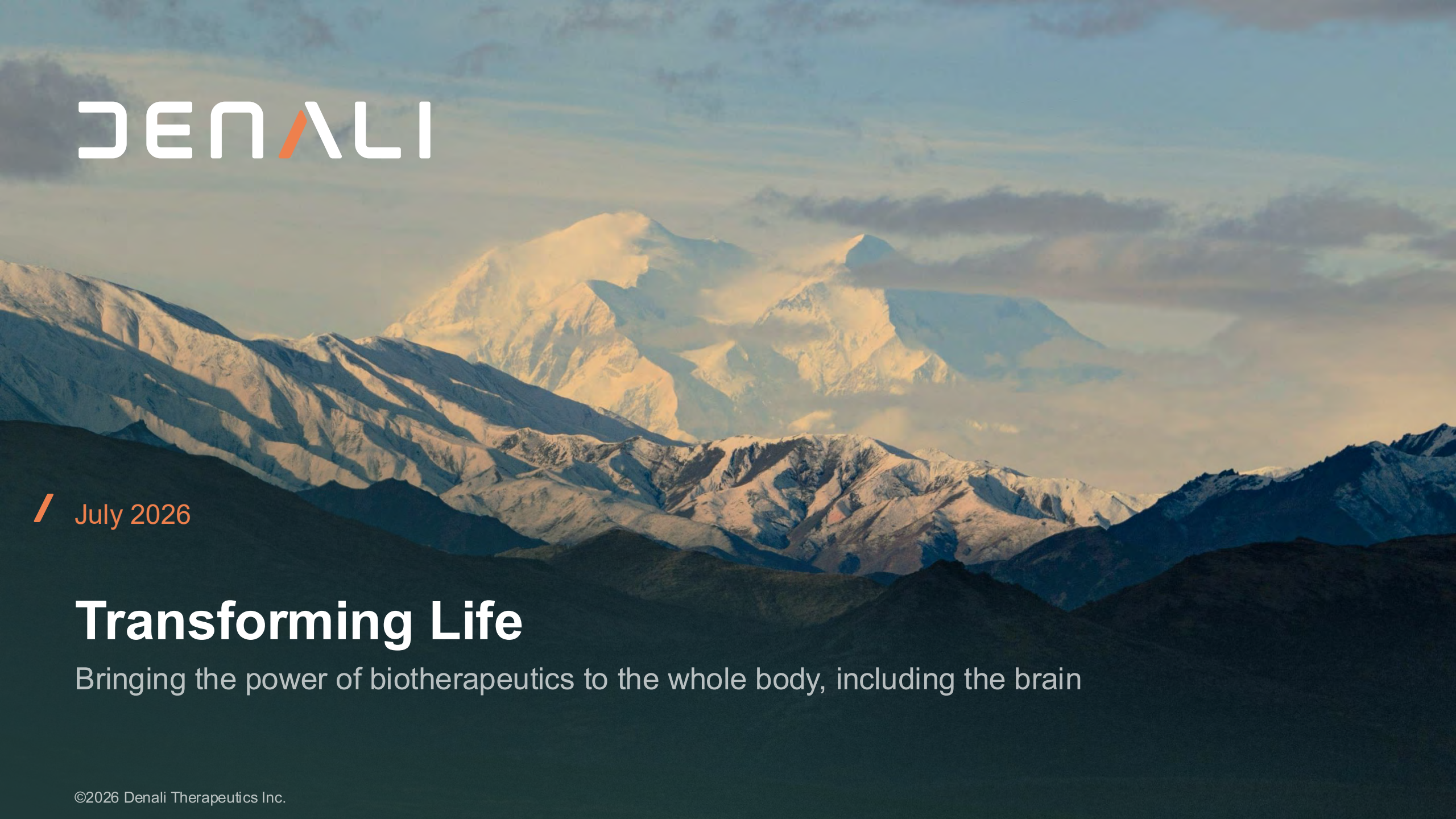


July 2026

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

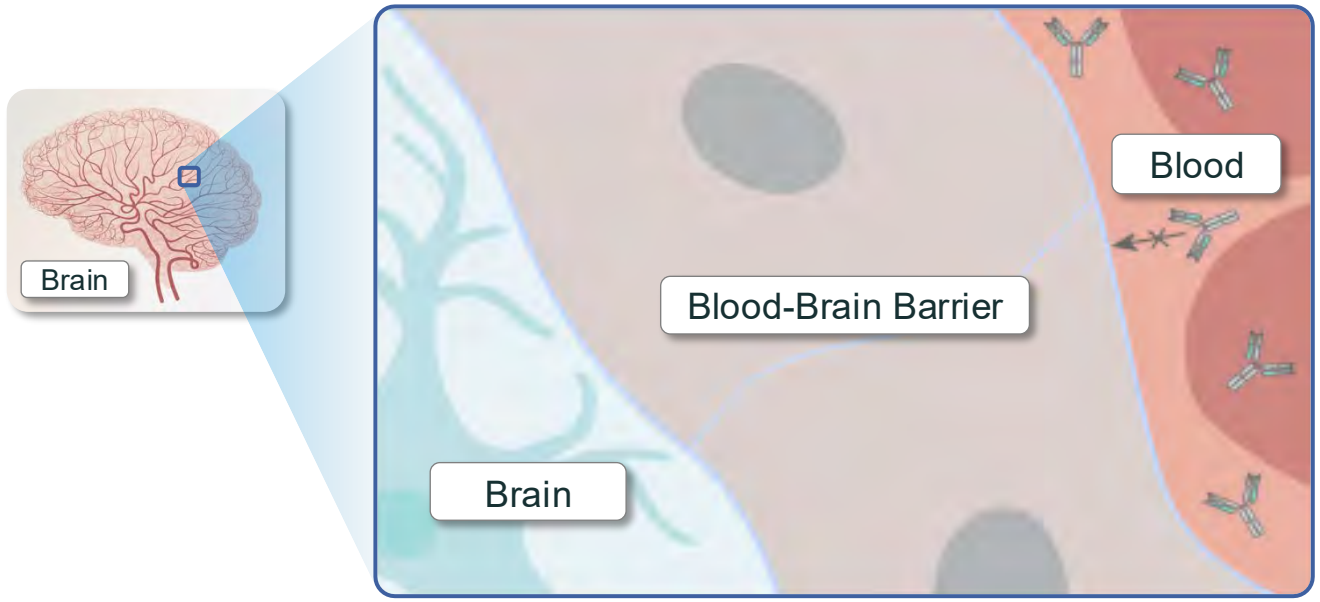
The Blood-Brain Barrier Has Blocked Medicine from the Brain

What the BBB Has Prevented

>95%
of drug candidates fail to reach therapeutic concentrations in the brain

Decades
of failed CNS drug programs despite huge development investment

0
FDA-approved brain-penetrant biologics before AVLAYAH™ (tividenofusp alfa-eknm)



Biologics – a powerful modern modality – cannot get into the brain without a special delivery system

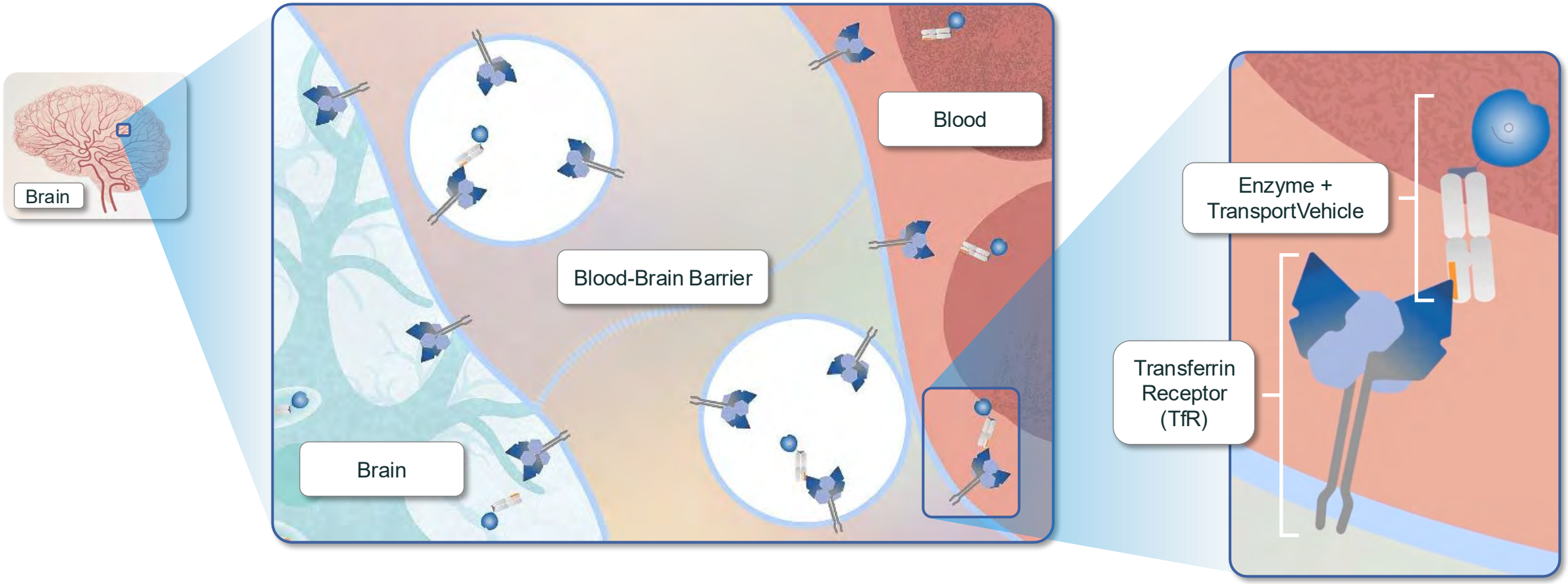
This has left Alzheimer's, Parkinson's, and rare brain diseases without the benefit of modern biotechnology

This has prevented the creation of major CNS biologic franchises for decades – until now

Tividenofusp alfa is approved only in the United States but does not currently hold a UK marketing authorization.

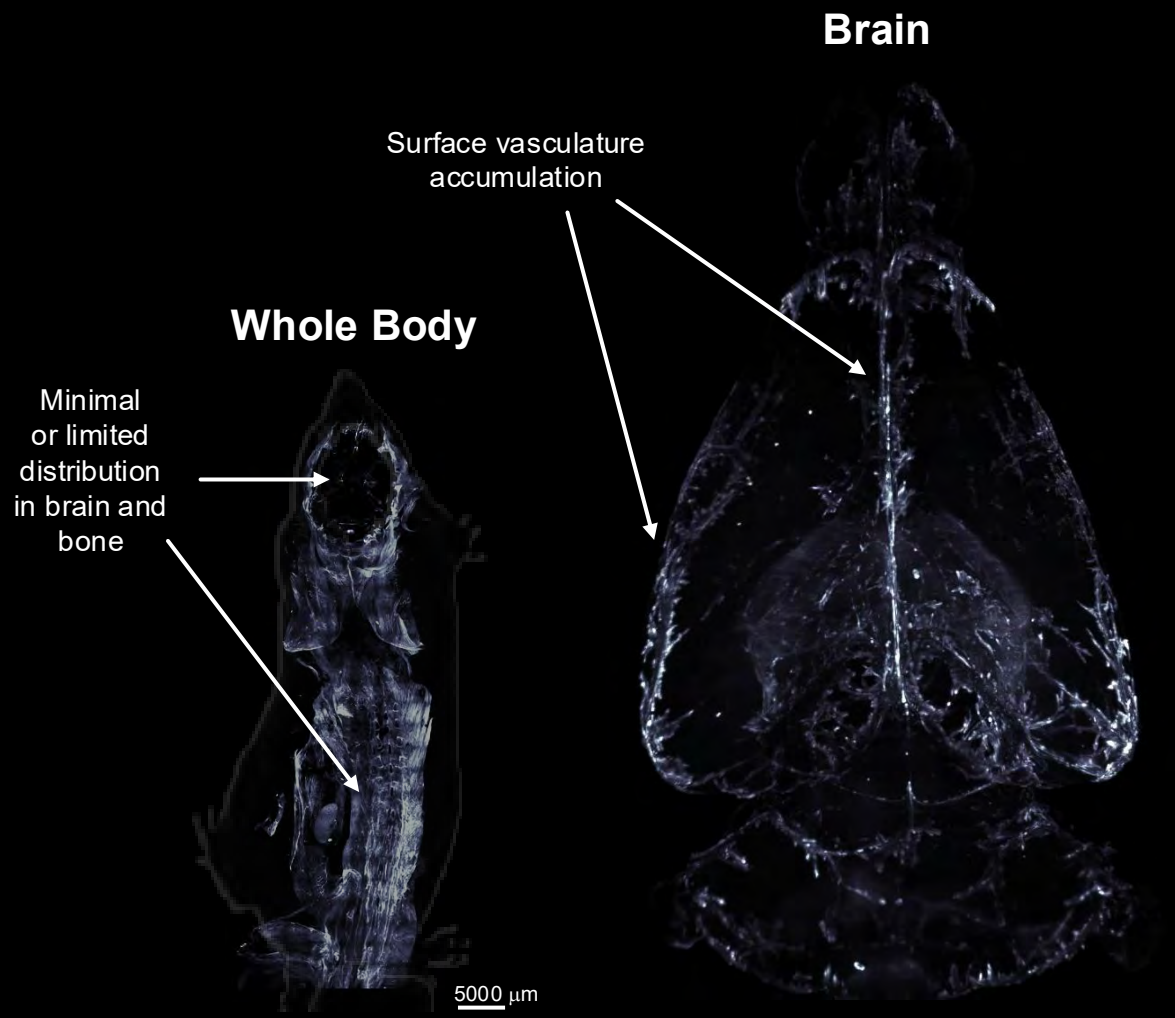
Addressing the Challenge of Delivering Therapy to the Brain

The TransportVehicle™ (TV) is engineered to deliver efficacious concentrations of biotherapeutics across the blood-brain barrier via receptor-mediated transcytosis

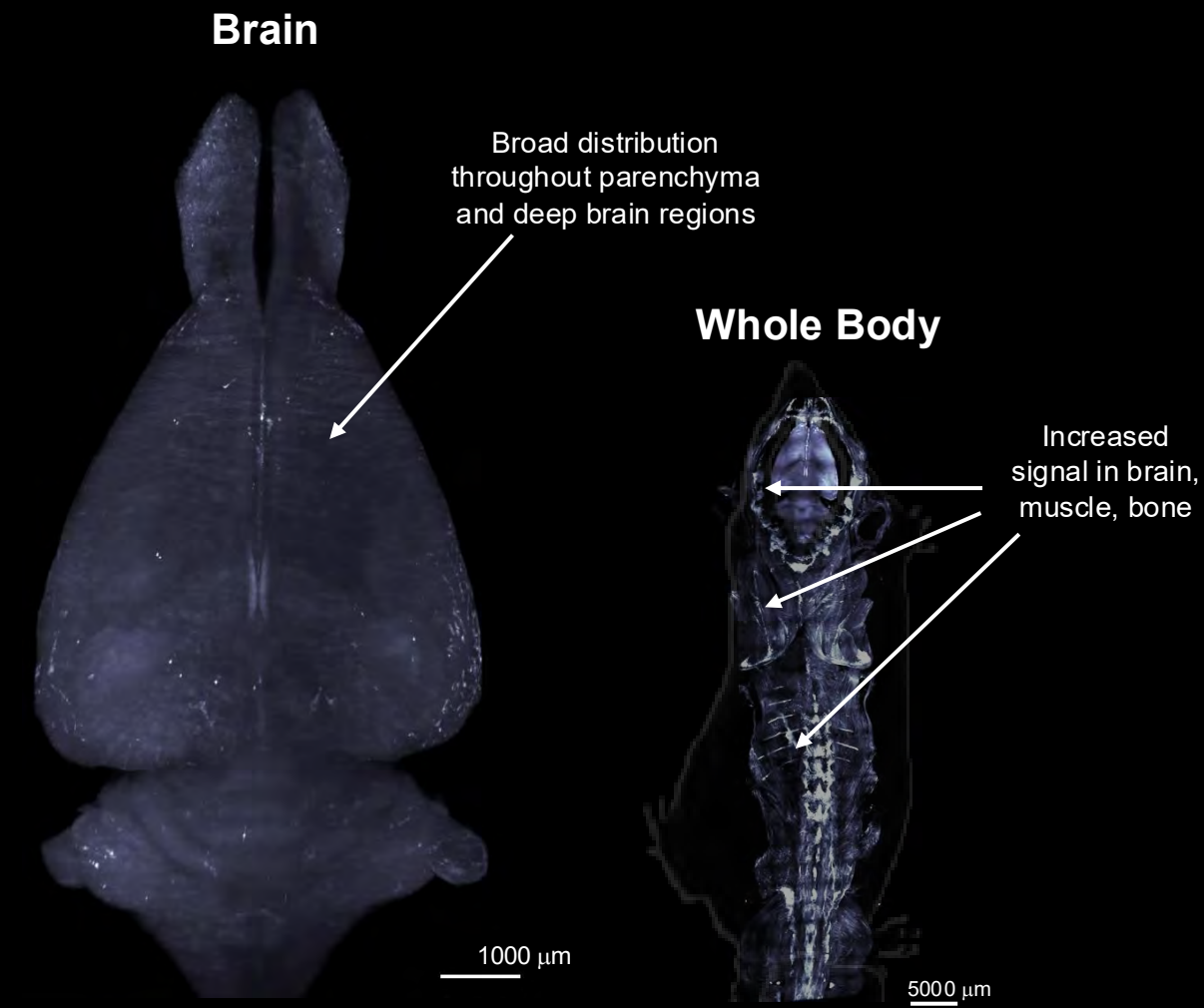


TransportVehicle Brain Distribution

Standard Antibody (IgG)



TV-enabled Antibody (TfR)



Source: Denali Therapeutics data

Our Broad Therapeutic Portfolio

Lysosomal Storage Disorders

Molecule	Indication	Stage
tividenofusp alfa-eknm (ETV:IDS)	MPS II	FDA Approved Phase 2/3
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
DNL151 LRRK2 Inhibitor	PD	Phase 2a (LRRK2)
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

2026-2027 Expected Milestones

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

2 Growing Brands

- AVLAYAH™
- 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

Integrated Capabilities to Execute for Long-Term Value

Scale and Infrastructure

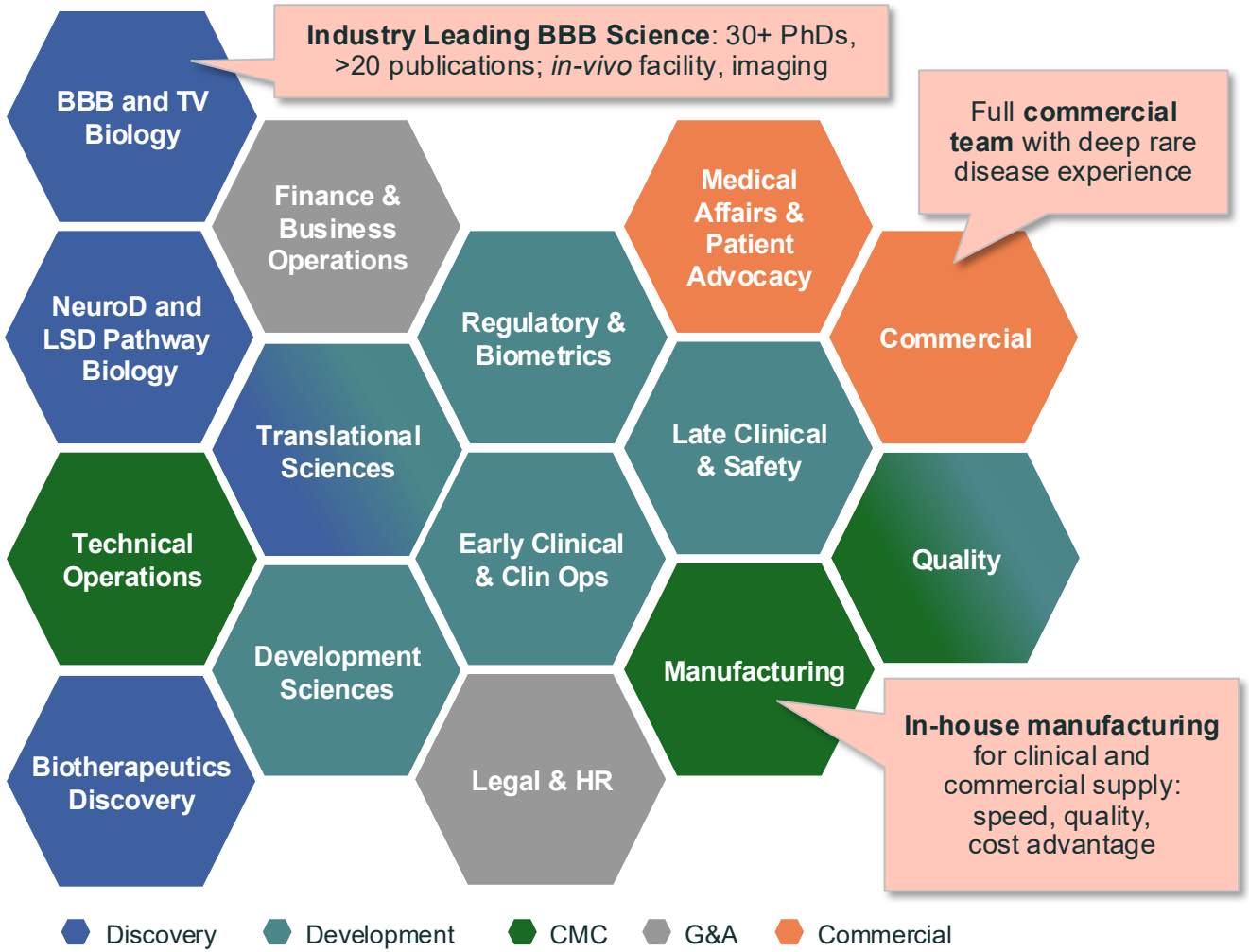
- **Scale** to successfully discover, develop, manufacture and commercialize
- **Integrated infrastructure** with ~520 full time employees in South San Francisco, Salt Lake City and Zürich

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 AVLAYAH™ and DNL126
- Focused R&D investments to accelerate and expand pipeline

Drive Capital Efficiency

- Apply learnings from AVLAYAH™ to develop next programs faster and at lower cost

Maintain Capital Optionality

- Partnerships remain core to strategy
- Diversifying sources of capital

Strong Financial Foundation

~$1.05B

Cash and investments as of Q1 2026

$195M PRV Sale[1]

Gross proceeds from sale of PRV awarded by FDA upon AVLAYAH™ approval

2 Near-term Commercial Launches

Potential revenues from AVLAYAH™ and DNL126

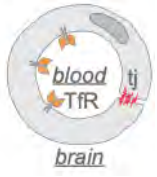
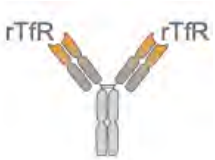
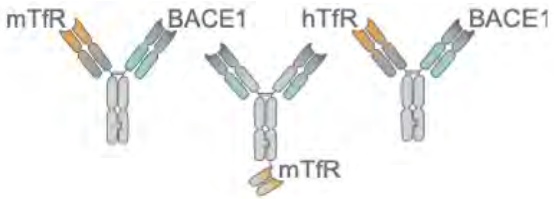
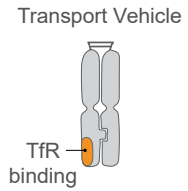
PRV – Priority Review Voucher; FDA – U.S. Food and Drug Administration

1. The PRV transaction is subject to customary closing conditions, including expiration of the applicable waiting period under the Hart-Scott Rodino Antitrust Improvements Act.

DENALI

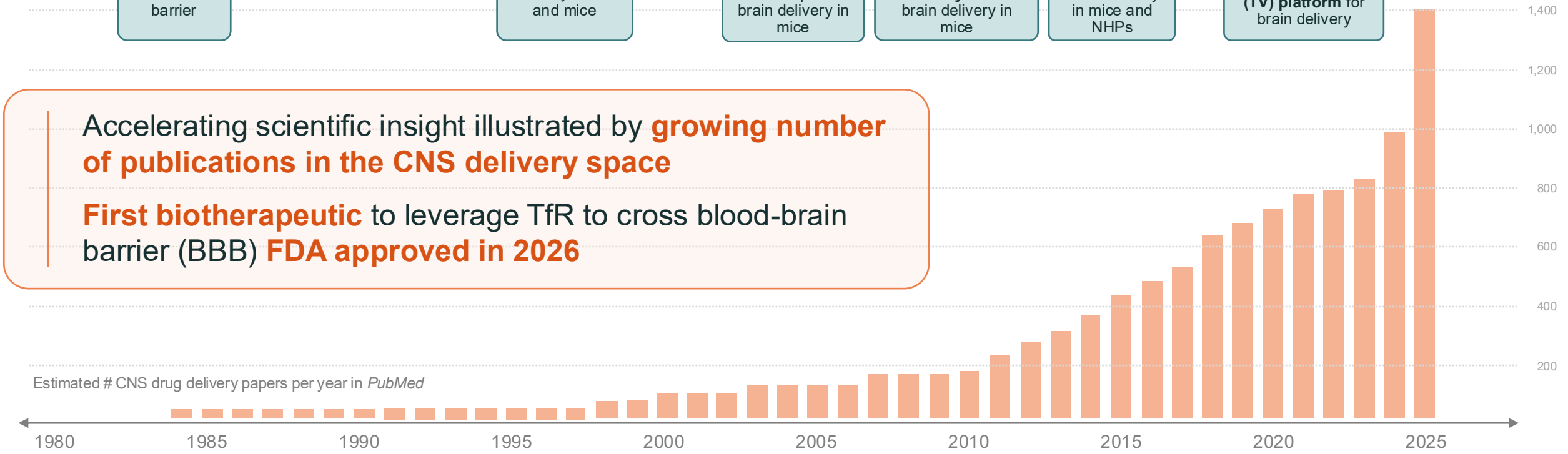
TransportVehicle™ Platform

Blood-Brain Barrier Technologies Accelerating

1980 – 1990	1990 – 2010	2010 – 2015	2015 – 2026	2026
				**March 2026** US FDA approval of AVLAYAH™ (tividenofusp alfa-eknm)
TfR at the blood-brain barrier	**TfR MAb** brain delivery in rats and mice	**Reduced affinity TfR MAb** bispecific brain delivery in mice	**Monovalent single chain Fab antibody fusion** brain delivery in mice **TfR bispecific** brain delivery in mice and NHPs	**TfR binding TransportVehicle (TV) platform** for brain delivery

Accelerating scientific insight illustrated by **growing number of publications in the CNS delivery space**

First biotherapeutic to leverage TfR to cross blood-brain barrier (BBB) **FDA approved in 2026**



Tividenofusp alfa is approved only in the United States.

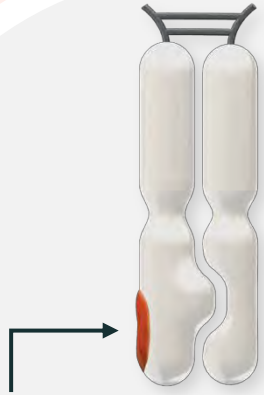
Our TransportVehicle™ Platform Sets the Bar for BBB Delivery

1 Modularity

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

2 Brain Uptake

Optimized affinity and epitope enhance brain delivery while limiting receptor degradation



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

3 Safety

Conditional effector function avoids reticulocyte loss and minimizes anemia liability potential

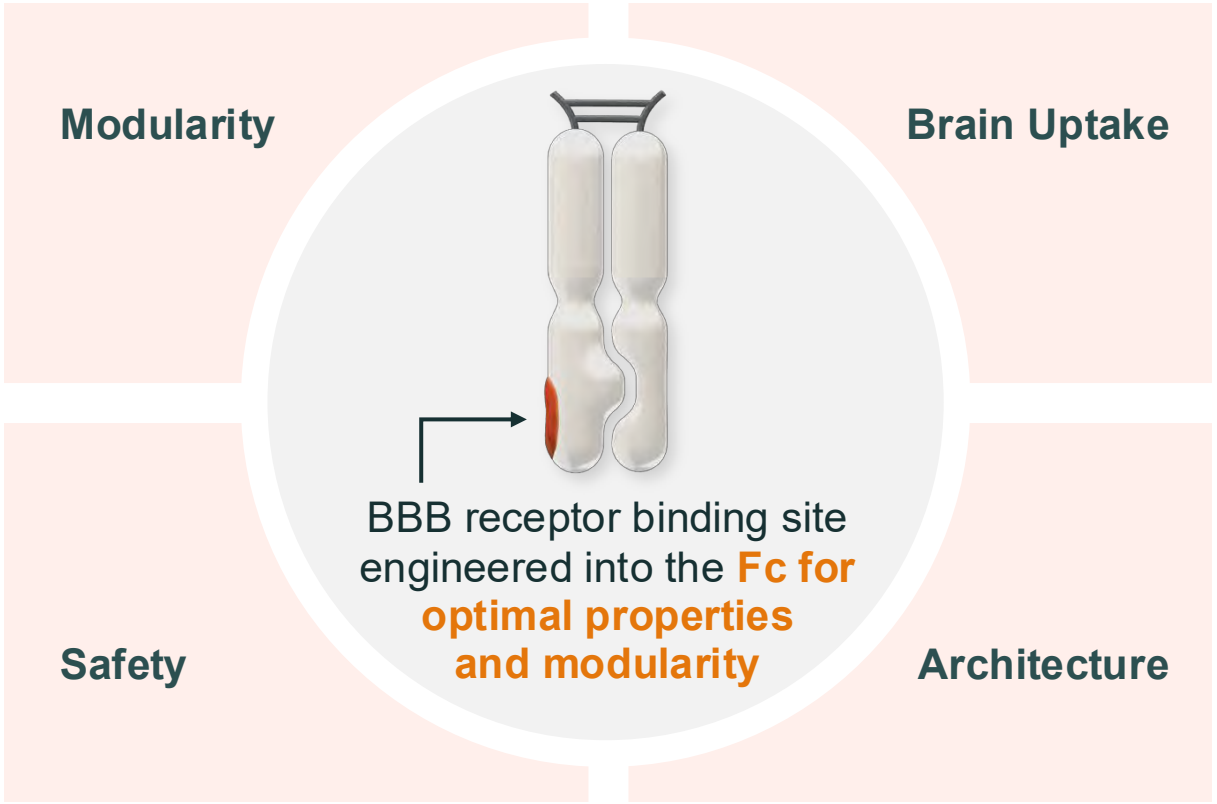
4 Architecture

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

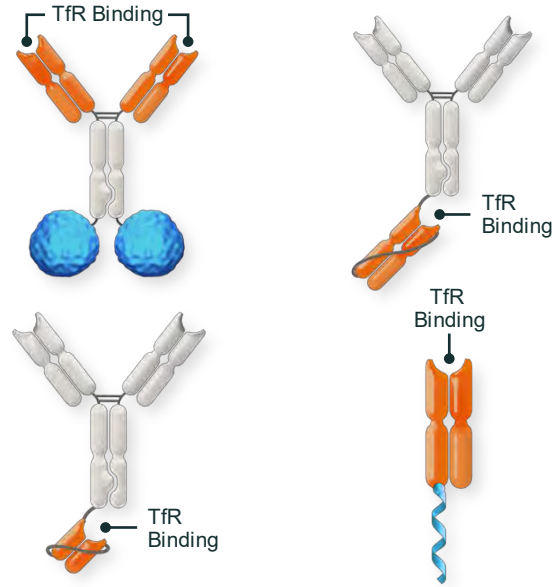
Our Fc-based TransportVehicle™ (TV) Is Designed & Engineered to Optimize Brain Delivery

TransportVehicle Engineered for Optimized Delivery

Fc-based TransportVehicle (TV) Is Designed and Engineered to Optimize Brain Delivery



Conventional Fab Approaches



- High affinity, bivalent binding leads to suboptimal brain biodistribution[1]
- Full effector function increases anemia risk
- Linker may adversely affect stability
- Low fidelity to natural protein may increase risk of immunogenicity

1. Arguello et al. *JEM* 2022; **BBB –** Blood-brain barrier

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

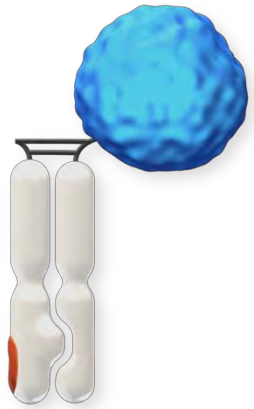
Industry Leading Platform

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

1. As of Oct 27, 2025; **2.** As of Nov 3, 2025; **3.** As of Dec 5, 2025. **BBB –** Blood-brain barrier; **Fc –** fragment crystallizable; **TfR –** Transferrin receptor; **NfL –** Neurofilament light chain

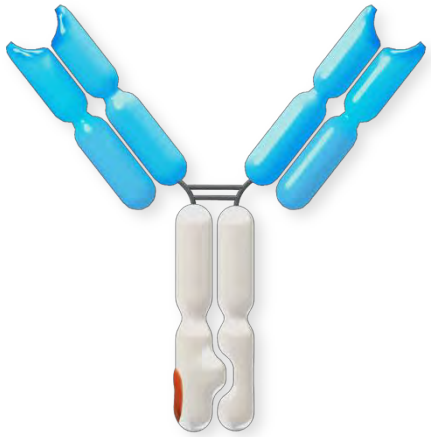
Delivering Multiple Modalities Across the BBB

Enzyme TV
(ETV)



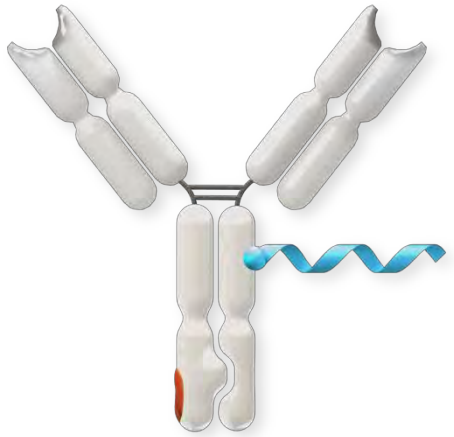
Enzyme replacement therapy for the body and brain

Antibody TV
(ATV)



Brain-penetrant immunotherapy for a wide range of diseases

Oligonucleotide TV
(OTV)



Genetic medicines for the brain, delivered systemically

The TransportVehicle (TV) Platform enables TfR-mediated brain biodistribution and enhanced tissue delivery of diverse biotherapeutics modalities

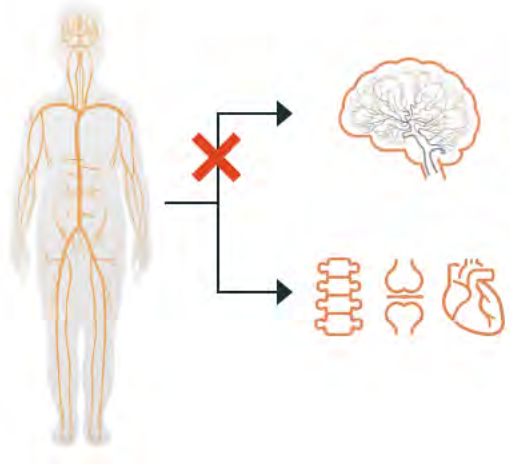
BBB – Blood-brain barrier; **TfR –** Transferrin receptor

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**

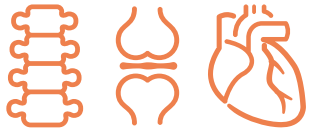


Traditional ERTs partially address somatic but not CNS symptoms

~80% historical ERT approval rate[1]

Targeting Brain & Body with ETV

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



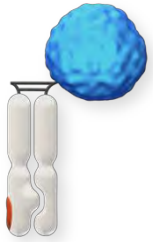
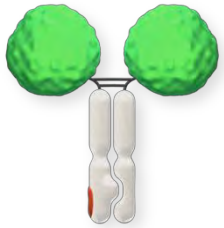
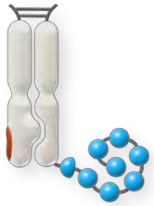
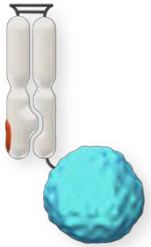
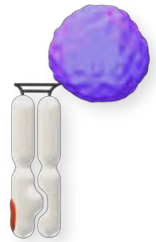
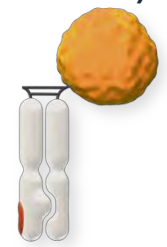
Potential to **enhance peripheral delivery**

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

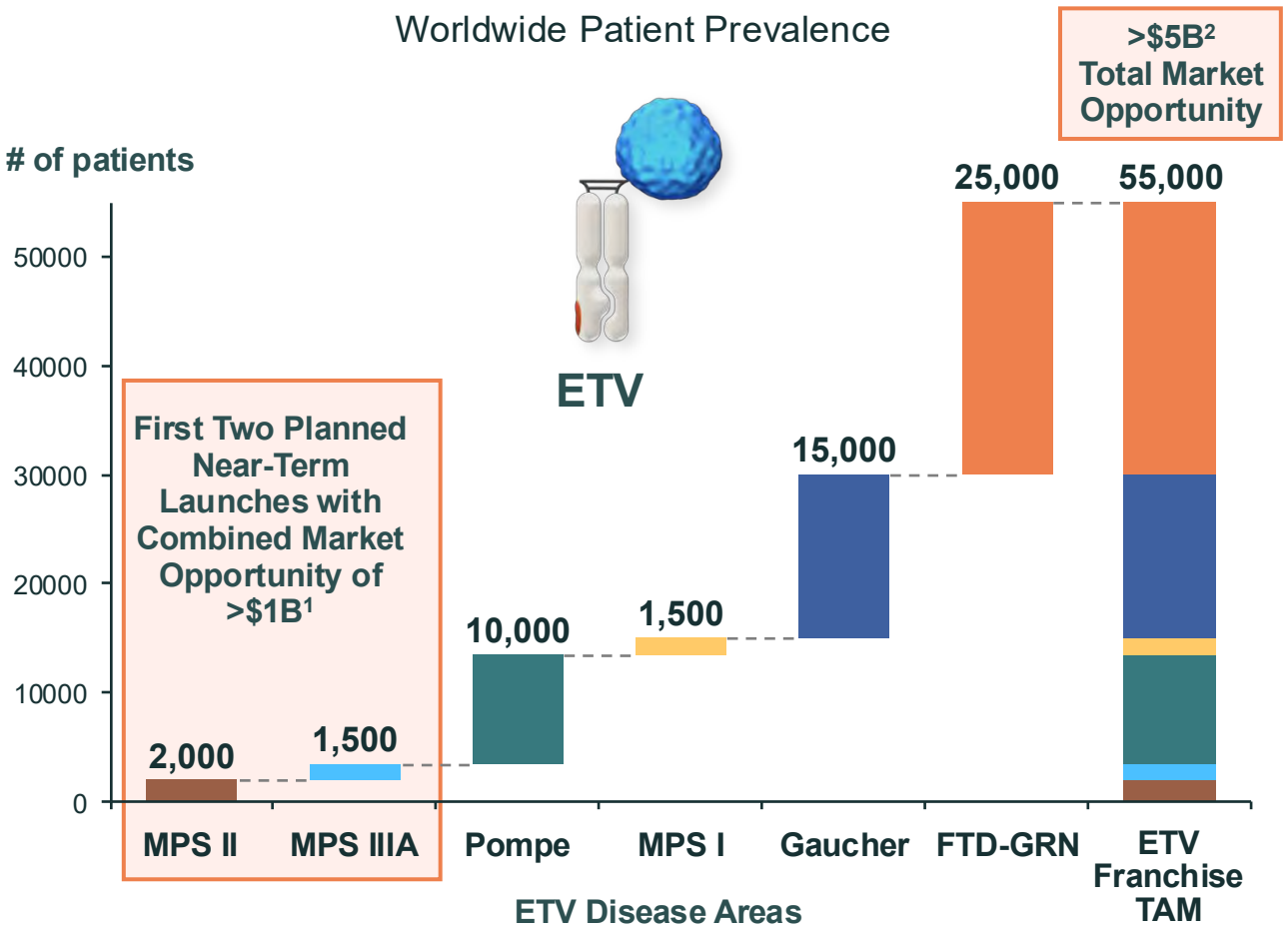
We are developing the next generation of enzyme replacement therapies designed to treat brain and body manifestations of serious genetic diseases

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

ETV: Foundational Franchise for Lysosomal Storage Disorders

ETV Franchise

Worldwide Patient Prevalence

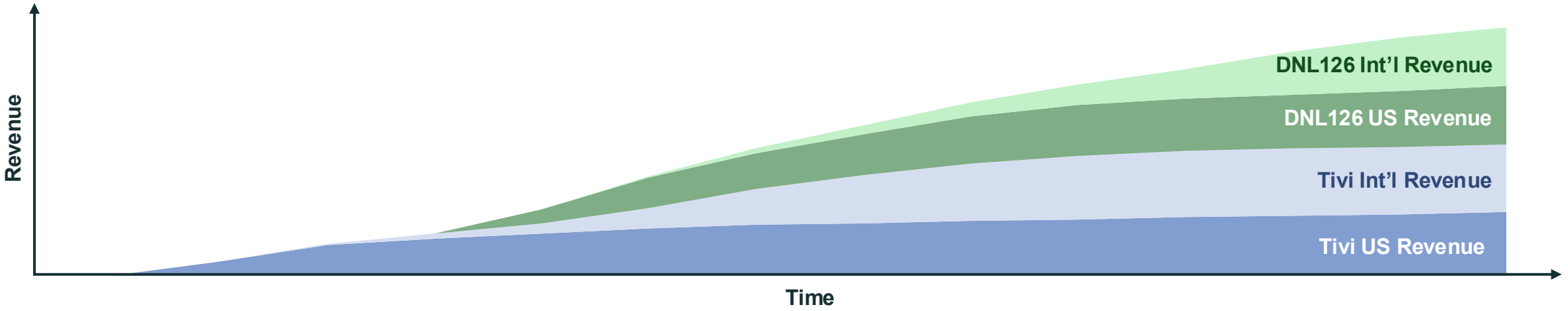


Delivering Next-Generation Enzyme Replacement Therapy (ERT)

- 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™

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.

AVLAYAH™ (tividenofusp alfa-eknm)

Mucopolysaccharidosis Type II (Hunter Syndrome)

Underlying Cause and Disease Impact

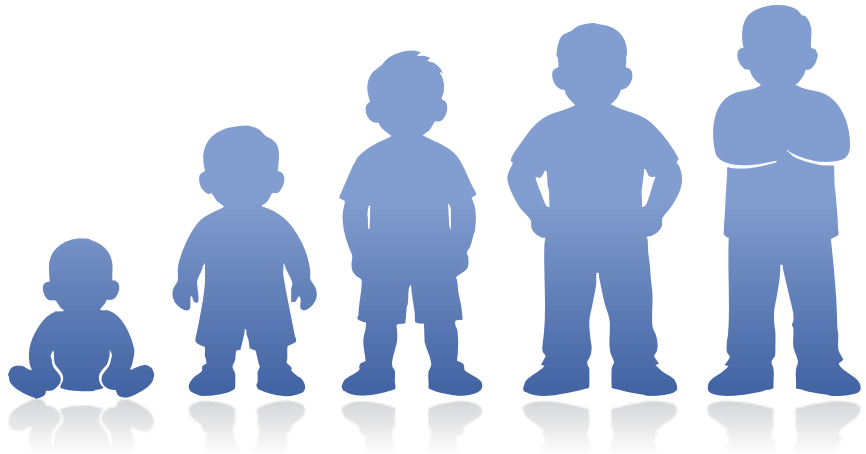
Genetic disorder caused by deficiency in the iduronate 2-sulfatase (IDS) enzyme[1]

Buildup of glycosaminoglycans (GAGs) affects systems throughout the entire body[1]

Gradual loss of function leads to increasing disability as the disease progresses[1]

Cardiac-respiratory failure is the most common cause of death in MPS II[2]

Clinical Course



Diagnosis[3] Birth ↔ 4 years

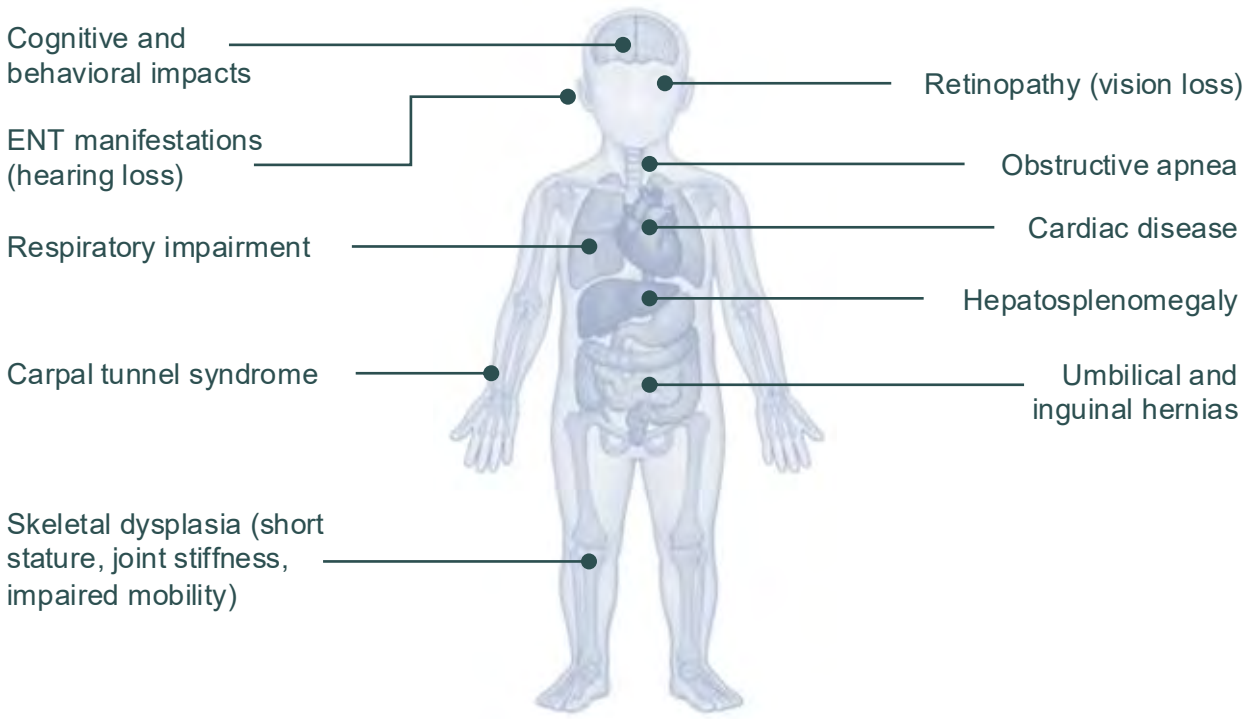
Progression[4] Rapid ← → Slow

Life Expectancy[1] Teens ↔ Mid-Age

MPS II – Mucopolysaccharidoses Type II; **GAG** – Glycosaminoglycan; **ENT** – Ear, nose, and throat; **1.** Hashmi MS, Gupta V. Mucopolysaccharidosis Type II. [Updated 2023 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. Accessed January 21, 2026. https://www.ncbi.nlm.nih.gov/books/NBK560829; **2.** D'Avanzo F, et al. *Int J Mol Sci*. 2020;21(4):1258; **3.** McBride KL, et al. *Genet Med*. 2020;22(11):1735-1742; **4.** Nan H, et al. *Biomed Res Int.* 2020:2408402.

MPS II: Progressive Spectrum Disease Affecting Body and Brain

Patients with MPS II are Affected in Most Organ Systems[1-4]



Neurologic Manifestations

- Cognitive[1,3,4], behavioral[1,3,4], hearing[1] and motor decline[5]
- Experienced by most patients[6,7]; severity spans the clinical spectrum

Peripheral Manifestations

- Multisystem involvement[8]
- Progressive somatic burden[8]

The broad range of systems impacted by MPS II necessitates a whole-body treatment approach

MPS II – Mucopolysaccharidoses Type II; **1.** Hashmi MS, Gupta V. Mucopolysaccharidosis Type II. [Updated 2023 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. Accessed January 21, 2026. https://www.ncbi.nlm.nih.gov/books/NBK560829; **2.** D'Avanzo F, et al. *Int J Mol Sci*. 2020;21(4):1258; **3.** Ream MA, et al. *Genet Med*. 2023;25(2):100330; **4.** McBride KL, et al. *Genet Med*. 2020;22(11):1735-1742.; **5.** Phillips D et al, *Medical Research Archives*, 2024;12(11). Accessed March 19, 2026. https://doi.org/10.18103/mra.v12i11.5915; **6.** Lau H et al, *Mol Genet Metab Rep* 2023; 37:101005.; **7.** Wraith JE, Scarpa M, Beck M, et al. *Eur J Pediatr*. 2008;167:267-277; **8.** Nan H, et al. *Biomed Res Int.* 2020:2408402.

Therapeutic Goal: Treat the Whole Body, Including the Brain

Unmet Needs with Current Standard of Care Enzyme Replacement Therapy

Neurologic Manifestations

Current ERT does not cross the BBB and does not reduce CNS GAG accumulation[1-5]

Cognitive and behavioral symptoms and hearing loss are inadequately addressed by current therapy

Peripheral Manifestations

Patients may experience above-normal levels of urine GAGs even after treatment with current IV ERT[5,6]

Cardiac and skeletal symptoms are also often not addressed by current therapy[7]

New therapies are needed to adequately address both the neurologic and peripheral manifestations of MPS II

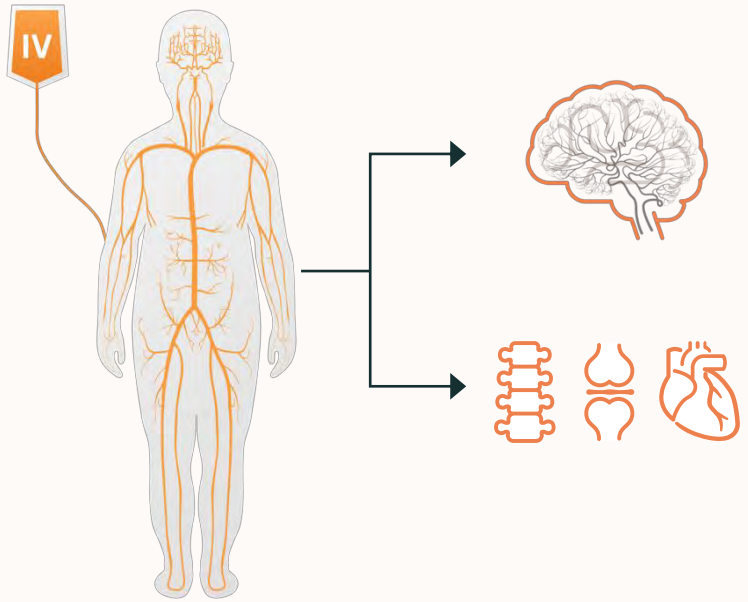
BBB – Blood-brain barrier; **CNS** – Central nervous system; **ERT** – Enzyme replacement therapy; **GAG** – Glycosaminoglycan; **IV** – Intravenous; **MPS II** – Mucopolysaccharidosis type II; **1.** Al-Hertani W, et al. *Int J Mol Sci.* 2024;25(16):8573; **2.** Giugliani R, et al. *Int J Mol Sci*. 2021;22(20):10938; **3.** Bhalla A, et al. *Int J Mol Sci*. 2020;21(15):5188; **4.** Argueta C, et al. *Mol Genet Metab.* 2025;144(3):109055; **5.** Muenzer J, et al. *Mol Genet Metab*. 2025;146(4):109284; **6.** Muenzer J, et al. *Genet Med*. 2011;13(2):95-101; **7.** Muenzer J. *Mol Genet Metab*. 2014;111(2):63-72.

Brain Delivery Is Critical Unmet Need of Hunter Syndrome Therapy

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

AVLAYAH™
tividenofusp
alfa-eknm

Tividenofusp alfa-eknm is a brain-penetrant ERT designed to reduce the substrate of IDS (heparan sulfate) throughout the body



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

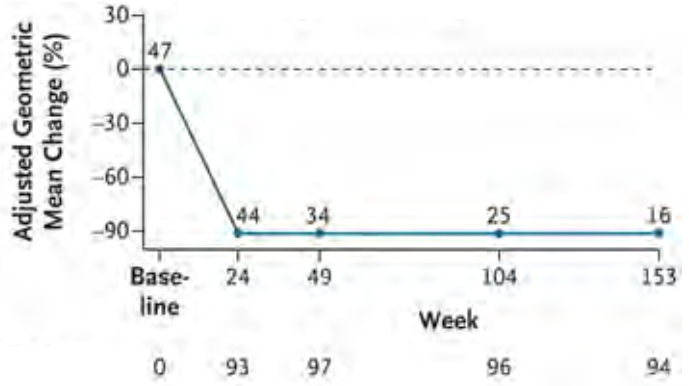
Tividenofusp alfa is approved only in the United States. **ERT** – Enzyme replacement therapy

Tividenofusp alfa-eknm Phase 1/2 Results in MPS II: Efficacy

Normalization of Brain Biomarkers

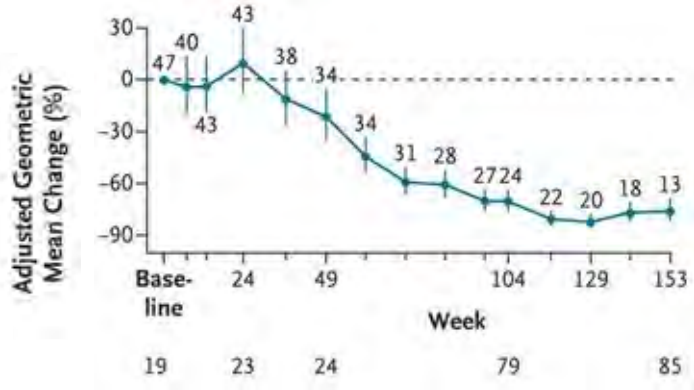
CSF HS

Biomarker of CNS disease



NfL

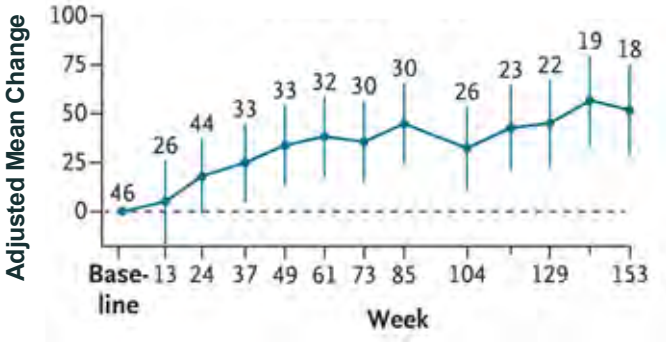
Biomarker of neuronal damage



Improvement in Clinical Outcomes

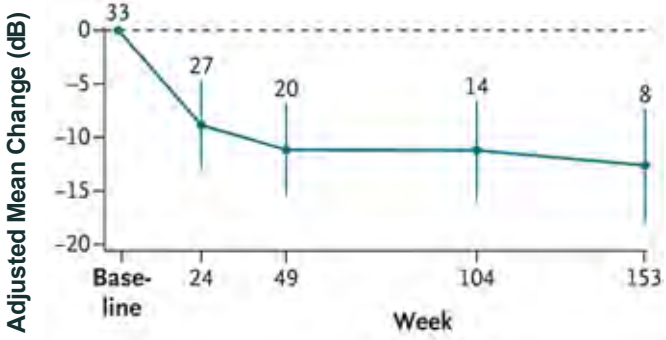
Adaptive Behavior

Vineland-3 Raw Score Composite



Hearing Threshold

Auditory Brainstem Response (PTA)



Treatment with tividenofusp alfa-eknm over a median duration of 2 years normalized key biomarkers with potential for improving clinical outcomes

Tividenofusp alfa is approved only in the United States.

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

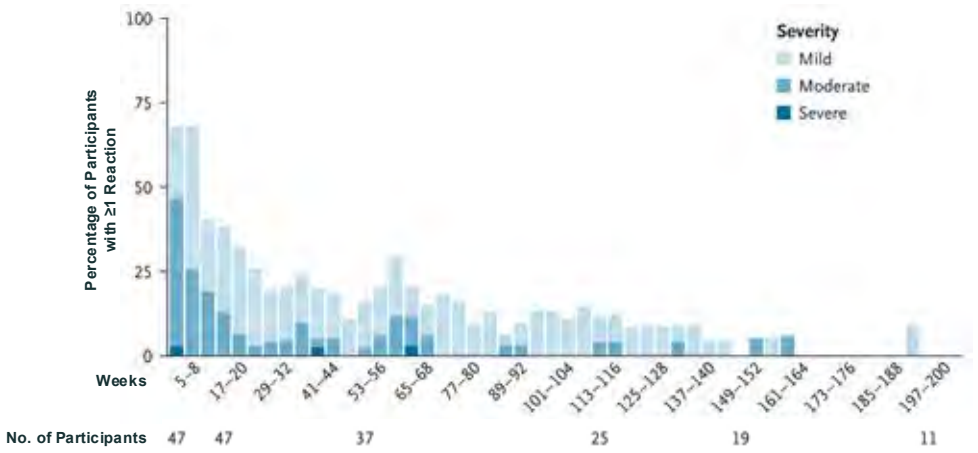
Tividenofusp alfa-eknm Phase 1/2 Results in MPS II: Safety

Summary of Adverse Events

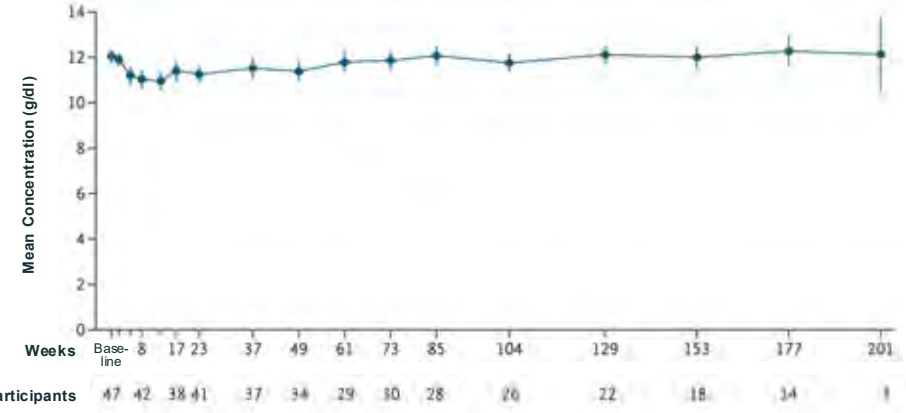
(Safety Analysis Population)

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

Tividenofusp alfa is approved only in the United States.

MPS II – Mucopolysaccharidoses Type II; **ERTs** – Enzyme Replacement Therapies; Source: Muenzer et al. *NEJM* 2026

Setting a New Bar for the Treatment of MPS II

AVLAYAH™
(tividenofusp alfa-eknm)

The first FDA-approved enzyme replacement therapy (ERT) to cross the **blood-brain barrier** to reach the brain in addition to the body

9 out of 10

individuals had normal levels* of CSF HS after 6 months and 12 months of treatment

At the start of the study, 0 individuals had normal levels* of CSF HS; the majority had previously received ERT

9 out of 10

individuals had normal levels* of uGAGs after 12 months of treatment

At the start of the study, 2 individuals had normal levels* of uGAGs; the majority had previously received ERT

* "Normal levels" refers to biomarker levels typically seen in people without Hunter syndrome; **MPS II** – Mucopolysaccharidoses Type II; **CSF** – Cerebrospinal fluid; **HS** – Heparan sulfate; **uGAGs** – Urine glycosaminoglycans; **ERT** – Enzyme replacement therapy; All strategies and tactics are subject to Legal review prior to implementation. Source: Muenzer et al. 2026 *NEJM*.

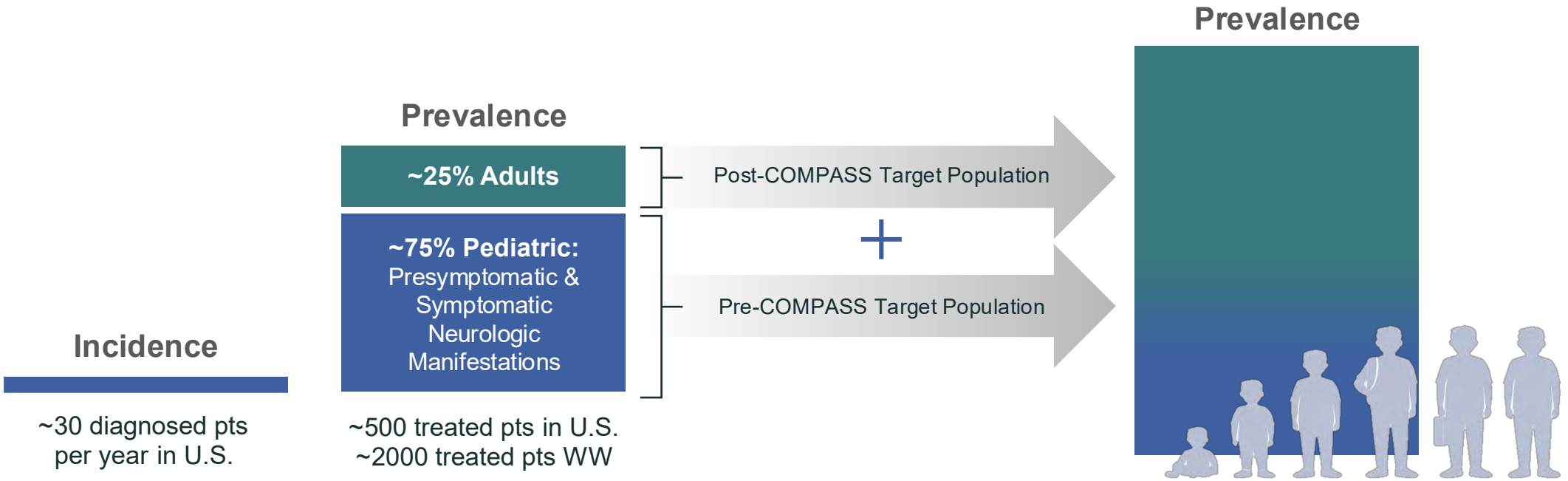
AVLAYAH™ Has the Potential to Reduce Disease Burden, Leading to Growth in the MPS II Population

Current Standard of Care Paradigm

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

Potential Future Treatment Paradigm

Potential for a larger MPS II population over time as disease burden is reduced



MPS II – Mucopolysaccharidosis type II; **Pts** – Patients; **WW** – Worldwide; All strategies and tactics are subject to Legal review prior to implementation.

Our Stakeholders Are Ready and Waiting for AVLAYAH™

Physicians[1]

90% **view AVLAYAH™'s data as highly motivating to prescribe**

- Recognize significant **unmet needs** across **brain and body**
- **No overall concerns** with safety profile

"This novel treatment should have a profound impact on individuals and families living with this devastating disease."

— MPS II HCP

Patients & Caregivers[2]

80% **are aware of new treatments coming and excited to try AVLAYAH™**

- Perceive significant **unmet needs**, across **brain and body**
- **Advocacy orgs** and **peer-to-peer** communications **most influential**

"We are hopeful a new treatment will be approved by the FDA that will benefit him neurologically, as well as his overall quality of life."

— Recently diagnosed Hunter family

Payers[3]

90% **of commercial lives represented in conversations with payers**

- **Perceive therapeutic benefit** due to ability to cross the BBB
- View AVLAYAH™'s **benefit/risk profile favorably**

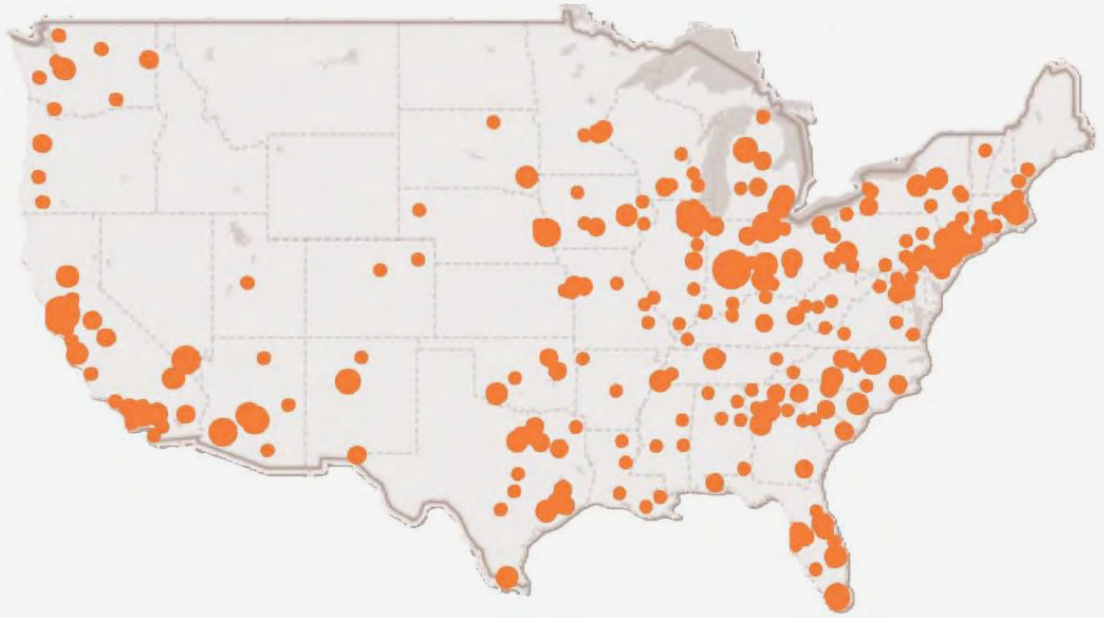
"We recognize the clinical need for the MPS II patients and will likely manage to FDA approved label."

— US Commercial Payer

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.

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

MPS II Patient Distribution



~500 patients in the U.S. on SoC ERT

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

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

Sales force **has profiled and segmented** all accounts with MPS II patients **to optimize execution**

MPS II – Mucopolysaccharidosis type II; **ERTs** – Enzyme replacement therapies; All strategies and tactics are subject to Legal review prior to implementation.

Built a Winning Team Ready for Launch

Launch Leadership Team

Significant Experience Across Functions

- Product Strategy
- U.S. and Global Marketing
- U.S. / Ex-U.S. Market Access
- Market Planning and Analytics
- Medical Affairs & Med Info
- Field Sales
- Field Medical
- Patient Advocacy

19 Product/Indication Launches for Global Blockbusters

- 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

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

Our 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

AVLAYAH™'s price reflects its therapeutic value and commitment to broad access

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

Denali Patient Services Supporting Patients and Caregivers

DENALI
Patient Services

We know every patient's journey is unique. **Denali Patient Services** offers personalized support services to patients, caregivers, and providers navigating therapy with AVLAYAH™

CARE

Compassion, Assistance, Resources, and Education

Your dedicated **Denali CARE Partner** is here for you throughout your treatment journey

Our Denali CARE Team is here to help with:

- **Insurance Coverage**
- **Treatment Coordination**
- **Information and Resources**
- **Financial Assistance**

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

AVLAYAH™ Aligned with Rare Disease Launch Dynamics

2026: Building the Foundation Across Key Stakeholders for Revenue Acceleration

Physicians

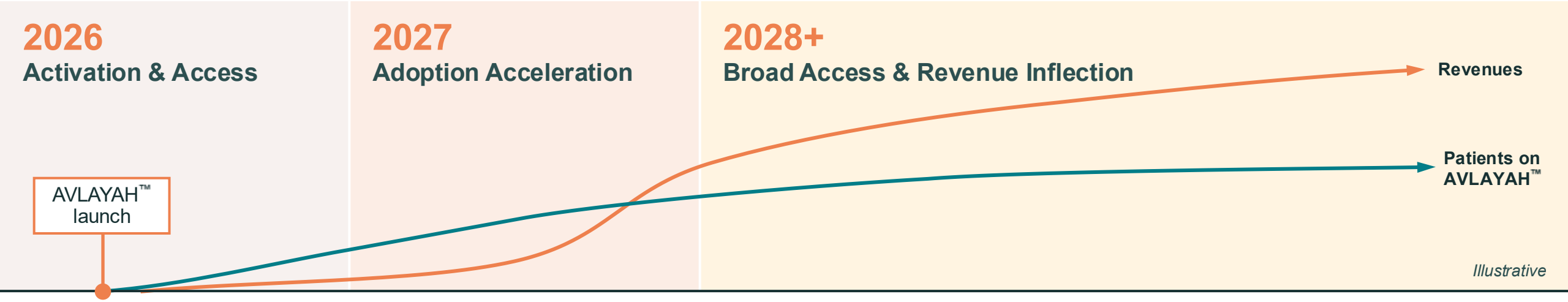
- Support procurement & access challenges
- Instill clinical belief of AVLAYAH™ Activate Centers of Excellence
- In-service & infusion education
- Scientific exchange

Payers

- Secure commercial coverage policies
- Advance Medicaid coverage
- Operationalize prior authorization and medical exception process
- Reduce time from prescription to coverage approval

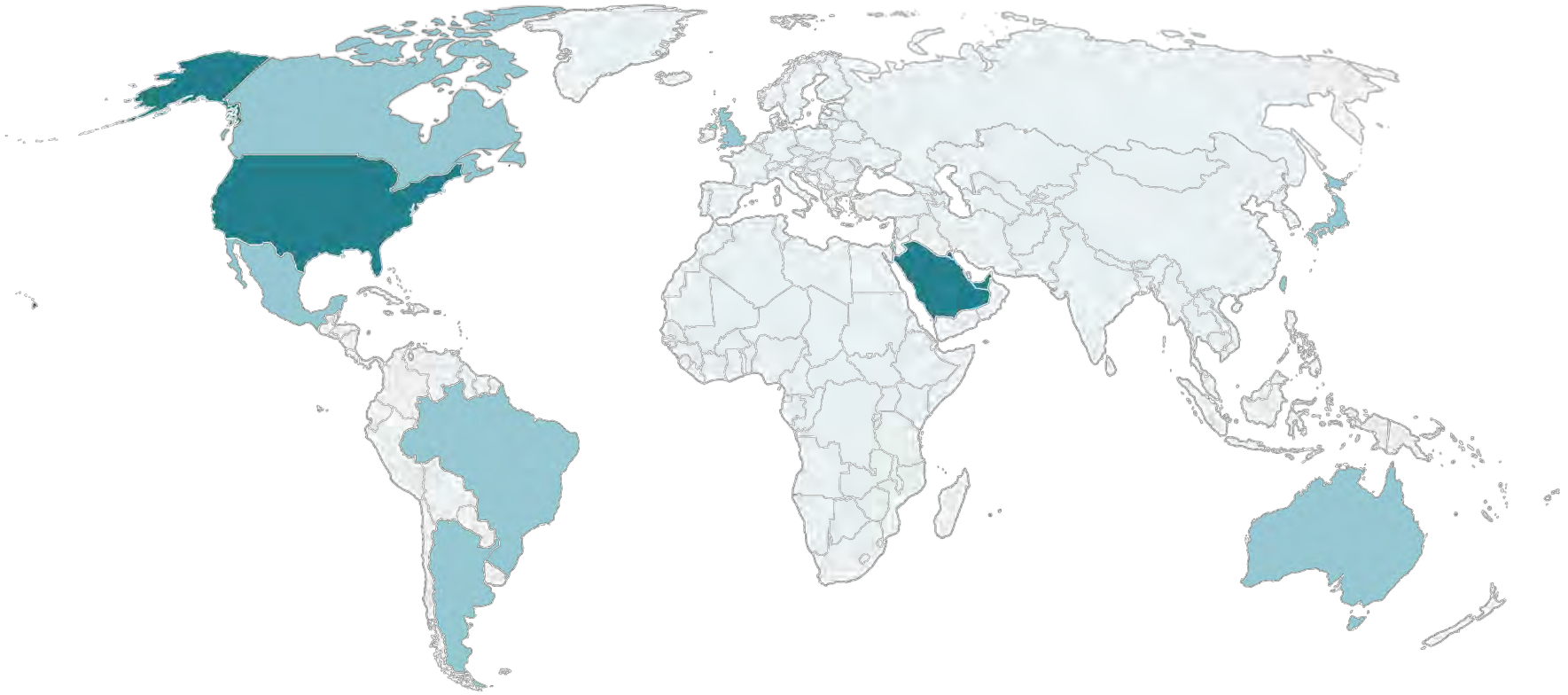
Patients & Caregivers

- Launch with the advocacy community
- Drive awareness and consideration
- Support patients access to treatment
- Reduce time from prescription to first infusion



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

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



~33% of Market
Short Term[1] (2026-2027)

~33% of Market
Mid-Term[1] (2027-2028)

~33% of Market
Longer Term (2028+)

- 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
- Distributor partnerships established across select LATAM and MENA

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

Clear Path from Accelerated to Full Approval

Phase 1/2 Study

47 participants

AVLAYAH™
(tividenofusp alfa-eknm)

U.S. Accelerated Approval Achieved

Supports Select Country Approvals

Phase 2/3 Confirmatory Study

63 participants

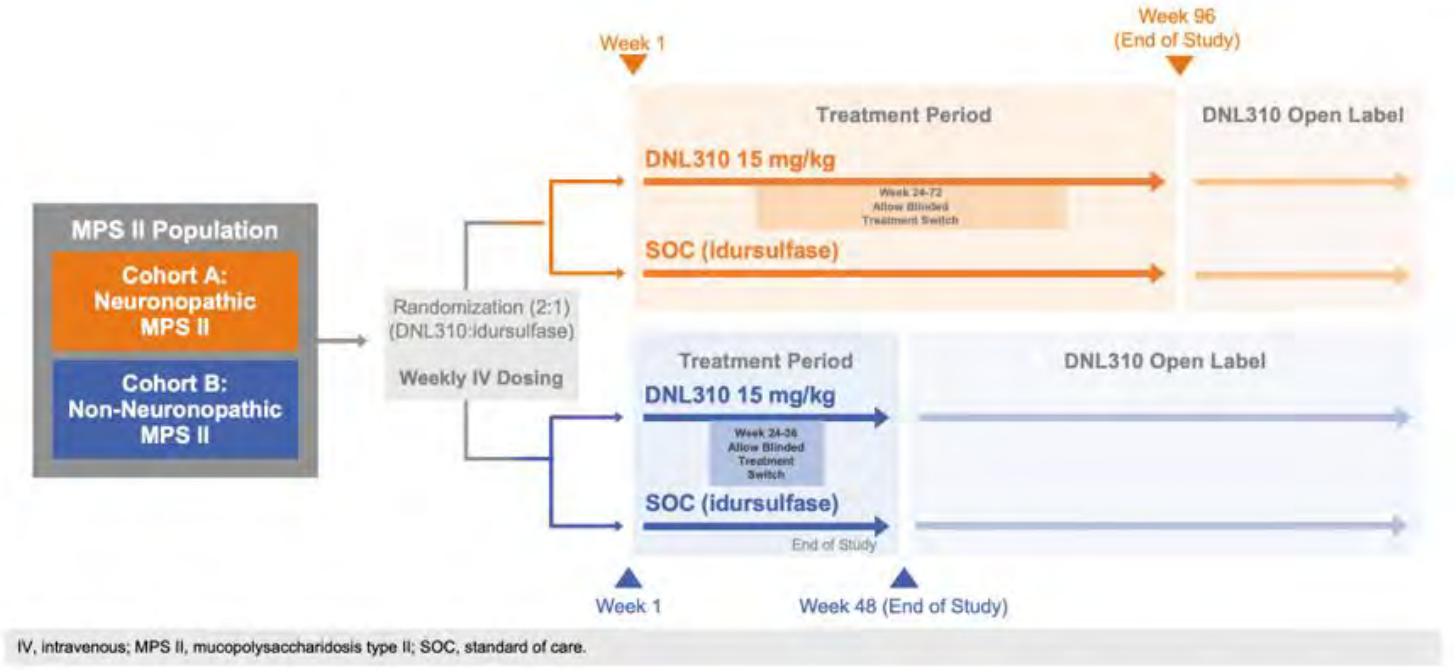
COMPASS

Supporting Conversion to U.S. Full Approval, Label Expansion and Global Approvals

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



NCT05371613

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

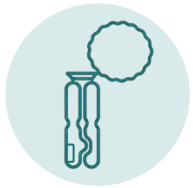
- **Cohort A:** CSF HS, Vineland-3, BSID-II, serum NfL
- **Cohort B:** 6MWT
- **Cohorts A & B:** Urine HS and DS, Liver and Spleen MRI volume, Patient / Caregiver Impression of Change, Safety

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

FDA Approved for MPS II and a Foundation for Future CNS-Targeted Therapies

AVLAYAH (tividenofusp alfa-eknm) is the first and only FDA-approved therapy for children with MPS II designed to reach the **whole body, including the brain**



The first FDA-approved biologic therapeutic in a new class of medicines **engineered to cross the blood-brain barrier (BBB)** and address a broad range of diseases

Brain transport technologies are now clinically validated and have shown promise in other CNS conditions, including Alzheimer's disease

AVLAYAH was granted US Accelerated Approval (AA) for the treatment of neurologic manifestations of Hunter syndrome (Mucopolysaccharidosis type II, MPS II) when initiated in presymptomatic or symptomatic pediatric patients weighing at least 5 kg prior to advanced neurologic impairment.

Tividenofusp alfa is approved only in the United States but does not currently hold a UK marketing authorization.

MPS II – Mucopolysaccharidoses Type II; **FDA** – U.S. Food and Drug Administration; **1.** AVLAYAH™ [package insert]. March 2026. FDA granted approval under the FDA's Accelerated Approval Program. Continued approval for this indication, which was based on reduction of cerebrospinal fluid heparan sulfate, may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Alzheimer's Disease Opportunity

Historic Barriers to Success in Neurodegeneration

Biology

Neurodegeneration is multifaceted, progresses over years, and is difficult to model

Biomarkers

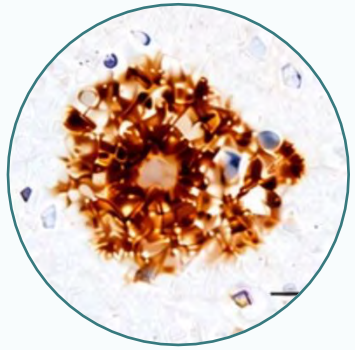
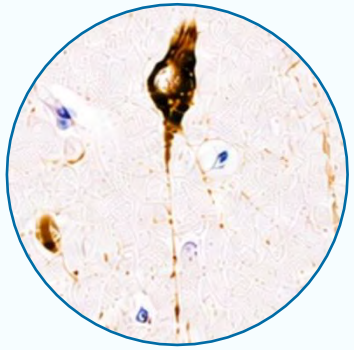
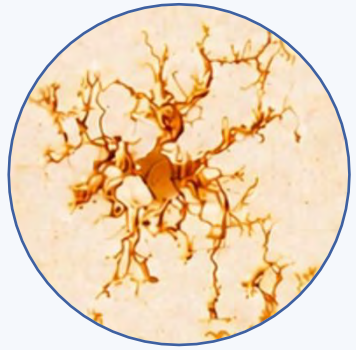
Diagnosis comes too late, and there are limited tools to determine if treatment works

Blood-Brain Barrier

Most therapies cannot effectively reach the brain, even at very high doses

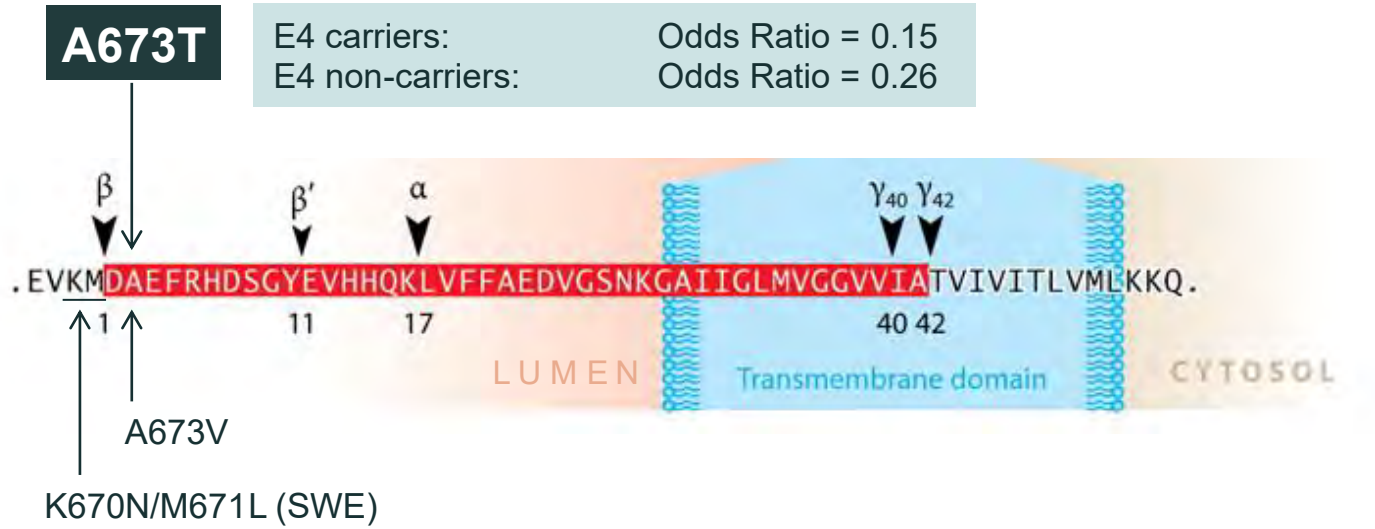
Incredible progress in all three historically challenging areas over the past decade has enabled a transformational period for accelerating neurodegeneration medicines

Validating Biology in Alzheimer's Disease

	TRIGGER	EXECUTIONER	CONTRIBUTORS
	Amyloid-beta (Abeta)	**Tau**	**Neuroinflammation & Lipid Metabolism**
	 Amyloid plaque	 Neurofibrillary tangle	 Microglia cell
GENETICS	***APP/PSEN1*** is the strongest genetic link for AD	In AD, Tau pathology is **driven by upstream amyloid burden**	***TREM2, CLU, APOE*** variants in microglial activation & lipid handling
DISEASE PATHOLOGY	Often thought to be the **"trigger"** that kicks-off the disease	Most closely associated with **cognitive decline**	Characterized by **microglial activation**
THERAPEUTIC STRATEGY	Clear Abeta plaques **(Clinically validated)**	Knockdown Tau **(Emerging)**	Multiple approaches **(Preclinical / Early Clinical)**

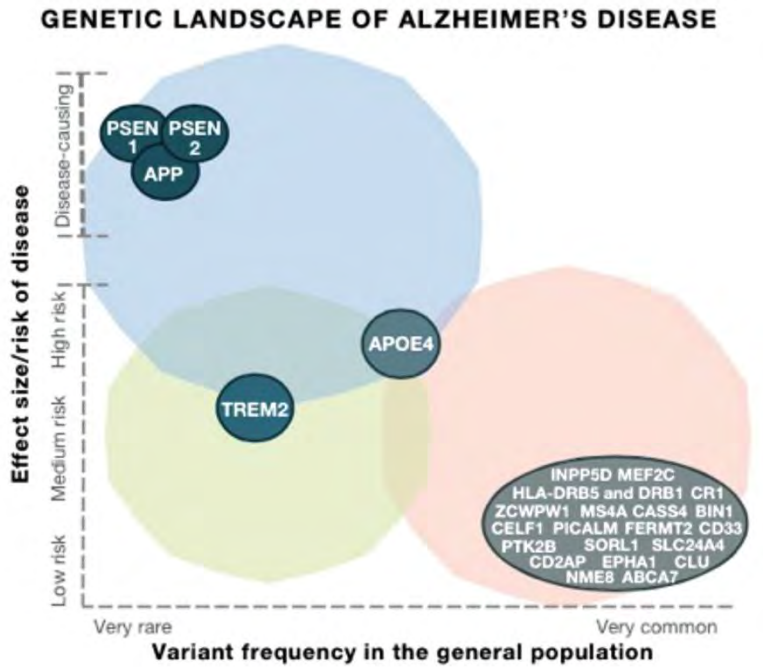
AD Genetics: Allelic Series for APP and Other Key Risk Genes

Identification of Protective *APP* Variant: A673T



- A673T Mutation in *APP* associated with decreased Abeta production protects against AD
- Other *APP* Mutations associated with increased Abeta production cause familial early onset AD

Alzheimer's Risk Gene: *ApoE4*

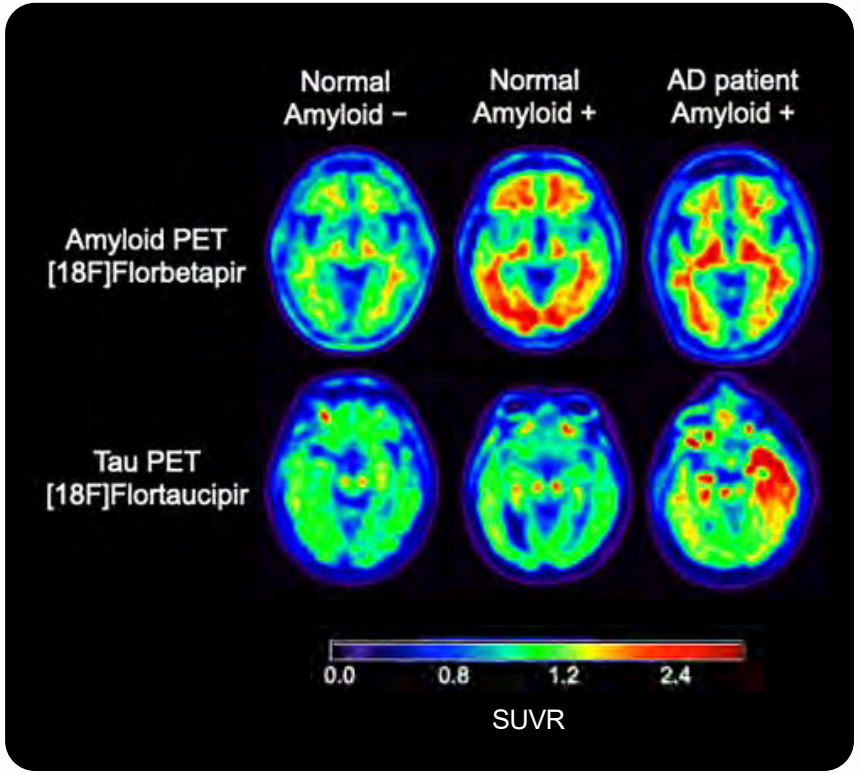


- *ApoE4* is the strongest common genetic risk factor in Alzheimer's disease (AD)

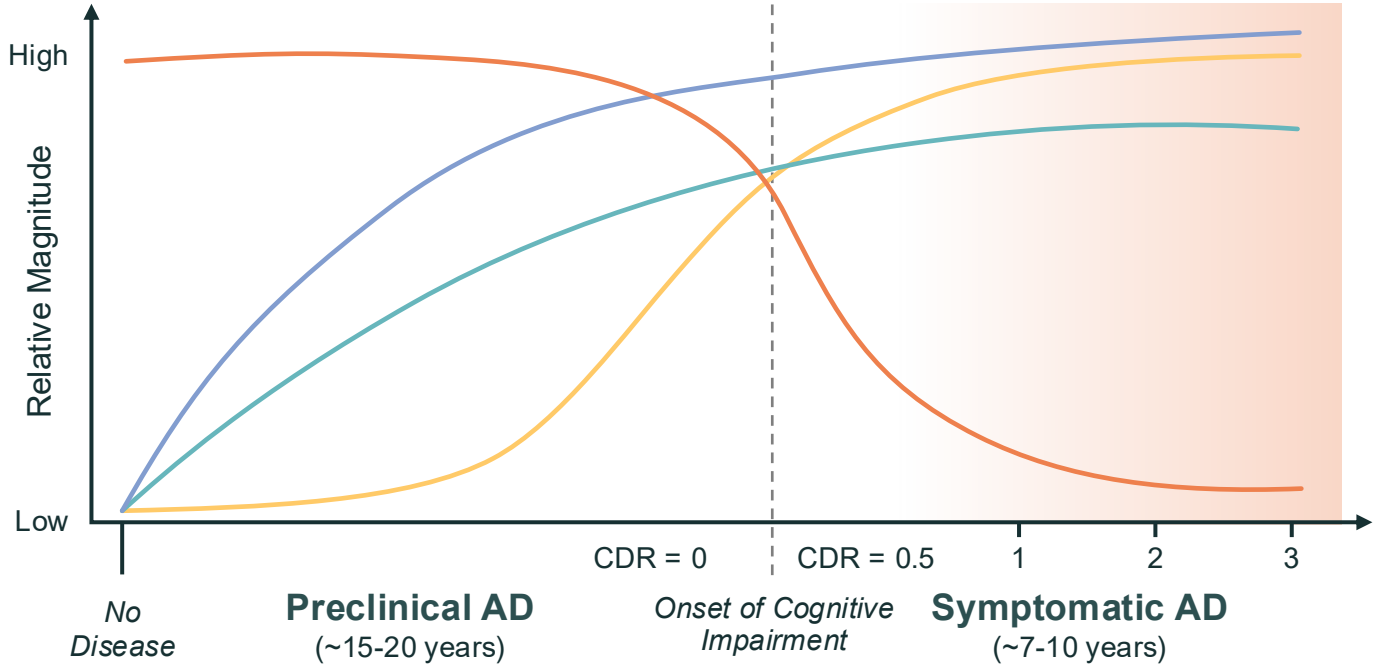
Left image adapted from Jonsson et al. *Nature* 2012; Right image from Guerreiro et al. *Cell* 2015

AD Biomarkers Emerge Decades Before Cognitive Symptoms

Hallmarks of AD Pathology

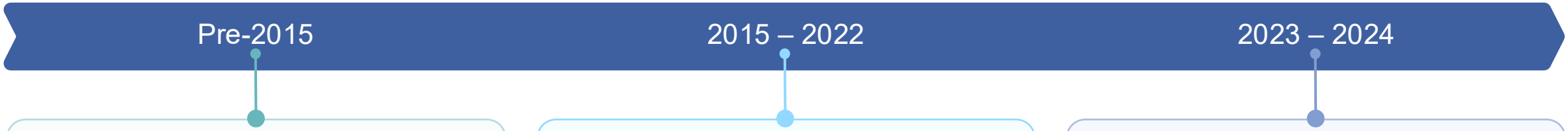


Major AD Pathophysiological Events in Relation to Clinical Course



Left image from Carney Institute for Brain Science / Brown University (HEAD Study); Right image adapted from Long and Holtzman *Cell* 2019

Decades of Effort Have Culminated in the First AD Approvals



Early Days

Target and Biomarker Identification

Amyloid plaques and tau tangles identified and therapeutic hypotheses developed

Translational Progress

Bapineuzumab, Solanezumab, Crenezumab, Gantenerumab, etc…
Failures

Some First-generation mAbs show Abeta plaque clearance

Molecule Approvals

Lecanemab & Donanemab Successes

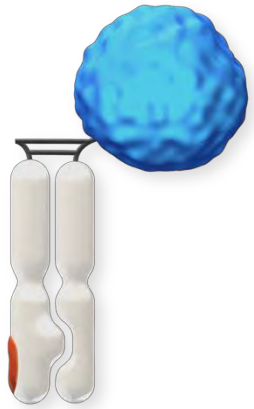
Second-generation mAbs show clinical benefit and receive regulatory approval

Initial approvals have validated the Abeta therapeutic hypothesis and demonstrated a clear link between established biomarkers and clinical outcomes

Adapted from Zhang et al. *Nature Review* 2023

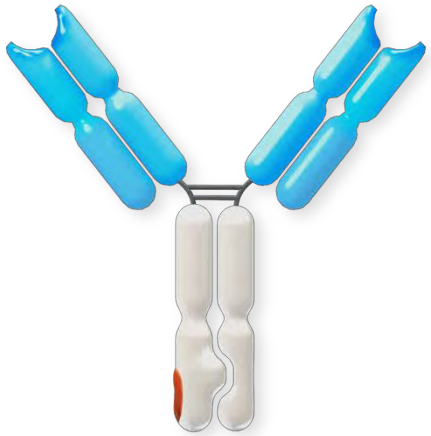
Delivering Multiple Modalities Across the BBB

Enzyme TV
(ETV)



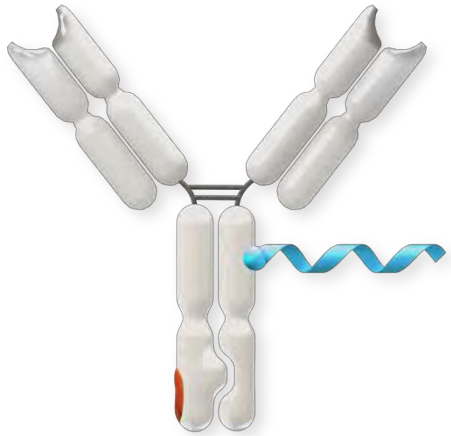
Enzyme replacement therapy for the body and brain

Antibody TV
(ATV)



Brain-penetrant immunotherapy for a wide range of diseases

Oligonucleotide TV
(OTV)

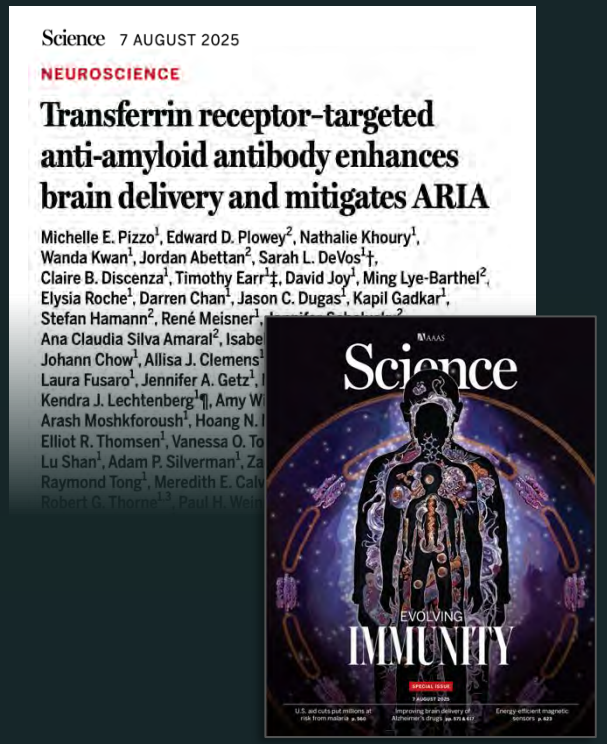


Genetic medicines for the brain, delivered systemically

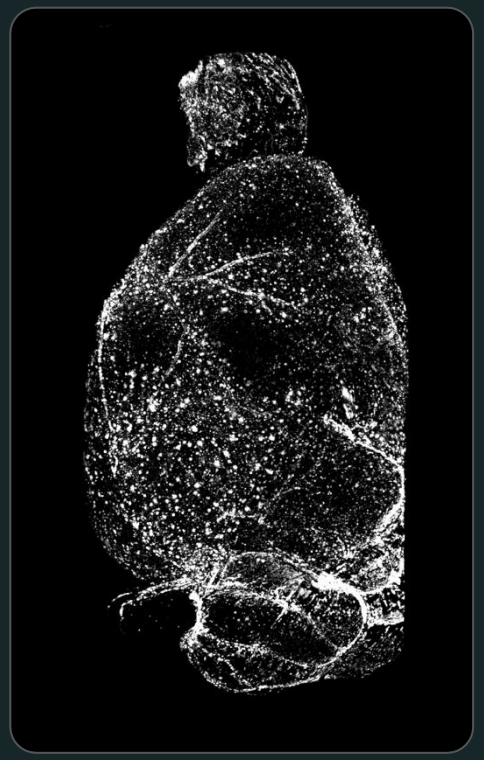
The TransportVehicle (TV) Platform enables TfR-mediated brain biodistribution and enhanced tissue delivery of diverse biotherapeutics modalities

BBB – Blood-brain barrier; **TfR –** Transferrin receptor

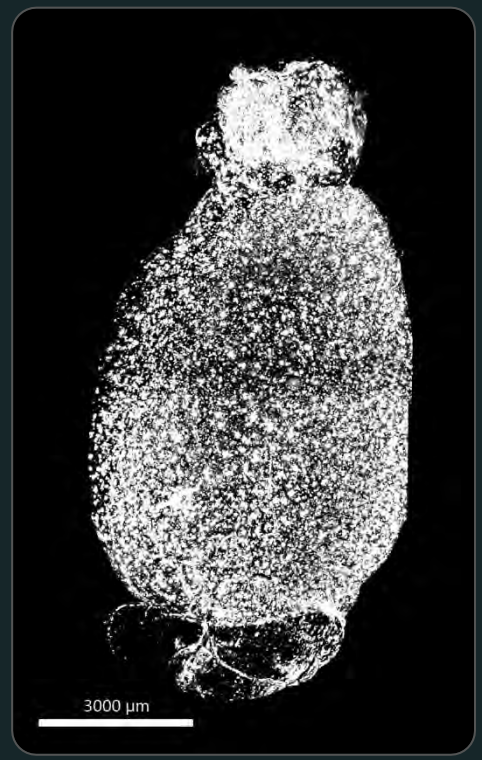
ATV:Abeta (DNL921) Exhibits Enhanced Target Engagement Compared to Standard Anti-Abeta in Mouse Model of AD



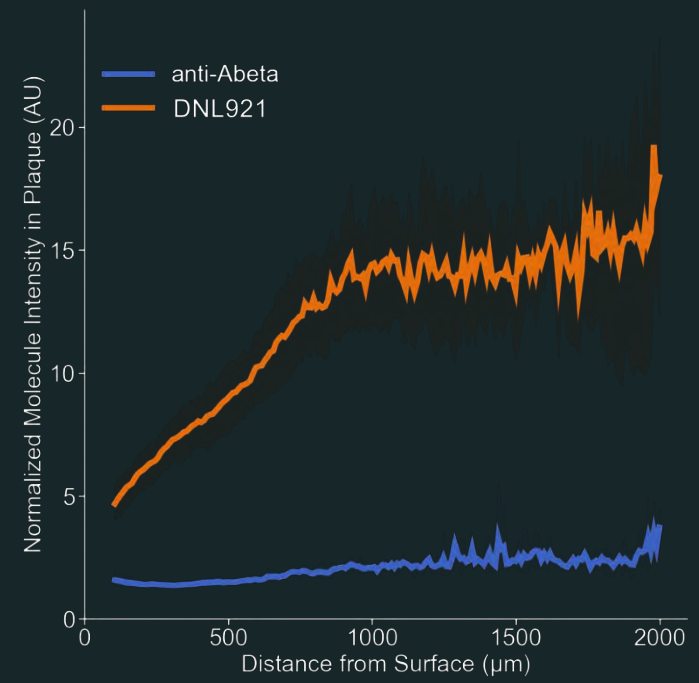
1st Generation Anti-Abeta



DNL921



Amyloid Plaque Target Engagement

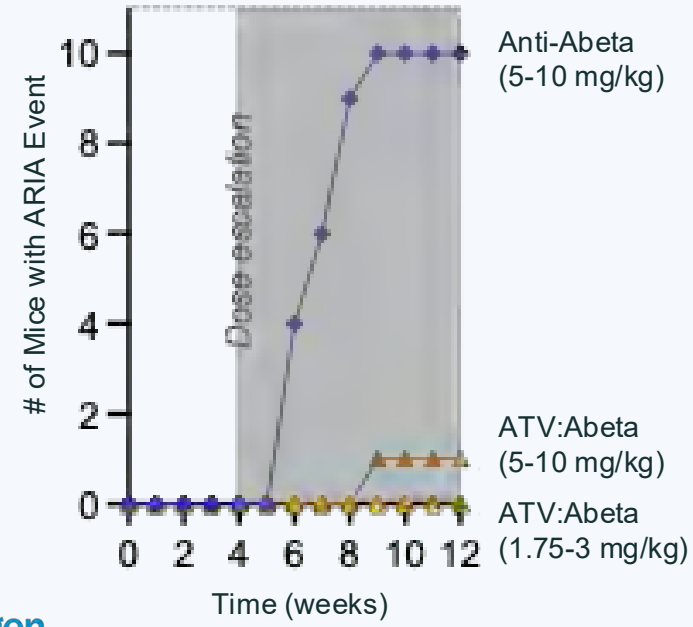


DNL921 (ATV:Abeta) is an investigational compound and has not been approved by any regulatory authority.
10 mg/kg, 24 hours post-dose, iDISCO-cleared hemibrain; signal represents amyloid plaque engagement; Source: Pizzo et al. *Science* 2025

ATV:Abeta Reduces ARIA Due to TfR-Mediated Capillary Delivery to Brain

Incidence of MRI Lesions

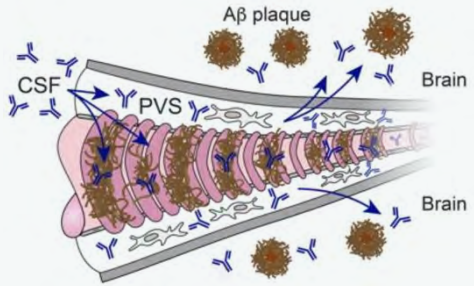
5xFAD; TfR$^{mu/hu}$ KI; QW IP



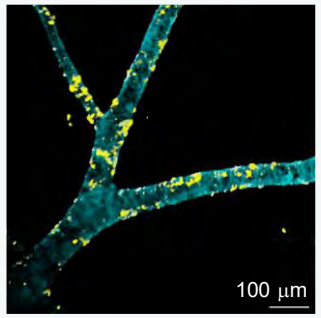
Biogen

Route of Entry into Brain

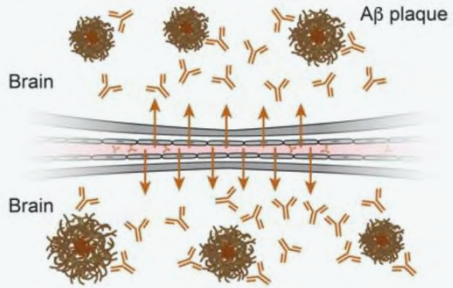
Conventional Anti-Abeta



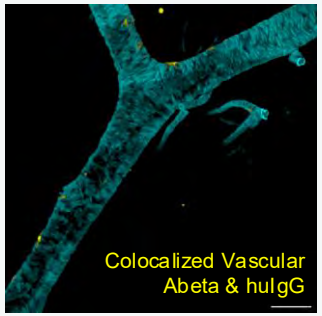
Artery / Arteriole Zone



ATV-Enabled Anti-Abeta



Microvessel (capillary) Zone



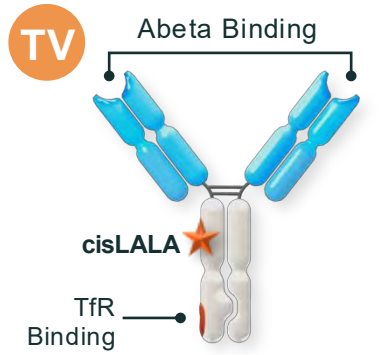
Bypassing arterial vascular plaque via TfR-mediated entry into the brain through capillaries and venules has potential to improve amyloid-related imaging abnormalities (ARIA)

DNL921 (ATV:Abeta) is an investigational compound and has not been approved by any regulatory authority.

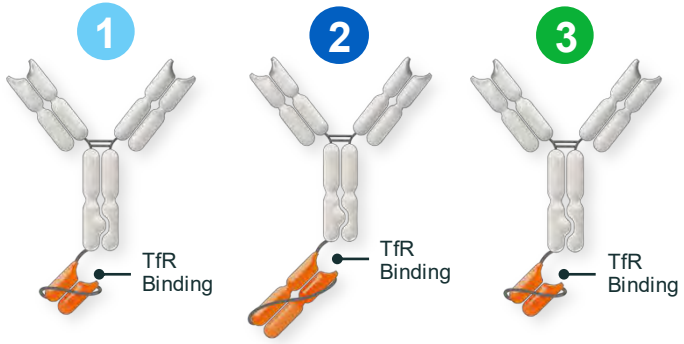
ARIA – Amyloid-related imaging abnormalities; **TfR –** Transferrin receptor; Source: Pizzo et al. *Science* 2025

DNL921 Optimized for Robust Brain Delivery, Safety & Stability

DNL921 (ATV:Abeta)

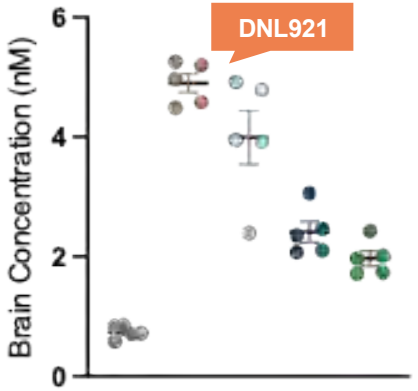


Fusion Molecules[1]

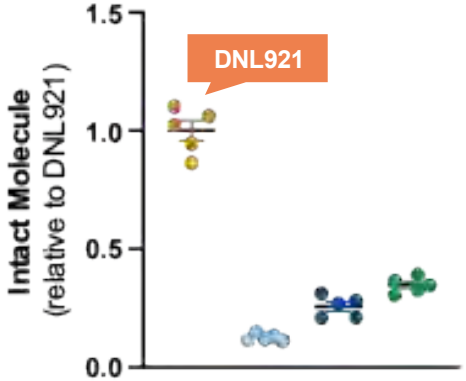


Molecule	Architecture	Epitope	Effector Function
Control	Control IgG	N/A	Full
DNL921	TV- TfR in Fc	Apical	Conditional
Molecule #1	C-term TfR	Protease	Full
Molecule #2	C-term TfR	Apical	Full
Molecule #3	C-term TfR	Apical	None

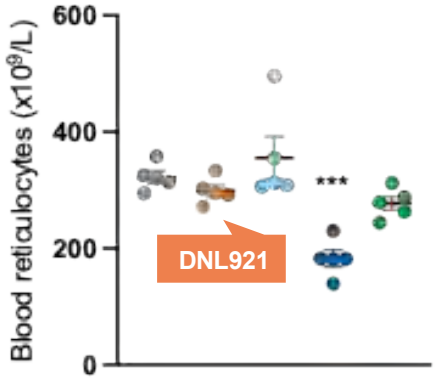
Brain Concentration[2]



Intact Molecule[2,3]



Immature Reticulocytes[2]

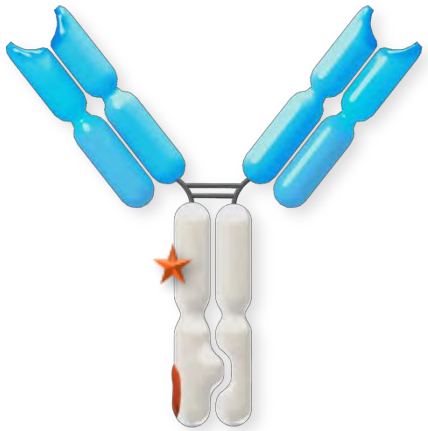


DNL921 (ATV:Abeta) is an investigational compound and has not been approved by any regulatory authority.

1. Fusion Molecules generated at Denali based on publicly available information on TfR-binding anti-Abeta antibodies currently under development; **2.** Single dose, IV 10 mg/kg (molar-matched), using a mouse model that expressed the full TfR extracellular domain; **3.** hIgG Capture vs. TfR Capture ELISA. Source: Denali Therapeutics data

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

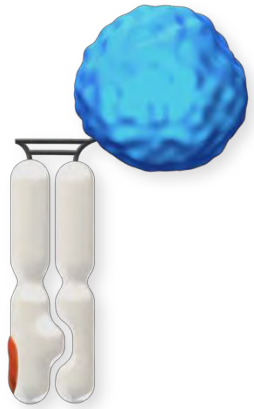
- **Duration:** 28 weeks
- **Study Type:** Randomized, placebo-controlled, double blind

CTA submitted 1H 2026 / Potential for safety and clinical proof of concept in 2027

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

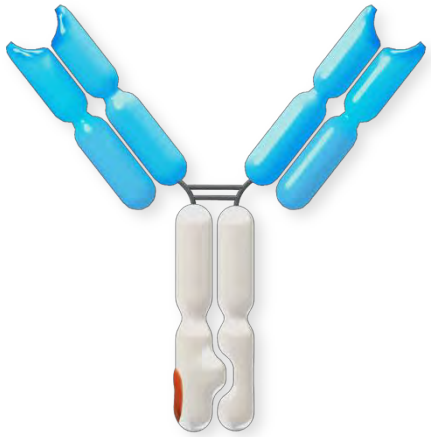
Delivering Multiple Modalities Across the BBB

Enzyme TV
(ETV)



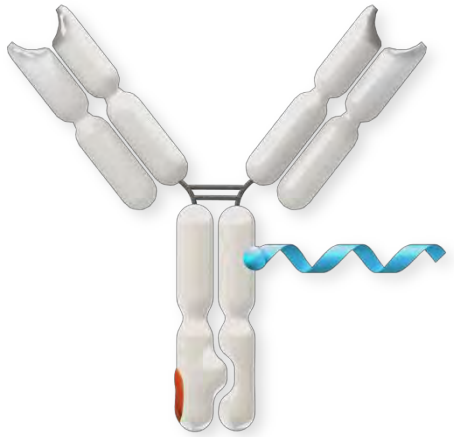
Enzyme replacement therapy for the body and brain

Antibody TV
(ATV)



Brain-penetrant immunotherapy for a wide range of diseases

Oligonucleotide TV
(OTV)



Genetic medicines for the brain, delivered systemically

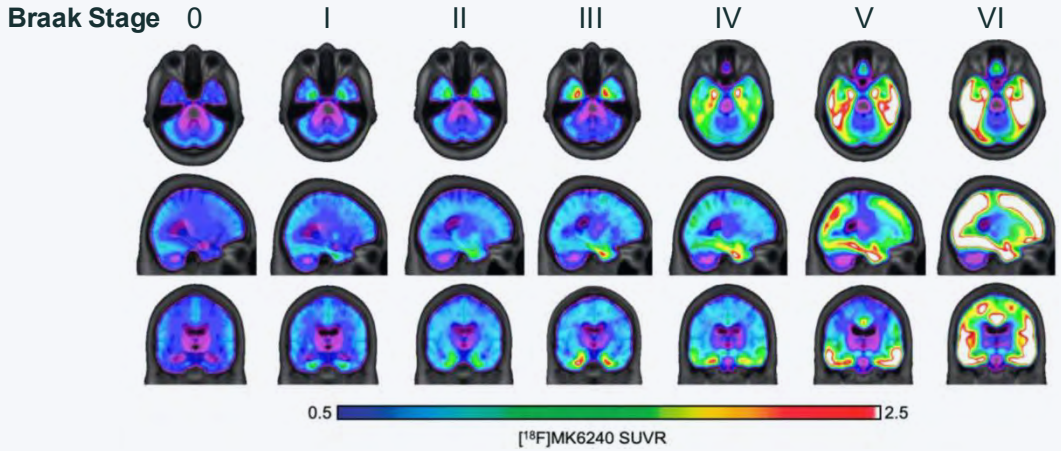
The TransportVehicle (TV) Platform enables TfR-mediated brain biodistribution and enhanced tissue delivery of diverse biotherapeutics modalities

TfR – Transferrin receptor

Tau is Becoming the Next Promising Target in AD

Biological Rationale

The Critical Role of Tau in AD Pathophysiology



- Tau PET has been demonstrated to be more closely correlated with disease progression than amyloid PET

Clinical Progress

Multiple Setbacks

Multiple clinical-stage mAbs targeting tau failed

Emerging Breakthroughs

MAPT knockdown via ASO has shown clinical promise

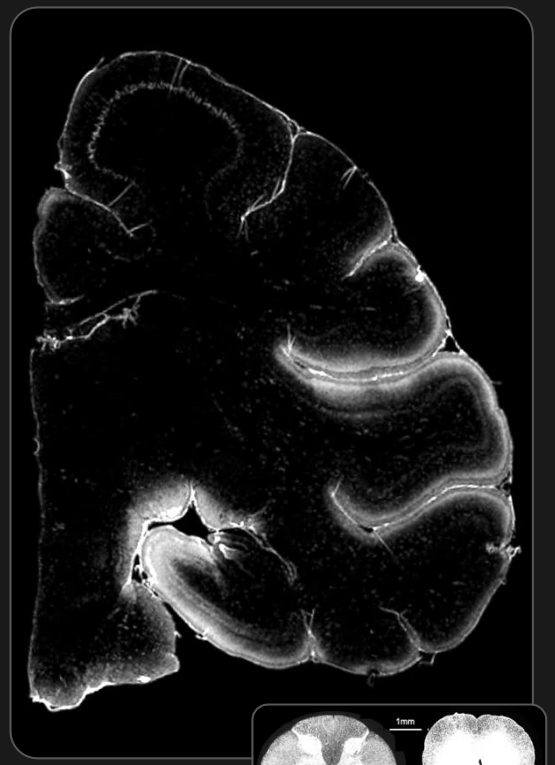
Improving Delivery

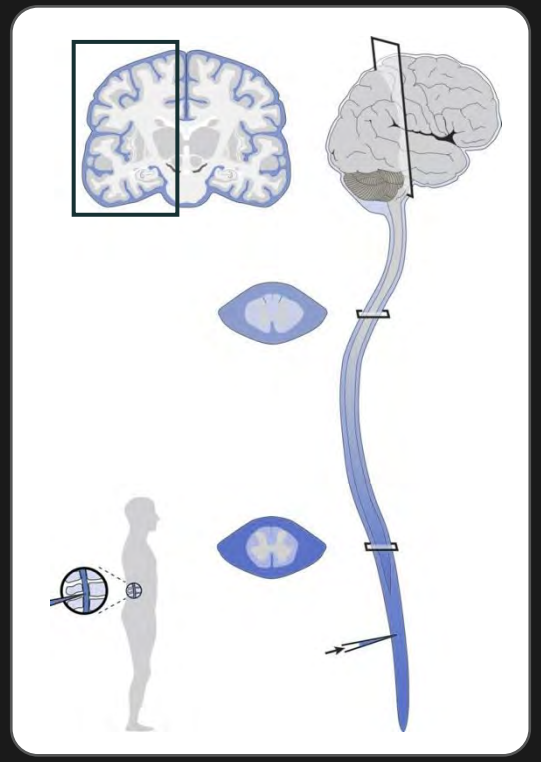
Brain transport-enabled tau therapies have entered the clinic

Left graph adapted from Therriault et al. *Nat Aging* 2022; Average [18F]MK6240 SUVRs across the whole brain for all participants grouped according to PET-based Braak stage
PET – Positron emission tomography; **mAb –** Monoclonal antibody; **ASO –** Antisense oligonucleotide

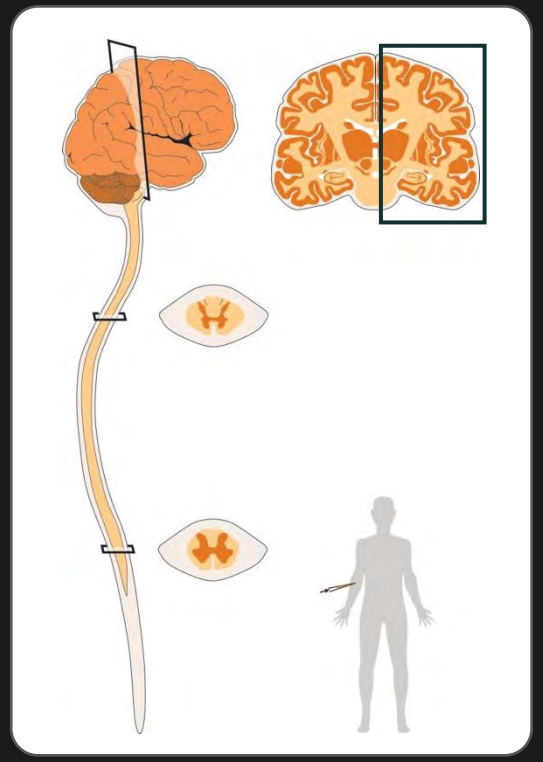
OTV Enhances Biodistribution of ASO Evenly Across Brain Regions

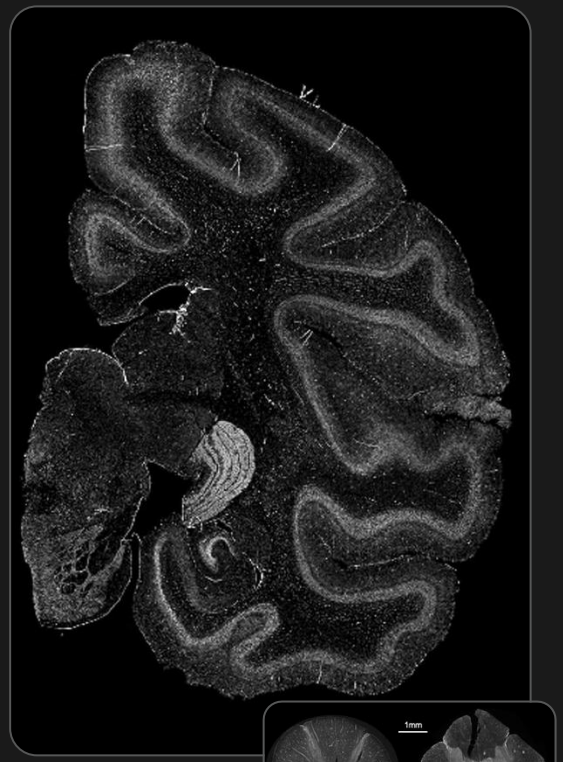
Limited biodistribution with intrathecal ASO





Widespread biodistribution with intravenous OTV:ASO



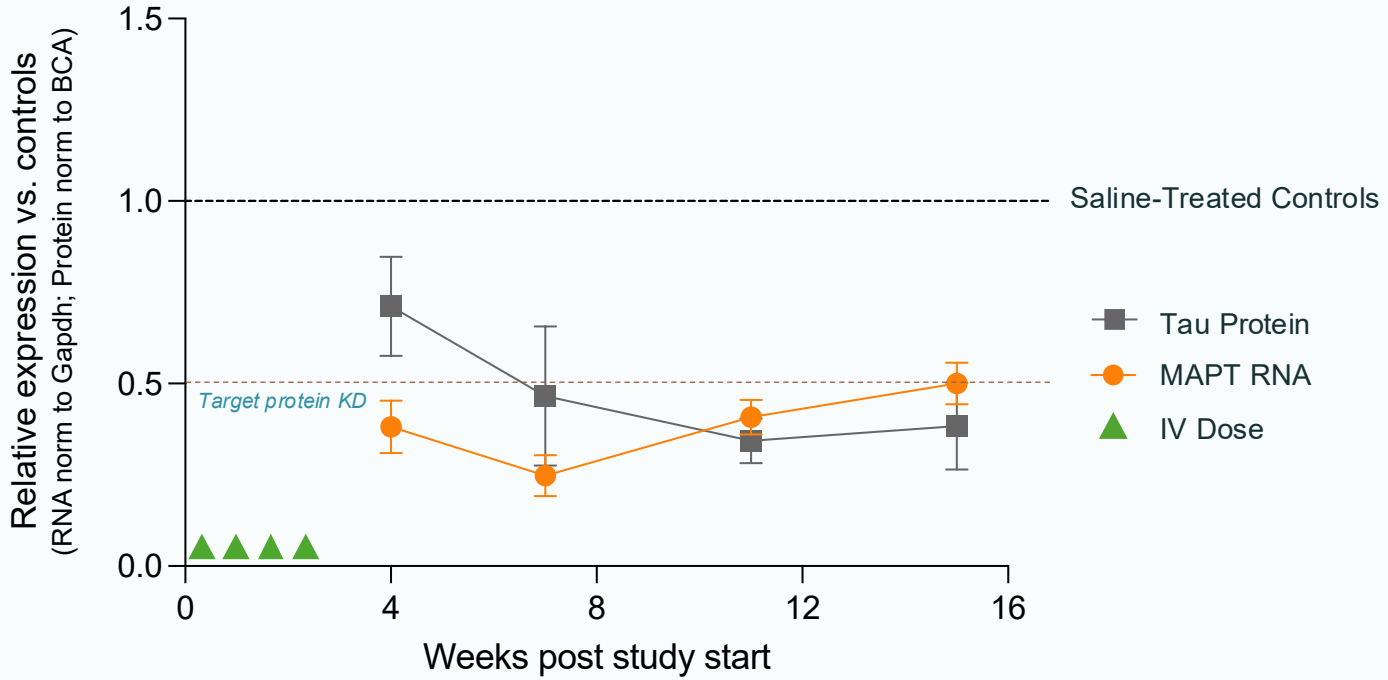


ASO Immunofluorescence hemibrain coronal section

Adapted from Barker et al. *Science Translational Medicine* 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

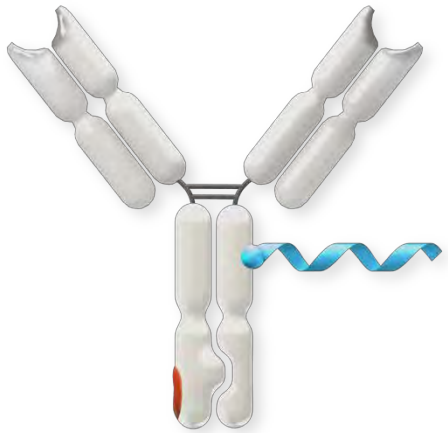


Robust and sustained reduction in tau protein with DNL628

DNL628 (OTV:MAPT) is an investigational compound and has not been approved by any regulatory authority.
Triangles indicate individual doses over two-week time period. Source: Denali Therapeutics data

DNL628 Phase 1b Clinical Study for Alzheimer's Disease

DNL628
(OTV:MAPT)



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

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 ongoing / Clinical biomarker data expected by 1H 2027

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

Now Is the Time to Accelerate Neurodegeneration Medicines

Biology

Validated therapeutic targets and better understanding of disease

Biomarkers

Tools that enable early diagnosis, patient selection, and treatment tracking

Blood-Brain Barrier

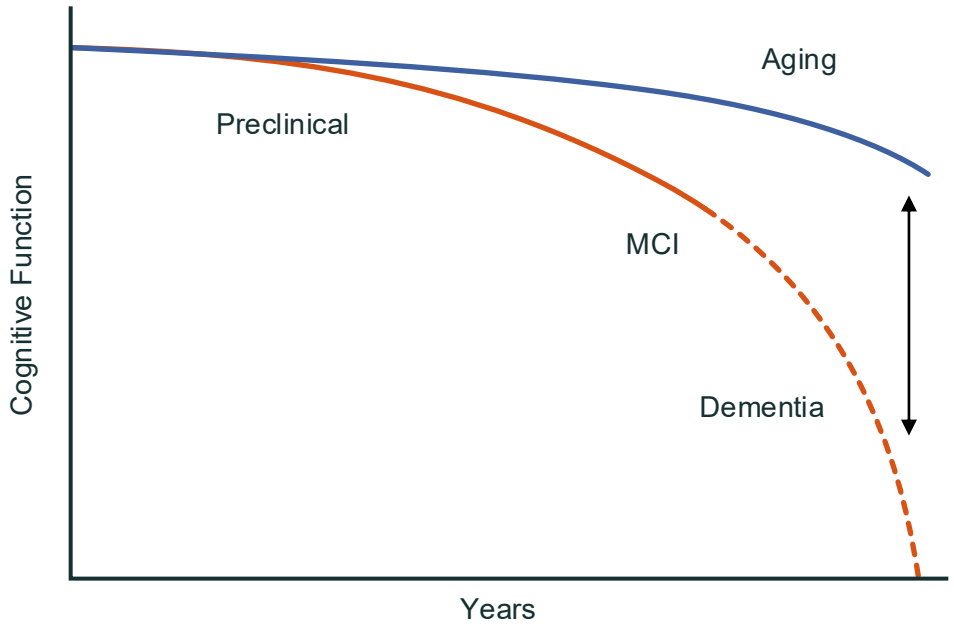
Validated delivery technologies that can get therapy to the brain

Recent developments have enabled major breakthroughs and set the stage for future development in the AD therapeutic space

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

Shifting the Paradigm

Reactive Care to Proactive Prevention



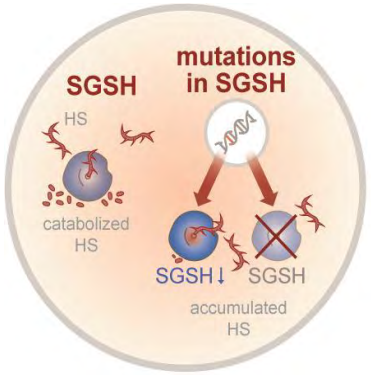
The Past		The Future
Limited awareness of genetic predisposition for AD		Proactive genetic screening identifies risk factors for AD (e.g., APOE)
AD diagnosis typically occurs following cognitive decline		Diagnosis is made during preclinical disease using blood-based biomarkers
Existing treatment may slow, but not stop progression, at the risk of ARIA		Safe, effective treatments are administered before symptoms arise
People with AD diagnoses experience inevitable cognitive decline		Cognitive decline is prevented

DNL126 (ETV:SGSH): Sanfilippo Syndrome Type A (MPS III A)

MPS IIIA Pathogenesis, Biomarkers, and Clinical Manifestations

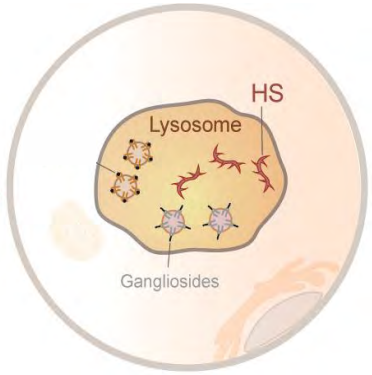
TARGET | **PATHWAY** | **CLINICAL**

Genetic Deficiency in SGSH Enzyme Activity



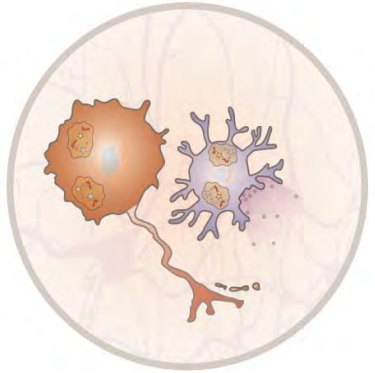
Accumulation of heparan sulfate

Lysosomal Dysfunction



Accumulation of lysosomal lipids (e.g., GM3)

Neurodegeneration



Elevated biomarkers of neurodegeneration and neuroinflammation (e.g., NfL)

Developmental delay and behavior problems, progressing to severe cognitive decline, and death in adolescence[1–4]

Impaired sleep[5]

Impaired hearing[5]

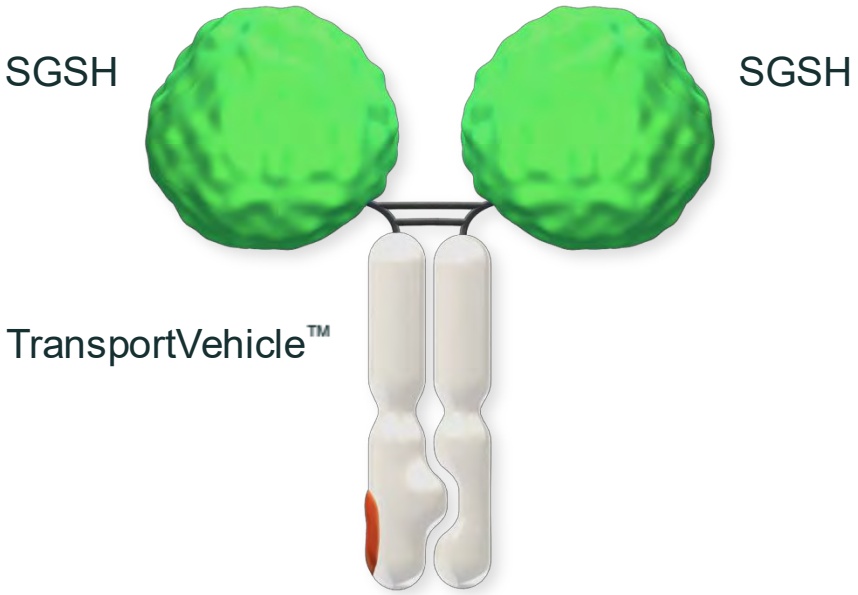
Somatic manifestations including diarrhea, hepatomegaly, and joint stiffness[3,6,7]

Currently, there are no approved therapies for MPS IIIA, representing a high unmet medical need

GM3 – ganglioside monosialic 3; **HS** – heparan sulfate; **MPS IIIA** – mucopolysaccharidosis type IIIA; **NfL** – neurofilament light chain; **SGSH** – sulfoglucosamine sulfohydrolase; 1. Lavery C et al. Orphanet *J Rare Dis* 2017;12:168; 2. Harmatz P et al. *Mol Genet Metab* 2022;136:249–59; 3. Shapiro EG et al. *Mol Genet Metab* 2017;122S:1–7; 4. Wijburg FA et al. *Acta Paediatr* 2013;102:462–70; 5. Buhrman D et al. *J Inherit Metab* Dis 2014;37:431–7; 6. Heon-Roberts R et al. *J Clin Med* 2020;9:344; 7. Muschol N et al. *Orphanet J Rare Dis* 2022;17:391.

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

ETV:SGSH



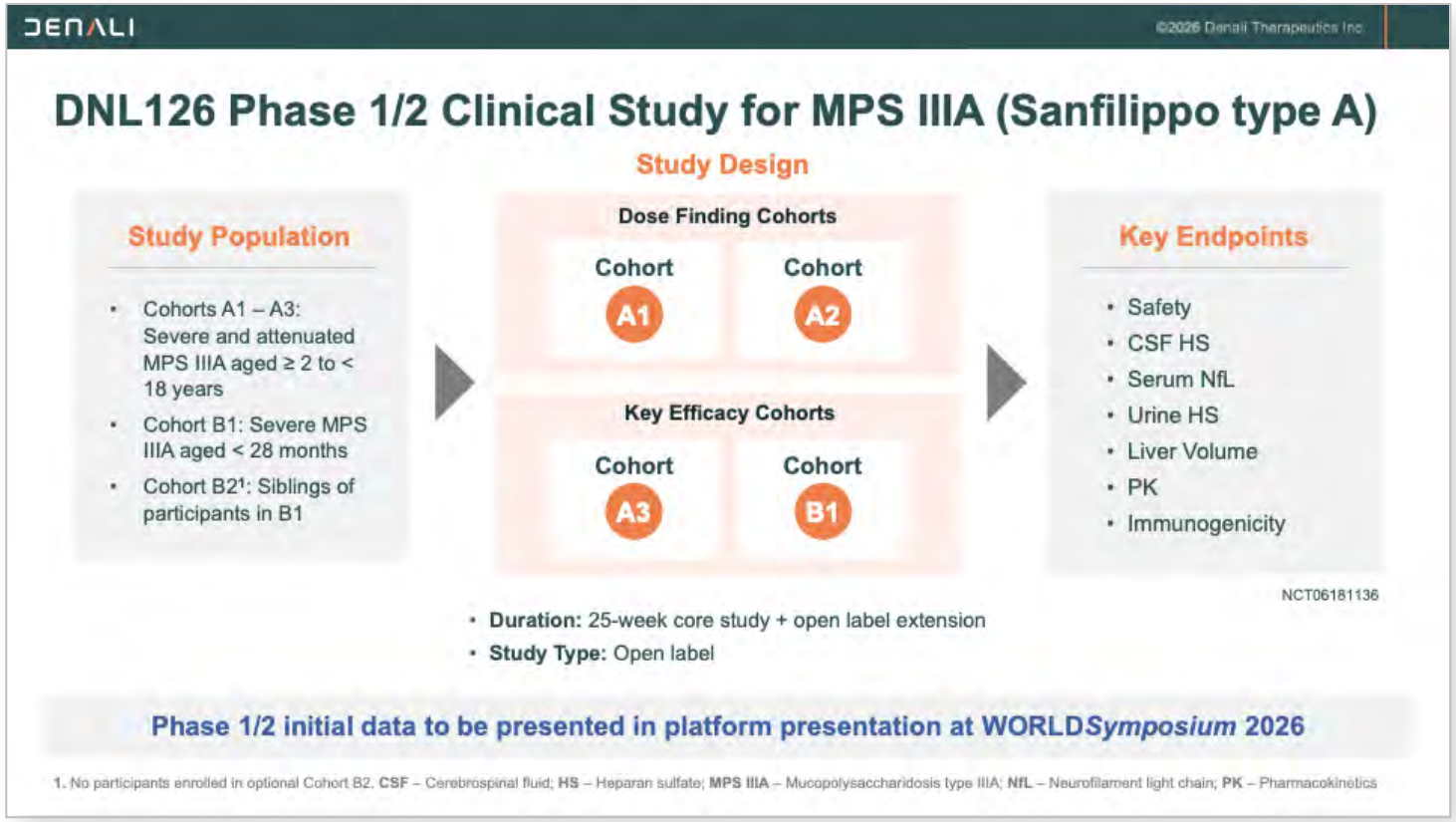
Program Status

- 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

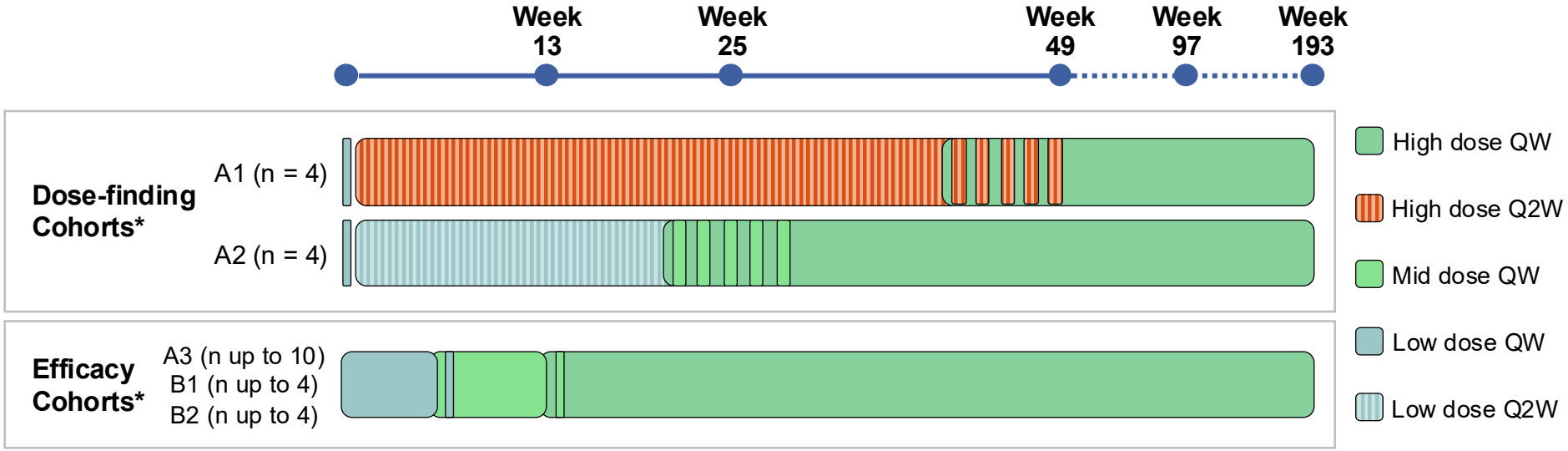
- At least 49 weeks of data for all participants (Cohorts A1-A3, B1; n=20)
- CSF HS reduction from baseline in key efficacy cohorts (n=12) – surrogate endpoint reasonably likely to predict clinical benefit
- Supportive data on central and peripheral biomarkers, clinical endpoints
- Long-term safety up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

Expected BLA submission and approval in 2027

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

DNL126 Phase 1/2 Study in Pediatric Participants with MPS IIIA

- Study DNLI-I-0001 is a multicenter, open-label, 25-week study followed by an open-label extension period through 193 weeks (NCT06181136) in up to 26 pediatric participants with MPS IIIA in up to 5 cohorts
- Preliminary data through cut-off date of June 4, 2025
  - **Safety Outcomes:** Dose-finding and efficacy cohorts (n = 14)
  - **Efficacy Outcomes:** Dose-finding cohorts only; at Week 49, dose finding cohorts were receiving the high dose either QW or Q2W (n = 8)



Cohort A1–A3: children with severe and attenuated phenotypes aged ≥ 2 to < 18 years
Cohort B1: children < 28 months of age with a predicted severe phenotype
Cohort B2: siblings of children in Cohort B1

Primary Endpoint

- Percent change from baseline in CSF HS at W49 *(efficacy cohorts only)*

Secondary Endpoints

- Percent change from baseline in urine HS at W49
- Change from baseline in liver volume at W49
- Percent change from baseline in serum NfL at W73
- Participants with CSF HS in normal range at W49 *(efficacy cohorts only)*

Study enrollment (n = 20) completed in September 2025

*Intraparticipant dose escalation occurred at varying times; **CSF** – cerebrospinal fluid; **QW** – once weekly; **Q2W** – once every 2 weeks; **W** – week. Source: Jalazo et al. WORLD*Symposium*™ 2026

All Cohorts: Participant Demographics and Characteristics

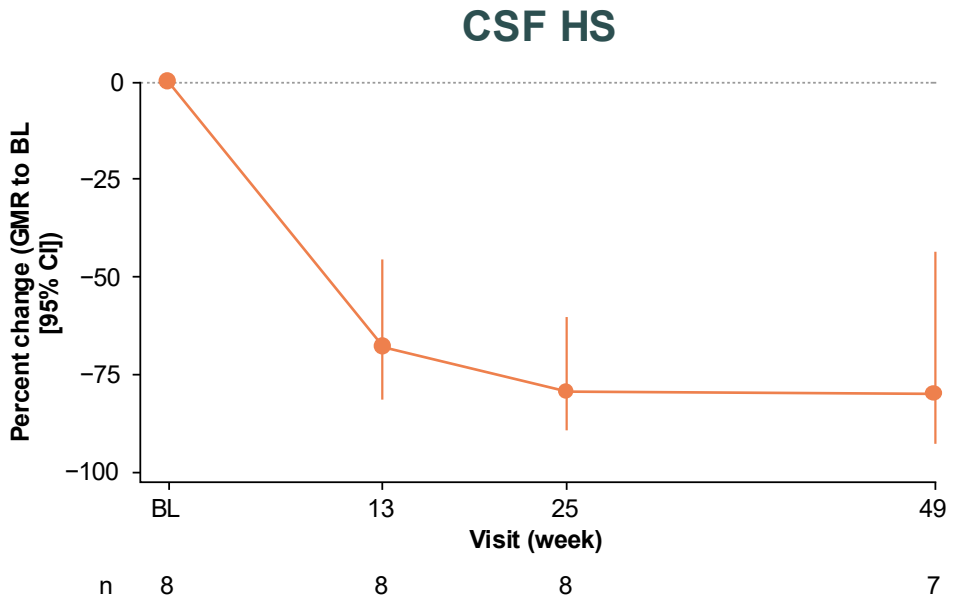
	Dose-finding Cohorts		Efficacy Cohorts*		
	Cohort A1 (n = 4)	Cohort A2 (n = 4)	Cohort A3 (n = 4)	Cohort B1 (n = 2)	All Cohorts (n = 14)
DNL126 Treatment Duration					
Completed up to Week 25	4 (100.0%)	4 (100.0%)	4 (100.0%)	1 (50.0%)	13 (92.9%)
Completed up to Week 49	4 (100.0%)	4 (100.0%)	0 (0.0%)	0 (0.0%)	8 (57.1%)
Age at Screening (months)					
Median	47.0	57.5	51.5	27.0	49.0
Min – Max	36.0 – 55.0	51.0 – 78.0	33.0 – 87.0	27.0 – 27.0	27.0 – 87.0
Sex					
Female	2 (50%)	4 (100%)	3 (75%)	0	9 (64.3%)
Male	2 (50%)	0	1 (25%)	2 (100%)	5 (35.7%)
Race					
White	4 (100%)	4 (100%)	4 (100%)	2 (100%)	14 (100%)
Ethnicity					
Hispanic or Latino	0	1 (25%)	0	0	1 (7.1%)
p.S298P heterozygous	1 (25%)	1 (25%)	1 (25%)	0	3 (21.4%)

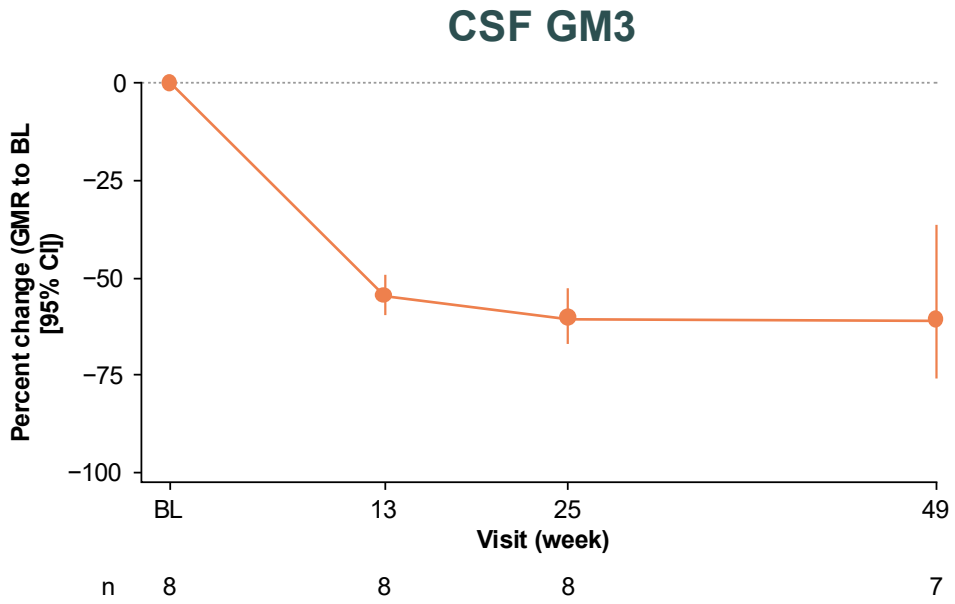
Study population includes a broad spectrum of pediatric ages and genotypes

*No participants were enrolled in Cohort B2. Source: Jalazo et al. WORLD*Symposium*™ 2026

Preliminary Data Phase 1 Dose-finding Cohorts (A1 and A2)

CNS Biomarkers: CSF Heparan Sulfate and GM3





Cohorts A1 and A2 at Week 49

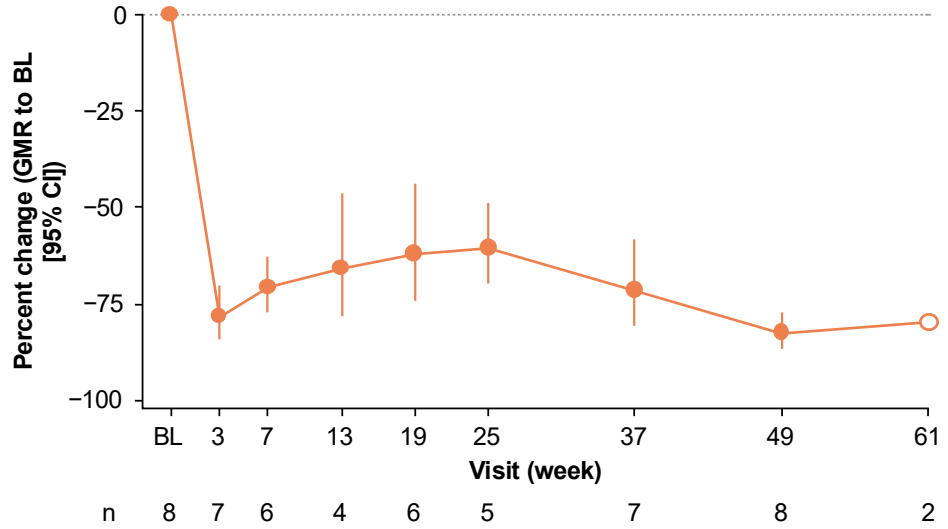
- Mean reduction of 80% in CSF HS with 3 of 7* participants within normal range**
- Mean reduction of 61% in GM3 with 6 of 7* participants within normal range***

*n = 7 at Week 49 as one participant had lumbar puncture performed early at Week 37. **Age-based biomarker reference ranges were established based on CSF samples from 67 individuals without MPS IIIA (median [min, max] age: 8.88 [0.06, 25.3] years). ***Age-based biomarker reference ranges were established based on GM3 samples from 70 individuals without MPS IIIA (median [min, max] age: 8.77 [0.06, 25.3] years); **BL** – baseline; **CI** – confidence interval; **CNS** – central nervous system; **GMR** – geometric mean ratio. Source: Jalazo et al. WORLD*Symposium*™ 2026

Preliminary Data Phase 1 Dose-finding Cohorts (A1 and A2)

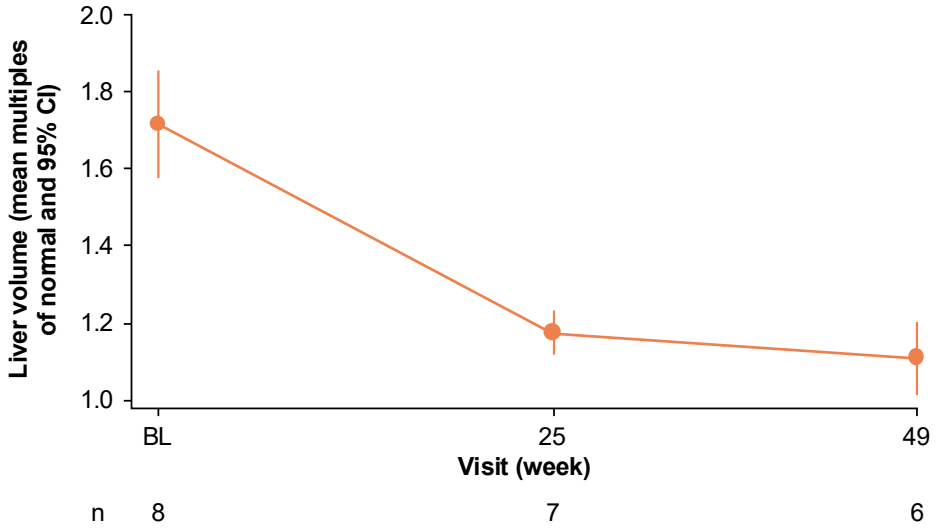
Peripheral Measures: Urine HS and Liver Volume

Urine HS



- Substantial reduction observed by Week 3
  - Variability in response beyond Week 3 due to intra participant differences in dose frequency and dose escalation

Liver Volume



- Mean liver volumes 1.72 times normal at baseline
- At Week 49, mean reduction of 0.6 (SD: 0.14) in liver volume multiples of normal

Cohorts A1 and A2 at Week 49

- Mean reduction of 83% in urine HS, 0 of 8 participants within normal range*
- Mild hepatomegaly improved by Week 25; 6 of 6 participants within normal range**

Open circles represent timepoints with less than three samples; **MRI** – magnetic resonance imaging; **SD** – standard deviation; * ULN ranges were determined as the 97.5th percentile using urine samples from 149 pediatric individuals without MPS IIIA (median [min, max] age: 4.93 [0.05, 17.2] years). **One participant had MRI performed outside of Week 49 analysis window, and one did not have data available at time of data cut. Values less than the upper bound of the 95% prediction interval for liver volume based on weight and height are defined as normal (Herden U et al. *Transpl Int* 2013;26:1217–24).
Source: Jalazo et al. WORLD*Symposium*™ 2026

All Cohorts: Safety Overview

- All participants (n = 14) experienced a TEAE assessed by the investigator as related to the study intervention
- The majority of participants experienced TEAEs with a maximum severity of Grade 1 or Grade 2
  - There were no Grade 4 or Grade 5 TEAEs
- Serious TEAEs were reported in 4 (28.6%) participants; none were considered treatment-related
- IRRs were common and reported in all participants
- There were no deaths or TEAEs that led to early discontinuation from the study intervention or the study

TEAEs Reported in >30% of Participants

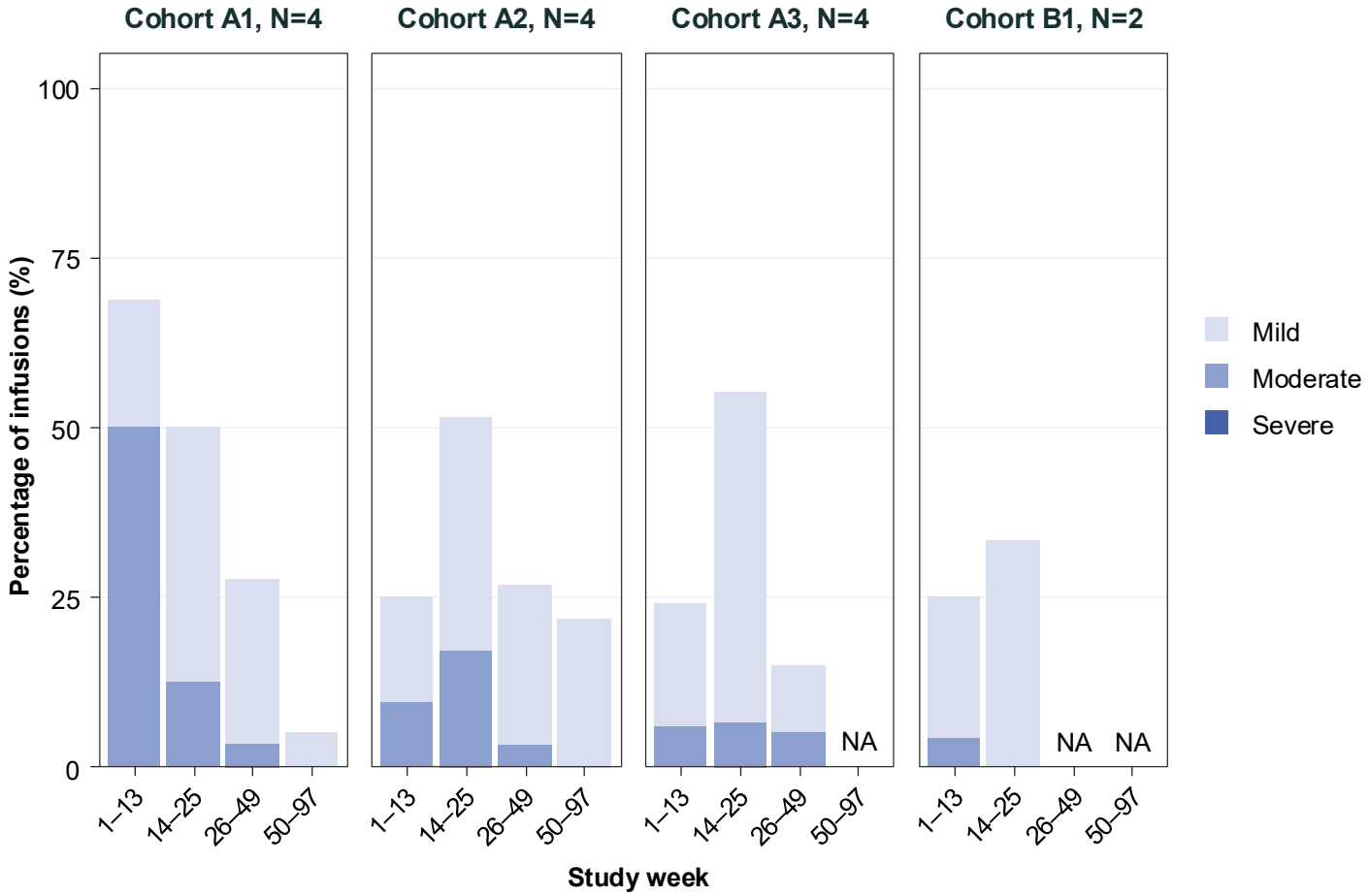
Preferred Term	All Cohorts (n = 14) [n (%)]
Infusion-Related Reaction	14 (100)
Upper Respiratory Infection	9 (64.3)
Vomiting	9 (64.3)
Nasal Congestion	7 (50.0)
Cough	6 (42.9)
Diarrhea	5 (35.7)
Ear Infection	5 (35.7)
Fall	5 (35.7)
Gastroenteritis	5 (35.7)
Irritability	5 (35.7)

Preliminary data demonstrate that the safety profile of DNL126 in children with MPS IIIA was generally consistent with estaåblished enzyme replacement therapies

AESI – adverse event of special interest; **IRR** – infusion-related reaction; **TEAE** – treatment-emergent adverse event. Source: Jalazo et al. WORLD*Symposium*™ 2026

All Cohorts: Infusion-related Reactions

Infusion-related Reactions by Cohort and Study Week



- IRR frequency and/or severity decreased after Week 25 in all cohorts (limited data available for Cohorts A3 and B1)
- Reduced IRR severity and/or frequency through Week 25 were observed in cohorts utilizing gradual dose escalation (Cohorts A2, A3 and B1)
- IRRs were manageable with premedications, infusion-rate adjustments, and/or infusion interruptions
  - Slow graduated rates adapted from Castells (2008) were utilized to prevent further IRRs in one participant

Source: Jalazo et al. WORLD*Symposium*™ 2026

Conclusions

Preliminary Results from Dose-finding Cohorts Demonstrate that 49 Weeks of DNL126 Treatment Resulted in Substantial Reductions in CSF and Peripheral Biomarkers, with Some Participants Achieving Normalization

- CSF HS: 80% mean reduction at Week 49, with normalization in 3 of 7 participants
- CSF GM3: 61% mean reduction at Week 49, with normalization in 6 of 7 participants
- Urine HS: 83% mean reduction at Week 49, no participants within normal range
- Improvement in mild hepatomegaly observed as early as Week 25, with normalization in 6 of 6 participants at Week 49

Preliminary Safety Data in Pediatric Participants with MPS IIIA Treated with DNL126 were Generally Consistent with Established ERTs

- All participants experienced TEAEs; the majority of TEAEs were mild or moderate in severity
- No treatment-related serious TEAEs, treatment discontinuations or study discontinuations were reported
- Frequently reported TEAEs included IRRs, upper respiratory infection, vomiting, nasal congestion, and cough
- IRRs were manageable and decreased in frequency and severity over time
  - Reduced IRR severity and/or frequency was observed in cohorts utilizing gradual dose escalation

On track for BLA filing for accelerated approval in 2027

Source: Jalazo et al. WORLD*Symposium*™ 2026

DNL593 (PTV:PGRN): Frontotemporal Dementia-Granulin (FTD-*GRN*)

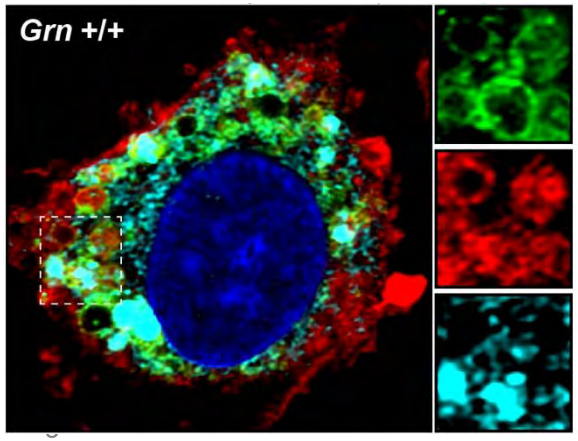
DNL593 (PTV:PGRN): PGRN Brain Delivery for FTD-*GRN*

DNL593 delivers PGRN to key cell types in brain

Rescue of a lysosomal storage disorder caused by *Grn* 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. Cherf,[1,7] Ankita Srivastava,[1,7,8] Sonnet S. Davis,[1] Ray Lieh Yoon Low,[1] Chi-Lu Chiu,[1] Meng Fang,[1] Fen Huang,[1] Akhil Bhalla,[1] Ceyda Llapashtica,[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. Lexa,[1] Devendra B. Srivastava,[1] Bettina van Lengerich,[1] Junhua Wang,[1] Yaneth Robles-Colmenares,[1] Do Jin Kim,[1] Joseph Duque,[1] Melina Lenser,[1] Timothy K. Earr,[1] Hoang Nguyen,[1] Roni Chau,[1] Buyankhishig Tsogtbaatar,[1] Ritesh Ravi,[1] Lukas L. Skuja,[1] Hilda Solanoy,[1] Howard J. Rosen,[2,3] Bradley F. Boeve,[3,4] Adam L. Boxer,[2,3] Hilary W. Heuer,[2,3] Mark S. Dennis,[1] Mihalis S. Kariolis,[1] Kathryn M. Monroe,[1] Laralynne Przybyla,[1,9] Pascal E. Sanchez,[1] Rene Meisner,[1] Dolores Diaz,[1] Kirk R. Henne,[1] Ryan J. Watts,[1] Anastasia G. Henry,[1] Kannan Gunasekaran,[1] Giuseppe Astarita,[1,5] Jung H. Suh,[1] Joseph W. Lewcock,[1] Sarah L. DeVos,[1,*] and Gilbert Di Paolo[1,10,*]



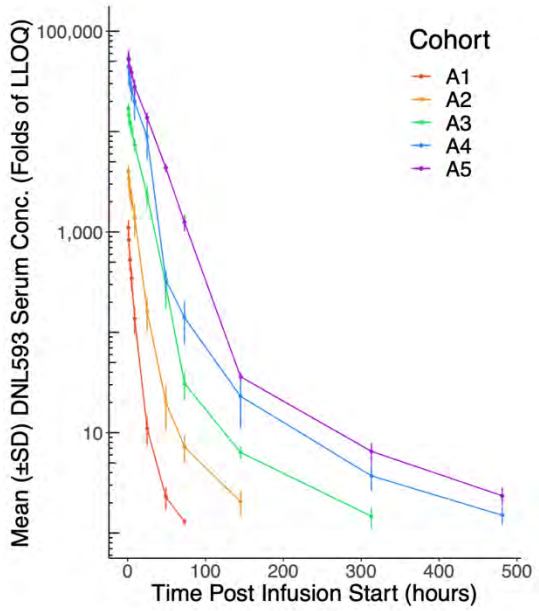
LAMP2
Lysosome Marker

BMP
Lipid critical for lysosome activity

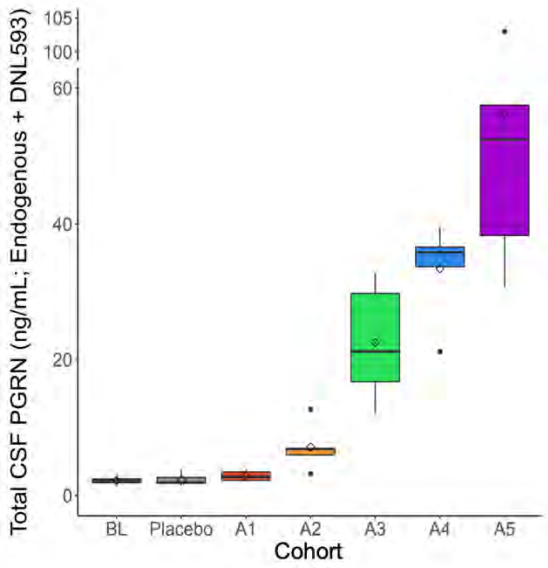
PGRN
Localized to lysosome

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

HV SAD Serum PK



HV SAD CSF PGRN (24 hr)

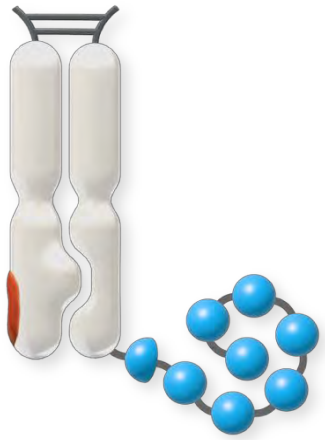


Ongoing Ph 1/2 study fully enrolled in patients with FTD resulting from a *GRN* mutation

PTV:PGRN – Protein Transport Vehicle:Progranulin; **FTD-*GRN*** – frontotemporal dementia granulin; **HVs** – healthy volunteers; **SAD** – single ascending dose; **CSF** – cerebrospinal fluid

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

DNL593
(PTV:PGRN)



Program status:
Regained full rights from Takeda

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

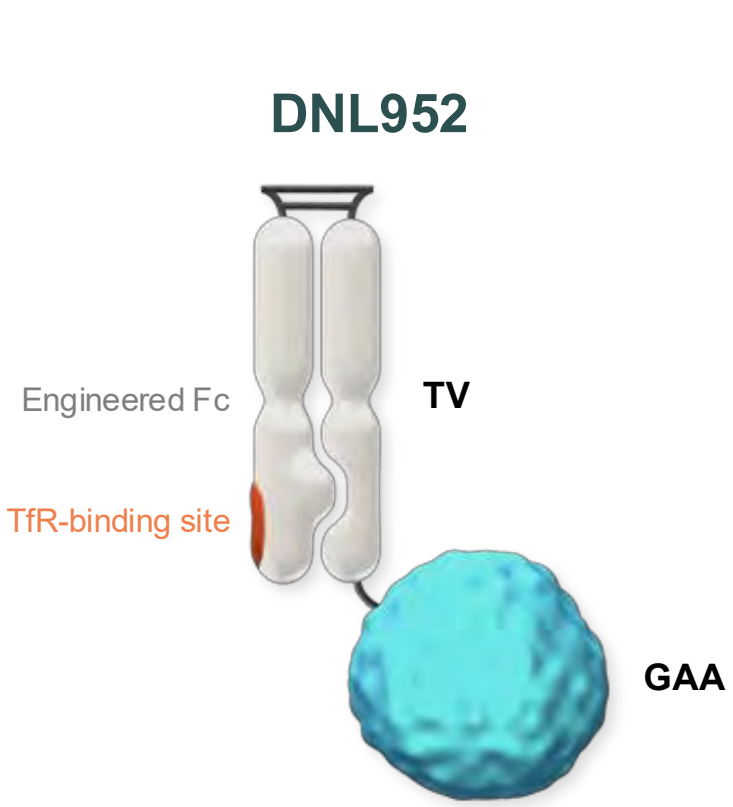
- **Duration:** 25-week core study + open label extension
- **Study Type:** Randomized, placebo-controlled, double blind

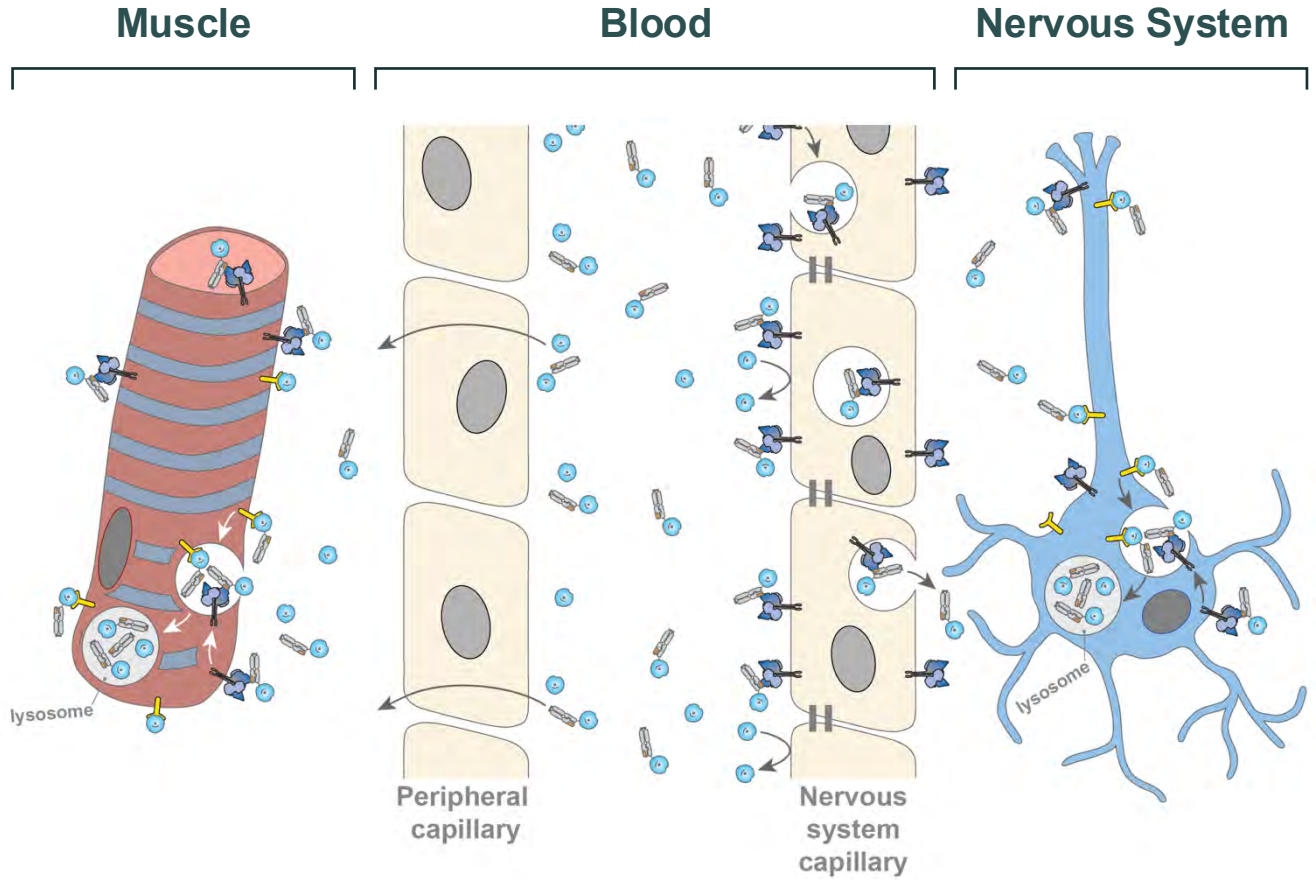
Phase 2 Part B interim data in patients with FTD-*GRN* expected to read out in 2026

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

DNL952 (ETV:GAA): Pompe Disease

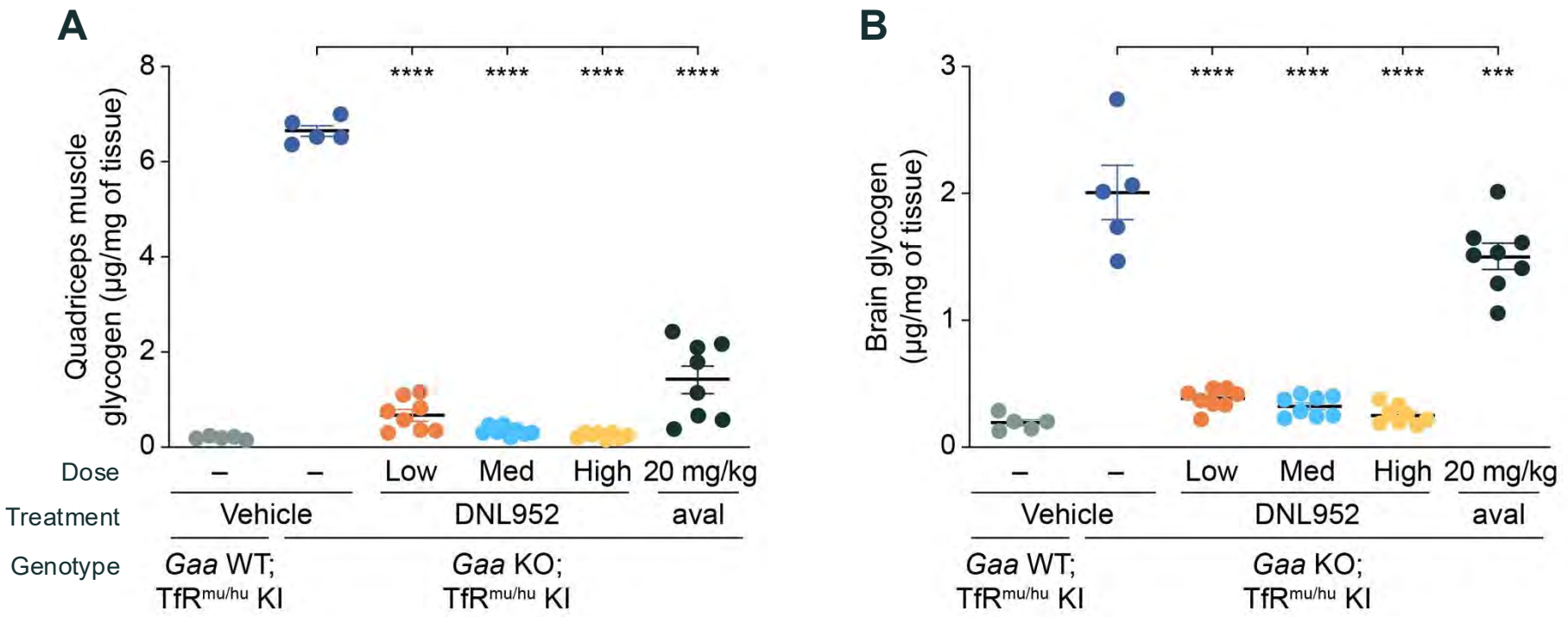
DNL952 is a Novel, Investigational ERT for Pompe Disease Designed to Improve GAA Delivery to Muscle and the Nervous System





Denali's TransportVehicle™ (TV) platform harnesses the transferrin receptor (TfR) to enhance distribution via receptor-mediated cellular uptake and transcytosis

PD Response of DNL952 After Multiple Doses Administered EOW Shows Near Normalization of Glycogen Levels in Muscle and Brain

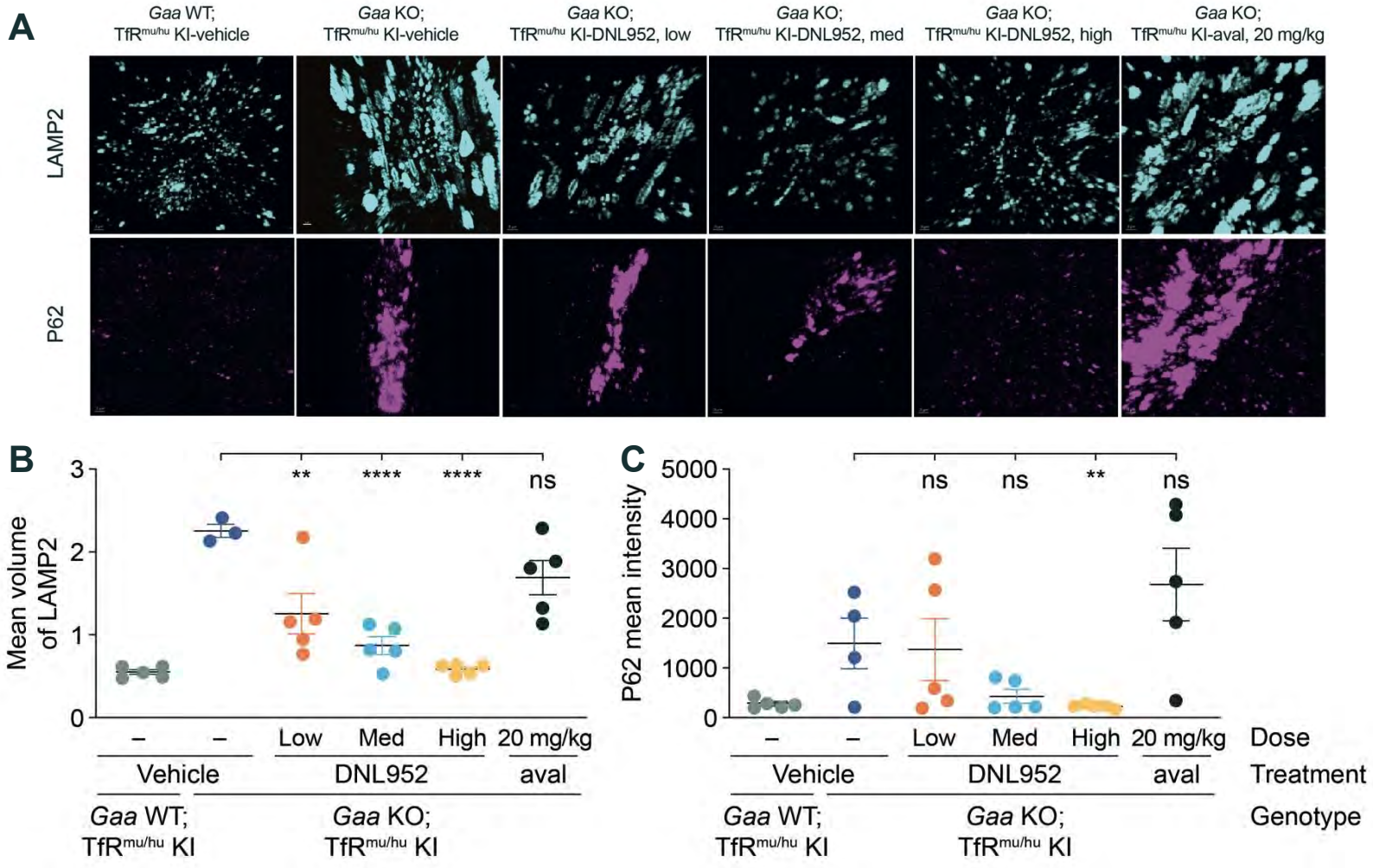


- Glycogen levels in (**A**) quadriceps muscle and (**B**) brain tissue measured at 14 days after the fifth dose

Repeated dosing with DNL952 achieved near-complete glycogen normalization in muscle and brain and demonstrated greater improvement than with avalglucosidase alfa

Gaa KO;TfR$^{mu/hu}$ KI animals (n = 8 per group) received five IV dosings of DNL952 (low, med, or high dose) or aval (20 mg/kg) administered EOW. Vehicle-treated *Gaa* WT;TfR$^{mu/hu}$ KI (n = 5) and *Gaa* KO; TfR$^{mu/hu}$ KI (n = 5) mice served as the nondisease and disease comparator groups, respectively. Levels were assessed using an LC-MS/MS–based method. Data are presented as mean ± SEM.
***P < 0.001; ****P < 0.0001

Multiple Doses of DNL952 Reduces Markers of Lysosomal and Autophagic Dysfunction



- Immunofluorescence staining with LAMP2 and P62 in quadriceps muscle after multiple doses

A Next-Generation ERT for Pompe Disease

Differentiated mechanism of action: Engaging the TfR + M6PR to improve cellular uptake & lysosomal delivery

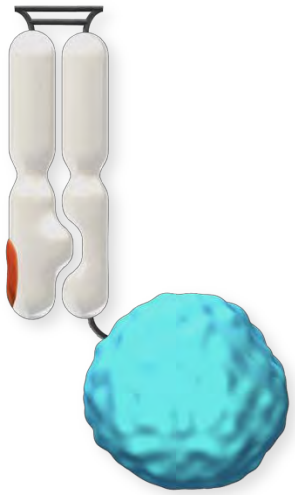
Improved pharmacodynamic response: Enhanced correction of glycogen & downstream pathology, including autophagy

Potential to address nervous system involvement that contributes to deficits in IOPD & possibly weakness in LOPD

(**A**) Representative images of immunofluorescence of LAMP2 (cyan) and P62 (magenta) of *Gaa* WT;TfR$^{mu/hu}$ KI (n = 5) and *Gaa* KO;TfR$^{mu/hu}$ KI mice treated with vehicle, DNL952 (low, med, or high dose), or aval (20 mg/kg) at 14 days after the final dose are shown; n = 3–5 per group. Scale bar = 2 mm. (**B**,**C**) Data are mean ± SEM of quantified (**B**) LAMP2 and (**C**) P62 signal.
$^{**}P < 0.01$; $^{****}P < 0.0001$.

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

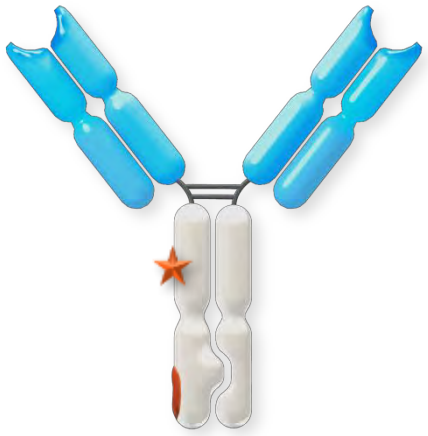
- **Duration:** 24-week core study + 24-week safety extension
- **Study Type:** Open label

Phase 1 biomarker data expected in 2027

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

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

DNL151 (LRRK2 Inhibitor): Parkinson’s Disease

DNL151 (LRRK2 Inhibitor) Clinical Studies in Healthy and PD Participants

	Phase 1/1b Healthy & PD Participant Study	Phase 2b LUMA Study in PD Participants	Phase 2a BEACON Study in LRRK2-PD Participants
Participants	• 186 healthy and 36 PD participants	Luma 201 STUDY • 650 participants with early-stage PD	• ~50 participants with PD associated with a pathogenic LRRK2 mutation
Treatment	• Single and multiple oral daily dosing over 28-day treatment period	• Oral daily dosing over a 48-week treatment period	• Oral daily dosing over a 12-week treatment period
Endpoints	• Safety • BIIB122 levels (pharmacokinetics) • Biomarkers of lysosomal pathway engagement	• Primary endpoint assessed using MDS-UPDRS	• Safety • BIIB122 levels (pharmacokinetics) • Biomarkers of lysosomal pathway engagement
Status	• Completed	• Did not meet primary or secondary endpoints (announced May 21, 2026) • Study operationalized by Biogen	• Recruiting; Data readout in 1H 2027 • Study operationalized by DENALI

Evolving Our Business

Entering a New Phase on the Path to the Summit

3-Year Goals (D3X3)

2 Growing Brands

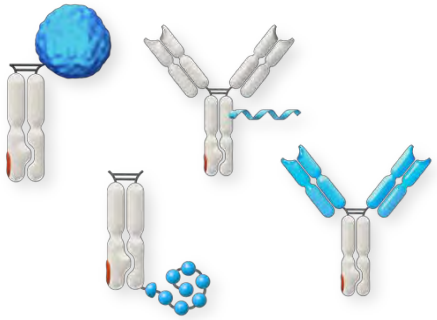
5 Clinical Proof of Concepts

4-6 New Clinical Programs

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

We Have Reached Our First Summit with AVLAYAH™

AVLAYAH™
(tividenofusp alfa-eknm)



Proof

1st FDA-approved biologic designed to cross the blood-brain barrier

Platform

TransportVehicle™ validated in humans, enabling a new class of biologic medicines

Pipeline

ETV franchise foundation fuels expansion into neurodegenerative and other serious diseases

Patients

From rare to common diseases, aiming to transform life for millions worldwide

We remain steadfast in our purpose of transforming life for patients

FDA – U.S. Food and Drug Administration; **ETV** – Enzyme TransportVehicle™

DENALI

Thank You