GRN* mutation carriers; symptomatic participants diagnosed with FTD-*GRN*; aged ≥ 18 to ≤ 80 years
- Part C: participants who complete Part B

Study Plan

Enrollment Completed

SAD Cohort A

MAD Cohort B

Optional OLE Ongoing

MAD Cohort C

Goals & Objectives

- Part A: safety, PK
- Parts B & C:
  - Safety, PK, PD biomarkers
  - Clinical, neuropsychology, and imaging outcomes

NCT05262023

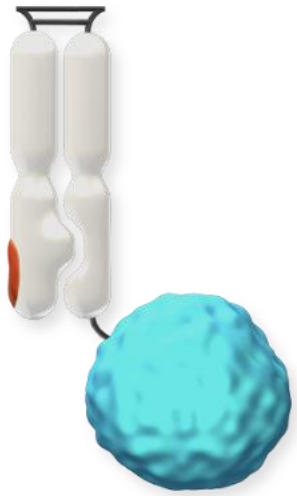
- **Duration:** 25-week core study + open label extension
- **Study Type:** Randomized, placebo-controlled, double blind

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

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

DNL952 Phase 1 Clinical Study for Pompe Disease

DNL952
(ETV:GAA)



Study Population

- Patients with Late Onset Pompe Disease (LOPD)
- 2nd Gen ERT experienced (A Cohorts) and optional naïve (B Cohorts)

Study Plan

2nd Gen Treatment-Experienced

Cohort A1

Cohort A2

Optional: Additional Cohorts

Optional: Treatment-Naïve

Cohort B1

Goals & Objectives

- Safety
- PK
- Analysis of clinically established biomarkers
- Immunogenicity

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

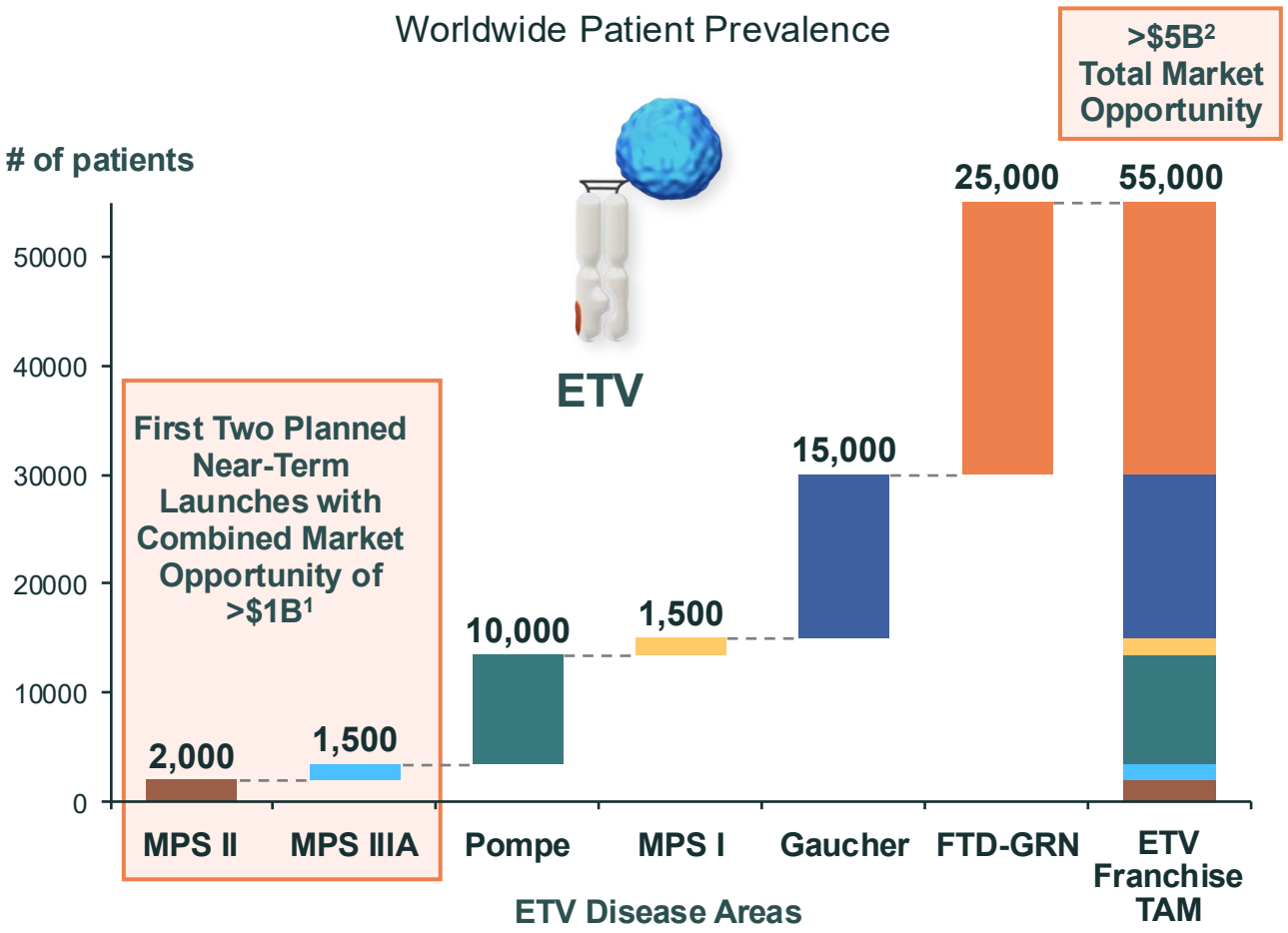
Phase 1 biomarker data expected in 2027

ERT – enzyme replacement therapy; **LOPD** – Late Onset Pompe Disease; **PK** – Pharmacokinetics

ETV: Foundational Franchise for Lysosomal Storage Disorders

ETV Franchise

Worldwide Patient Prevalence



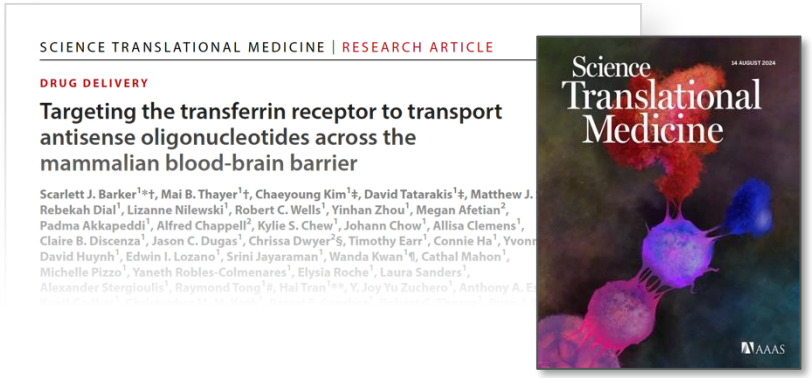
Delivering Next-Generation Enzyme Replacement Therapy (ERT)

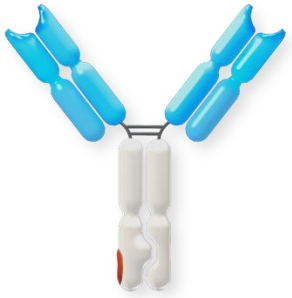
- 23 ERTs currently marketed[3]; ~80% historical ERT approval rate[4]; ~$9B in sales[5]
- Traditional ERTs do not penetrate CNS whereas ETVs address full disease spectrum
- $1B+ opportunity between MPS II & MPS IIIA
  - Plan to leverage existing Denali infrastructure across both launches
  - Ability to redeploy resources to translate into favorable margins
- Established relationships with key stakeholders in the lysosomal storage disorders community
- Ability to drive increasingly fast launches and product uptake throughout franchise

1. Internal estimate for global market opportunity across MPS II and MPS IIIA **2.** Global market opportunity based on Denali internal assessment as of Nov '25 and other syndicated data (Evaluate Pharma, Historic Annual WW Product Sales 2024, downloaded Dec 1 2025, GC Pharma 2024 Investor Day Deck (https://www.gcbiopharma.com/eng/upload/CAO/C55/202510/9e38f129-d9f2-4307-bc4f-ca54f2340512.pdf); **3.** Based on systemic ERTs with regulatory approvals in at least one major market (US, EU, Japan), excluding two ERTs that have been discontinued (Adagen and Ceredase); **4.** Based on Denali internal assessment of ERTs that launched in any major market as a ratio of ERTs that have entered clinical development. **5.** Based on Denali internal assessment as of Nov '25 and other syndicated data (Evaluate Pharma, Historic Annual WW Product Sales 2024, downloaded Dec 1 2025, GC Pharma 2024 Investor Day Deck (https://www.gcbiopharma.com/eng/upload/CAO/C55/202510/9e38f129-d9f2-4307-bc4f-ca54f2340512.pdf). Protalix 2024 10-K, GMI Report 2024 (Oct'24, https://www.gminsights.com/industry-analysis/exocrine-pancreatic-insufficiency-treatment-market). USA vs QOL Medical Lawsuit (Filed July'24, https://www.mass.gov/doc/qol-medical-lawsuit/download). **TAM** – Total Addressable Market; **ETV –** Enzyme TransportVehicle™

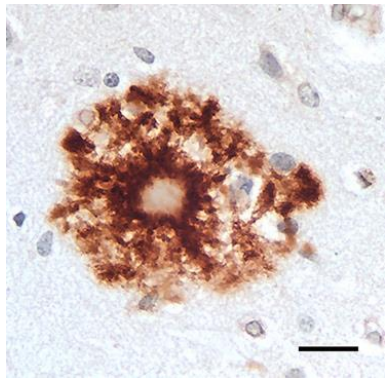
Alzheimer's Disease Opportunity

Aiming to Transform Treatment of Alzheimer's Disease

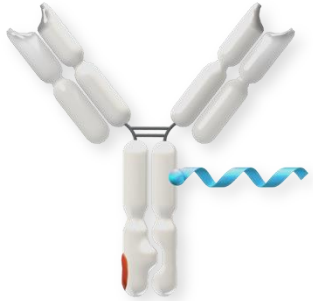




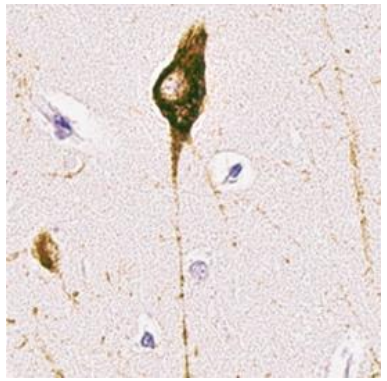
ATV
Targeting Abeta Plaques



Walker L, *Free Neuropath*, 2020



OTV
Targeting Tau Tangles



Bengoa-Vergniory et al, *Acta Neurop*, 2021

TransportVehicle™ Therapeutics Are Designed to Improve Safety and Efficacy

Reduce risk of amyloid-related imaging abnormalities (ARIA)

Clear amyloid plaque faster via better brain biodistribution

Address tau pathology by suppressing MAPT expression

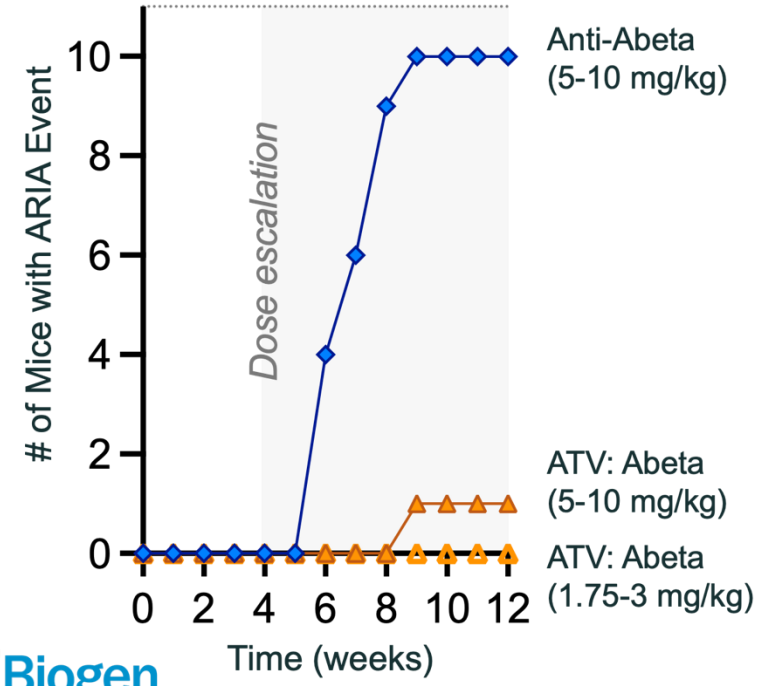
Unmet medical need provides opportunity for BBB-enabled AD therapeutics with $5B+ market potential[1]

1. Alzheimer's disease market opportunity based on Denali internal assessment as of Nov '25 and Evaluate Pharma Analyst Consensus Forecasts 2024 to 2034, Oct '25
ATV – Antibody TransportVehicle™; **OTV –** Oligonucleotide TransportVehicle™; **AD** – Alzheimer's disease

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

Incidence of MRI Lesions

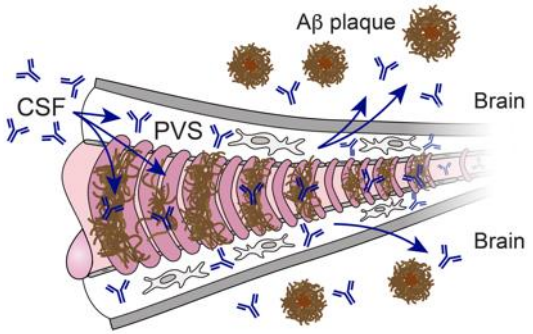
5xFAD; TfR$^{mu/hu}$ KI; QW IP



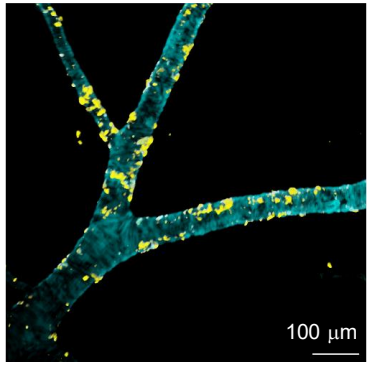
Biogen

Route of Entry into Brain

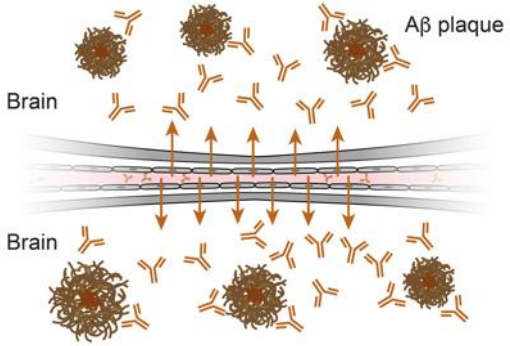
Conventional Anti-Abeta



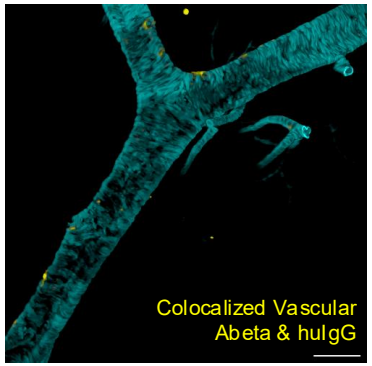
Artery / Arteriole Zone



ATV-Enabled Anti-Abeta



Microvessel (capillary) Zone

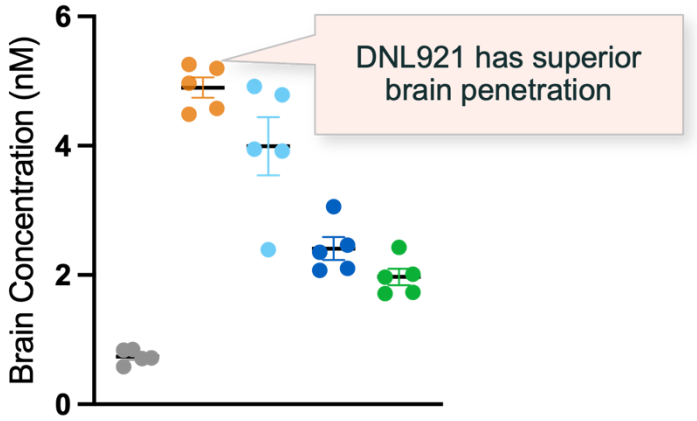


Bypassing vascular plaque via TfR-mediated entry into the brain through capillaries and venules improves ARIA safety

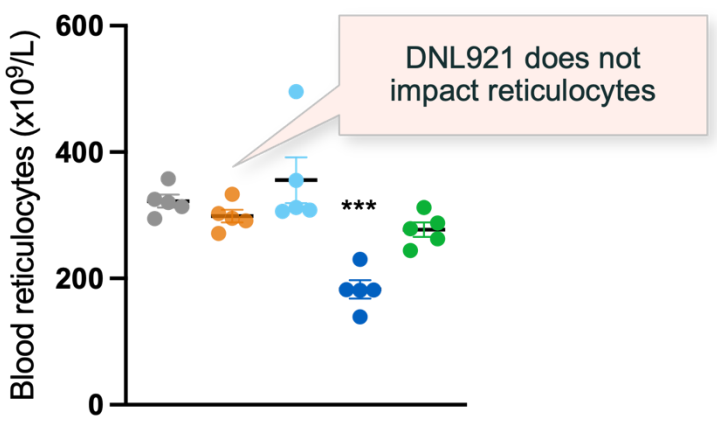
Pizzo et al., *Science*, 2025. **ATV –** Antibody TransportVehicle™; **ARIA –** amyloid related imaging abnormalities; **TfR –** transferrin receptor; **MRI –** magnetic resonance imaging; **QW IP –** once weekly intraperitoneal; **CSF –** cerebrospinal fluid; **PVS –** perivascular space; **Aβ –** amyloid beta

DNL921 Optimized for Robust Brain Delivery, Safety & Stability

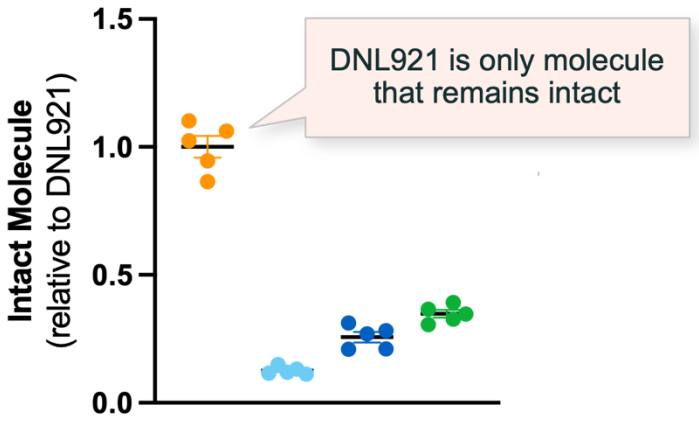
Brain Concentration[1]



Immature Reticulocytes[1]

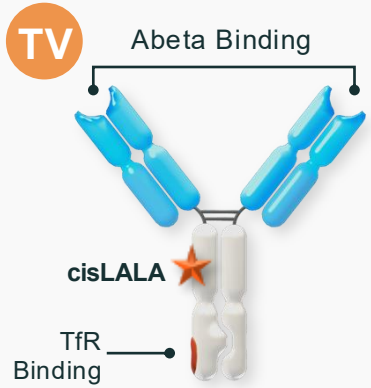


Intact Molecule[1,2]

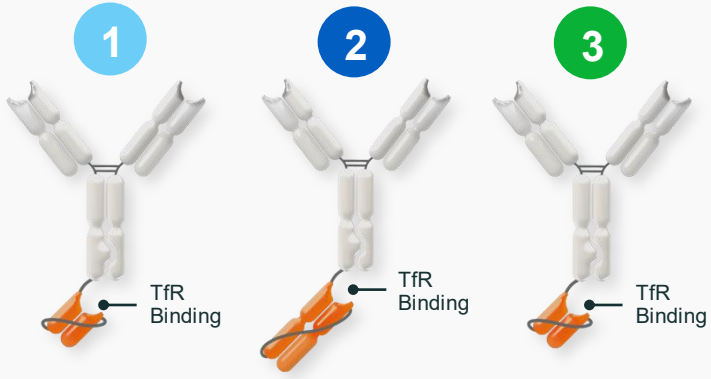


Molecule	Architecture	Epitope	Effector Function
Control	Control IgG	N/A	Full
DNL921	TV- TfR in Fc	Apical	Conditional
Competitor #1	C-term TfR	Protease	Full
Competitor #2	C-term TfR	Apical	Full
Competitor #3	C-term TfR	Apical	None

DNL921 (ATV:Abeta)



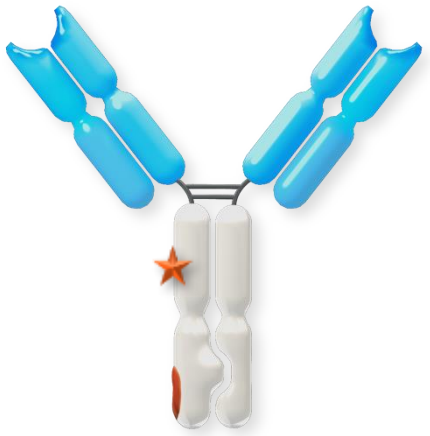
Competitor Molecules[3]



1. Single dose, IV 10 mg/kg (molar-matched); **2.** hIgG Capture vs. TfR Capture ELISA; **3.** Competitor Molecules generated at Denali based on publicly available information on TfR-binding anti-Abeta antibodies currently under development

DNL921 Phase 1/1b Clinical Study for Alzheimer's Disease

DNL921
(ATV:Abeta)



Phase 1/1b → **Phase 3**

Study Population

SAD: Healthy Volunteers

MAD: Patients with biomarker confirmed Alzheimer's disease

Study Plan

- **SAD**
- **MAD Cohort A**
- **MAD Cohort B**
- **MAD Cohort C**

Goals & Objectives

- Safety
- Impact on amyloid plaque load
- Dose selection
- Additional biomarkers/imaging

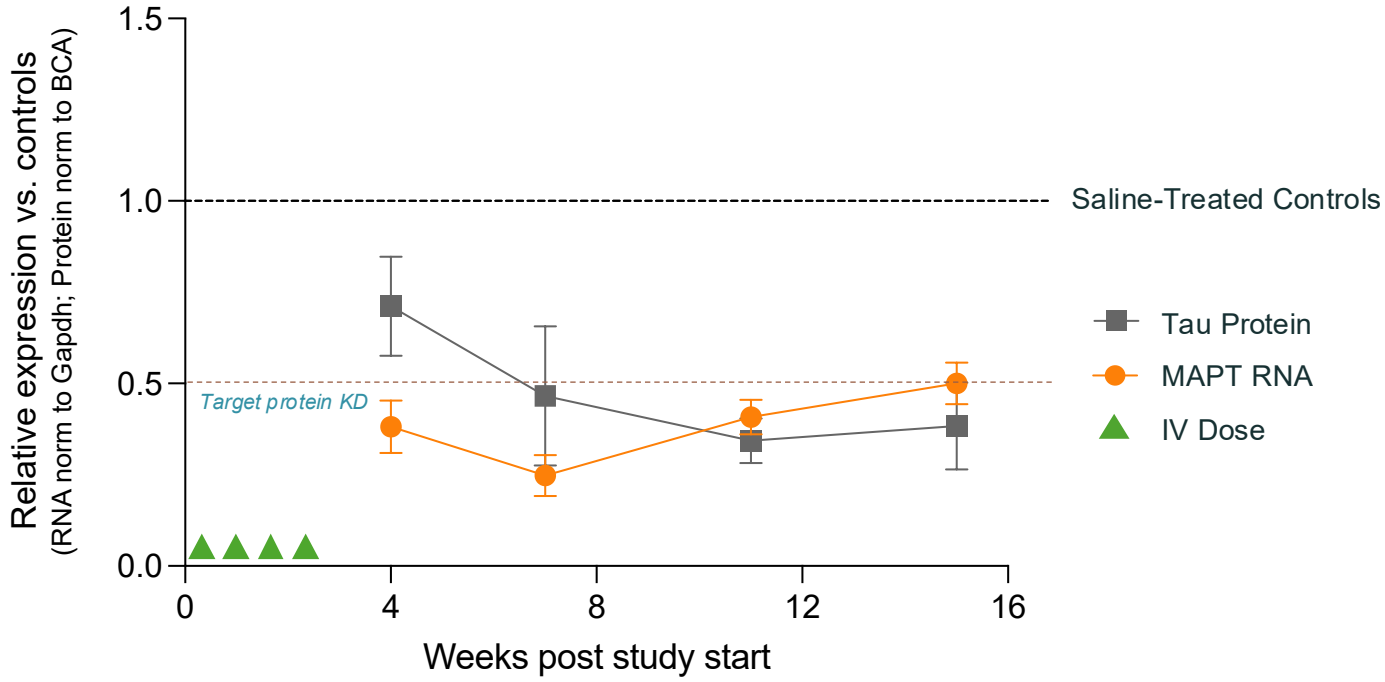
- **Duration:** 28 weeks
- **Study Type:** Randomized, placebo-controlled, double blind

IND/CTA submission planned for 1H 2026 / Potential for safety and clinical proof of concept in 2027

SAD – Single Ascending Dose; **MAD** – Multiple Ascending Dose; **PET –** positron emission tomography

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

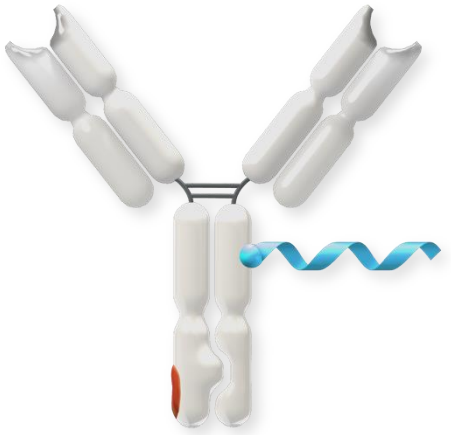


Robust and sustained reduction in tau protein with DNL628

DNL628 Phase 1b Clinical Study for Alzheimer's Disease

Phase 1b | **Phase 2** | **Phase 3**

DNL628
(OTV:MAPT)



Study Population

Patients with biomarker confirmed early Alzheimer's disease (CDR 0.5 to 1, MMSE 20-30)

Study Plan

- **MAD Cohort A**
- **MAD Cohort B**
- **MAD Cohort C**

Phase 1b Objectives

- Safety
- Impact on tau levels
- Dose selection
- Additional biomarkers/imaging

NCT07328451

- **Duration:** 24 weeks
- **Study Type:** Randomized, placebo-controlled, double blind

Phase 1b initiation 1H 2026 / Clinical biomarker data expected by 1H 2027

CDR – Clinical Dementia Rating; **MMSE –** Mini-Mental State Examination; **MAD –** Multiple Ascending Dose; **CSF –** cerebrospinal fluid

Evolving Our Business

Integrated Capabilities to Execute for Long-Term Value

Scale and Infrastructure

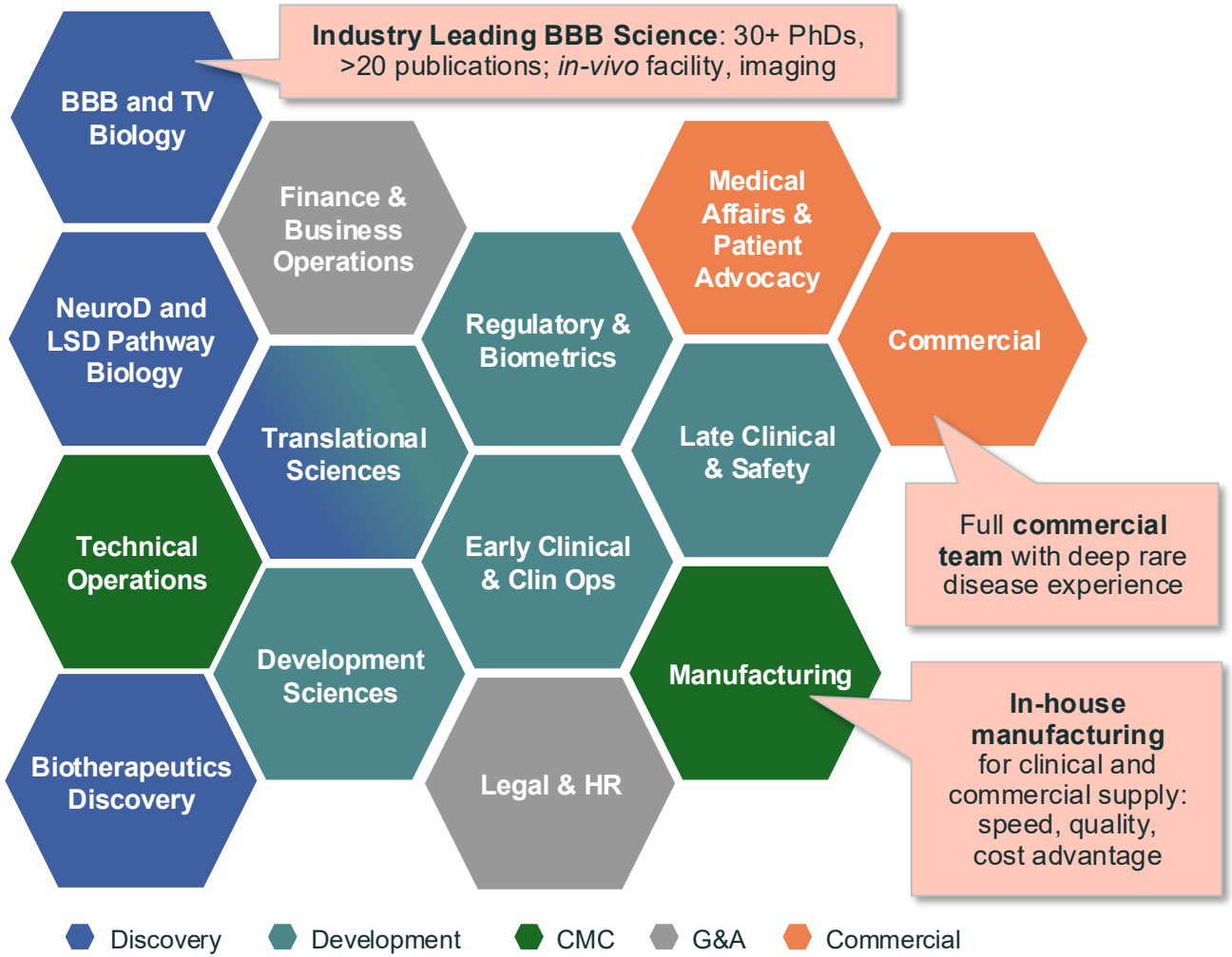
- **Scale** to successfully discover, develop, manufacture and commercialize
- **Integrated infrastructure** with ~520 full time employees in South San Francisco, Salt Lake City and Zürich

South San Francisco, California

Salt Lake City, Utah

Zurich, Switzerland

Established Capabilities



BBB – blood-brain barrier; **TV –** TransportVehicle™; **NeuroD –** neurodegeneration; **LSD –** lysosomal storage disorders; **Clin Ops –** Clinical Operations; **HR –** Human Resources; **CMC –** Chemistry, Manufacturing & Controls; **G&A –** General & Administrative

Capital to Execute

Key Capital Allocation Priorities

Invest Strategically

- Successful launches of tividenofusp alfa and DNL126
- Focused R&D investments to accelerate and expand pipeline

Drive Capital Efficiency

- Apply learnings from tividenofusp 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 + $488M

Cash and investments as of Q3 2025 plus royalty financing[1] and equity capital raise[2] (Dec '25)

2 Near-term Commercial Launches

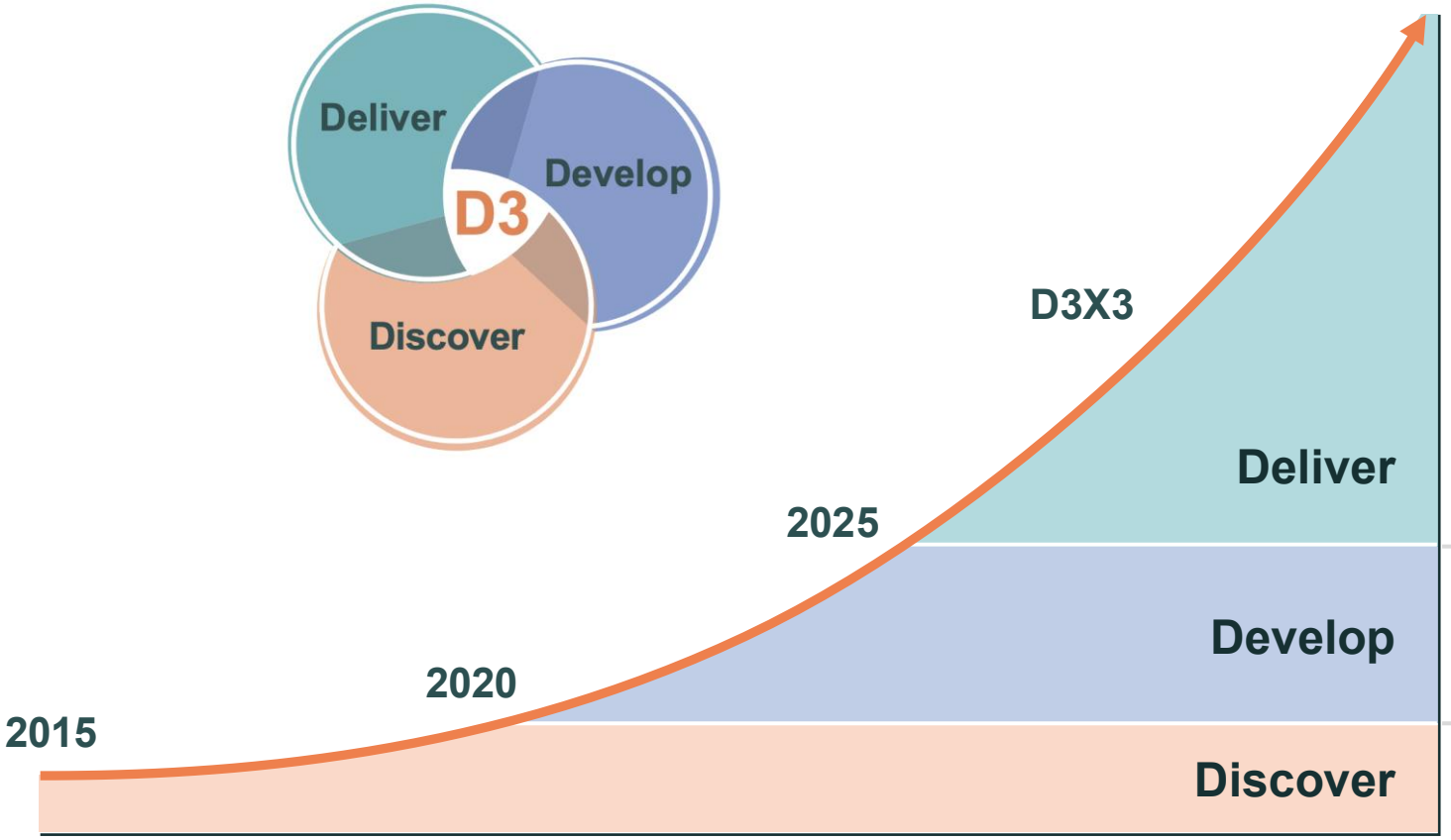
Potential revenues from Tivi and DNL126

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; **2.** Approximately $213M in gross proceeds related to underwritten public offering in December 2025 of shares of Denali's common stock and, in lieu of common stock to certain investors, pre-funded warrants

Entering a New Phase on the Path to the Summit



3-Year Goals (D3X3)

2 Growing Brands

5 Clinical Proof of Concepts

4-6 New Clinical Programs

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

DENALI

Thank You