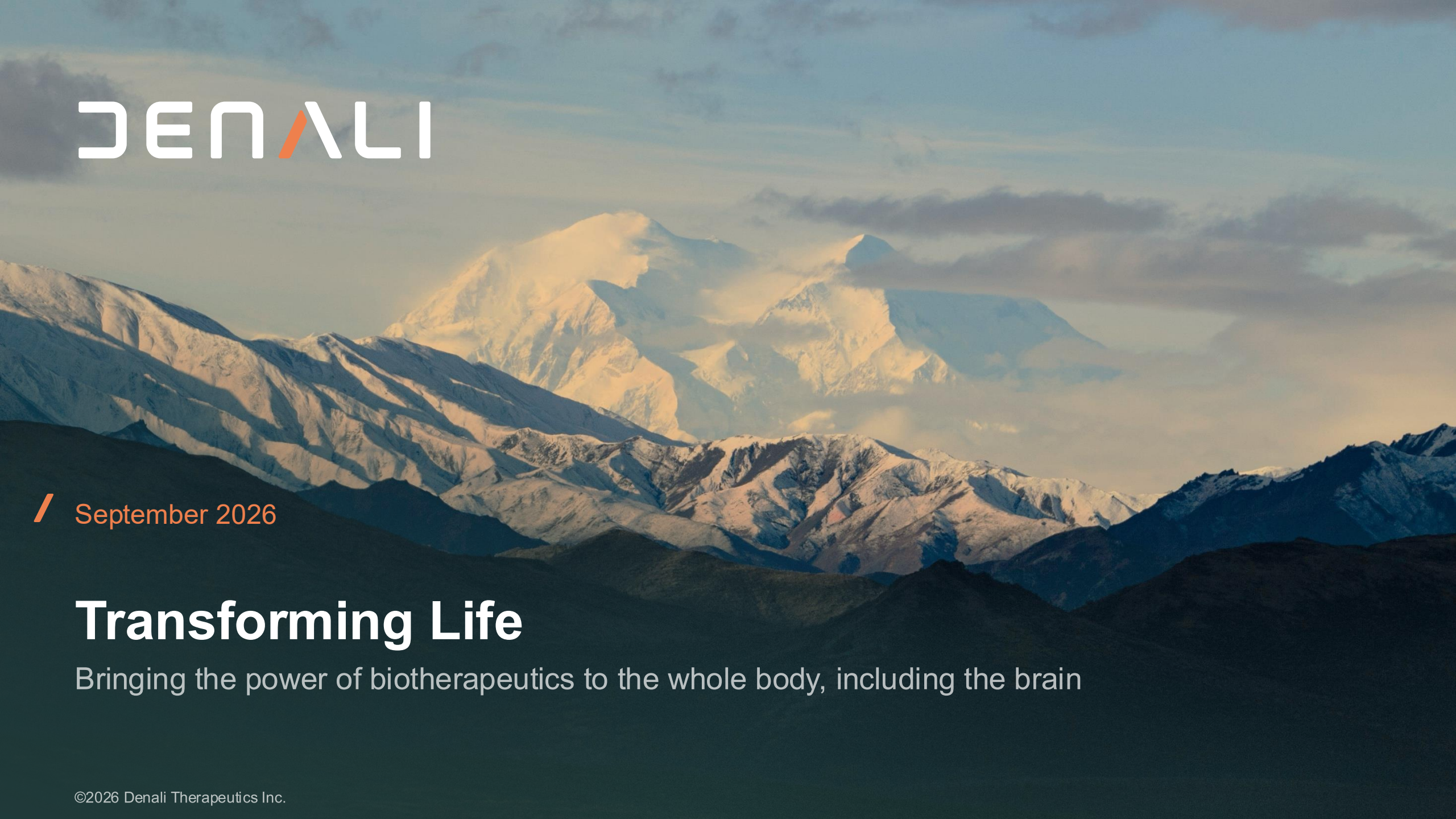


DENALI

September 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 "Company"); Denali’s business strategy and business plans, forecasts for revenue and operating expenses, expected progress and expansion, and expected key milestones for Denali's therapeutic portfolio in 2026, 2027, and beyond; plans, timelines, and 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 and first-in-class; plans, timelines, and expectations related to the ETV franchise and ETV-enabled programs, including ETV:SGSH, PTV:PGRN, ETV:GAA, ETV:GCase, and ETV:IDUA, their therapeutic and commercial potential, and the number of patients worldwide for each program; plans, timelines, and expectations relating to AVLAYAH™, including planned launch dynamics, estimated patient and revenue growth, and the likelihood of becoming standard of care for Hunter syndrome; expectations relating to DNL310 and the ongoing Phase 2/3 COMPASS study, including the timing, likelihood, and scope of regulatory approvals and the potential to support a broader indication for AVLAYAH™; plans, timelines, and expectations related to DNL126 (ETV:SGSH), including the timing and likelihood of regulatory approval; plans, timelines, and expectations related to AD treatments and their therapeutic and commercial potential; plans, timelines, and expectations relating to DNL921 (ATV:Abeta), including its best-in-class potential, the Phase 1/1b clinical study, and the timing and availability of data; plans and expectations relating to DNL628 (OTV:MAPT), including its first-in-class potential and the timing and availability of data from the ongoing Phase 1b study; plans and expectations regarding DNL593 (PTV:PGRN), the ongoing Phase 1/2 study, the timing and availability of data, and the potential for accelerated approval; 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; 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.

Except for AVLAYAH™, the product candidates being developed by Denali are investigational and their safety and efficacy profiles remain unestablished. Except for AVLAYAH™, 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: Transforming Life for People with Serious Diseases

We bring the power of biotherapeutics to the whole body, including the brain.

Rare Genetic Diseases

Hunter (MPS II) / Sanfilippo (MPS IIIA) / FTD-*GRN* / Pompe / Gaucher / Hurler (MPS I)

>30,000

Patients Worldwide[1]

Common Neurodegenerative Diseases

Alzheimer's disease / Parkinson's disease

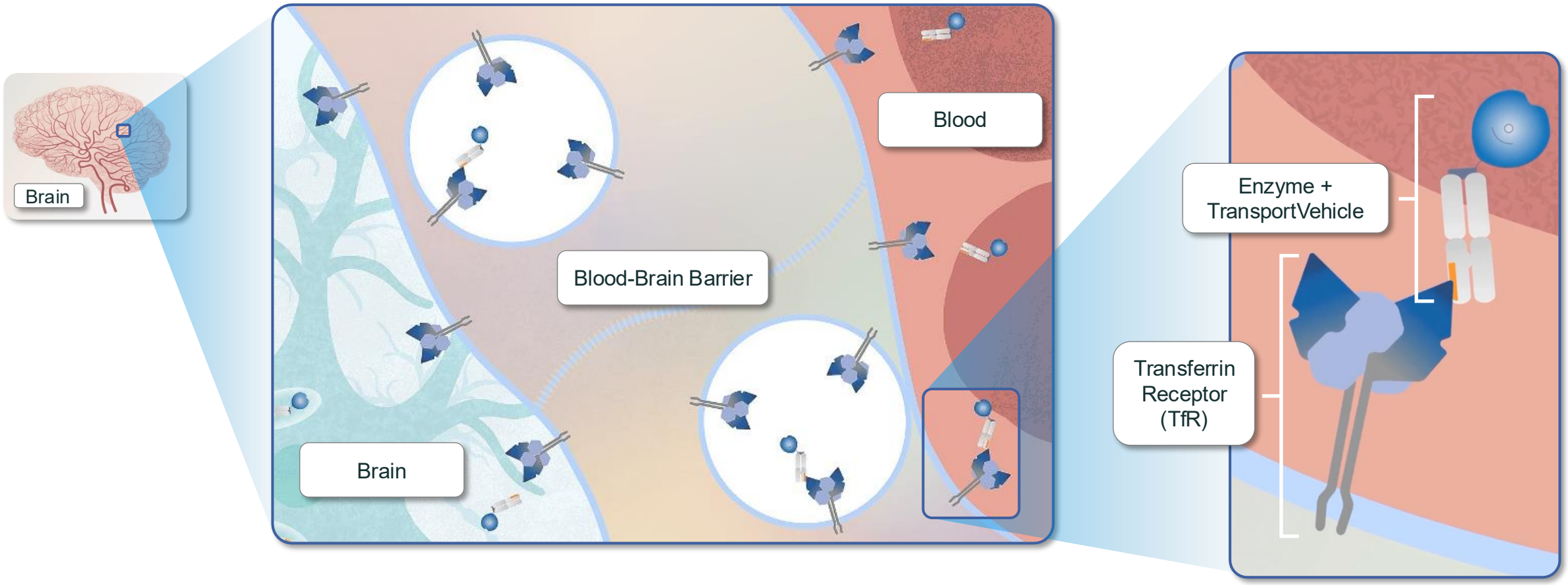
>40M

Patients Worldwide[1]

1. Denali estimates of worldwide aggregate prevalence, excluding China and India for the lysosomal storage disorders; MPS – Mucopolysaccharidosis

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



Now Approved in the U.S.

AVLAYAH™

(tividenofusp alfa-eknm)

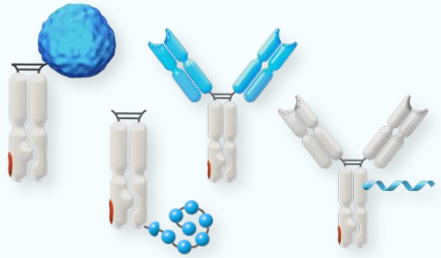
AVLAYAH™ (tividenofusp alfa-eknm), an enzyme replacement therapy, received accelerated approval from the U.S. Food and Drug Administration for the treatment of neurologic manifestations of Hunter syndrome (mucopolysaccharidosis type II) when initiated in presymptomatic or symptomatic pediatric patients weighing at least 5 kg prior to advanced neurologic impairment.

A Powerful Combination: Product, Pipeline, Platform, Capital

AVLAYAH™
(tividenofusp alfa-eknm)

Commercial Product

First FDA-approved product designed to cross the BBB; strong commercial launch and growing brand

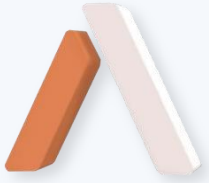


Broad Pipeline

7 clinical programs from rare diseases to Alzheimer's; market opportunity >$10B

Validated TV Platform

Leading BBB technology and team: >350 patents, >20 high-impact publications, >200 patients dosed, >30 dedicated PhD BBB scientists



Operational & Financial Scale

Fully integrated capabilities from discovery to commercial, including own manufacturing; >$1B cash[1]

Denali is built to deliver near-term growth and long-term value

1. Includes cash, cash equivalents and marketable securities of ~$940.0 million as of June 30, 2026, and $195 million in gross proceeds received in July 2026 from the sale of a Priority Review Voucher
FDA – U.S. Food and Drug Administration; TV – TransportVehicle; BBB – blood-brain barrier

Integrated Capabilities to Execute for Long-Term Value

Scale and Infrastructure

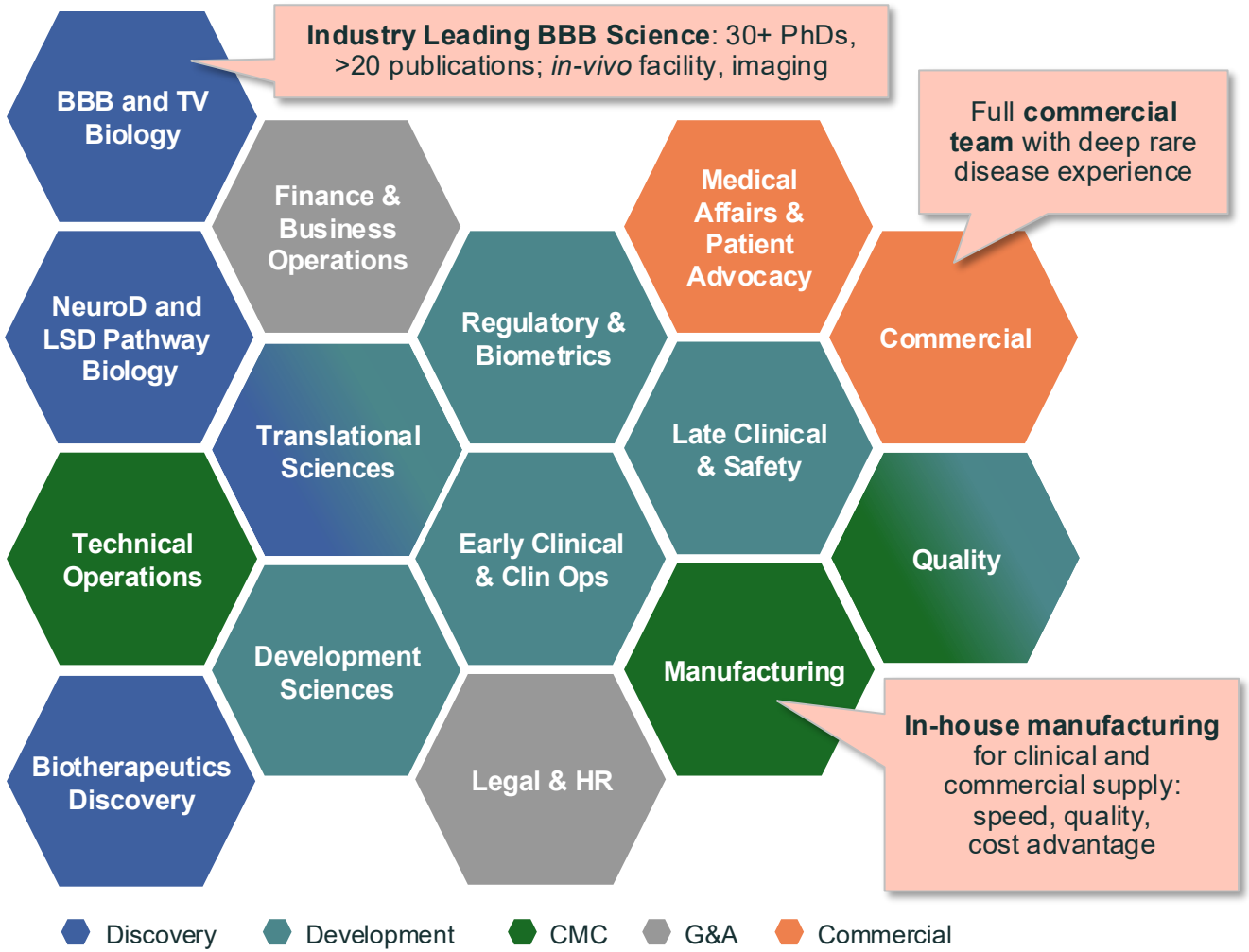
- **Scale** to successfully discover, develop, manufacture and commercialize
- **Integrated infrastructure** with ~520 full time employees in South San Francisco, Salt Lake City and Zürich

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

On Track to Deliver Denali's D3X3 Goals Over 2026-2028

2 Growing Brands

- AVLAYAH™
- **zafinofusp alfa**

4-6 New Clinical Programs

- Continued leadership and invention on BBB technologies

5 Clinical Proofs of Concept

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

DENALI

TransportVehicle™ Platform

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

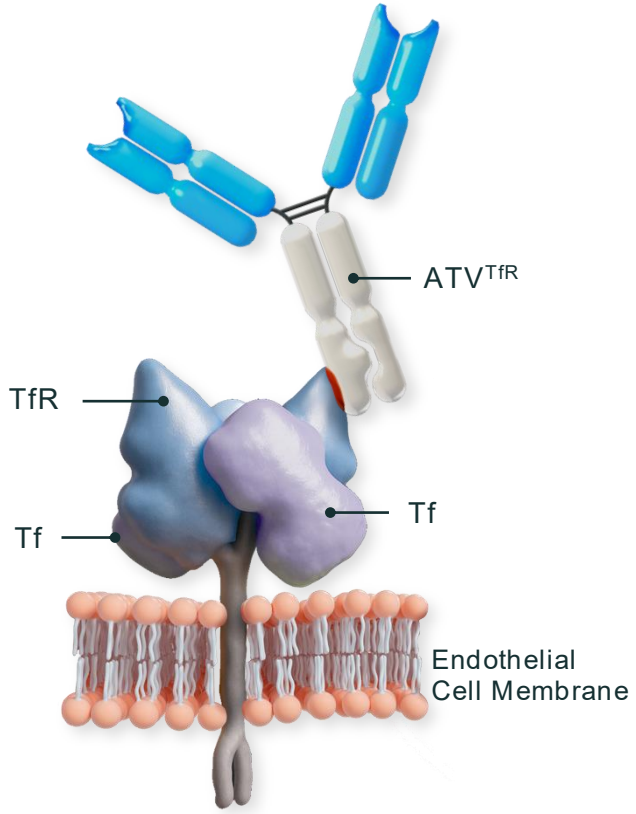
Conditional effector function avoids reticulocyte loss and minimizes anemia liability potential

4 Architecture

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

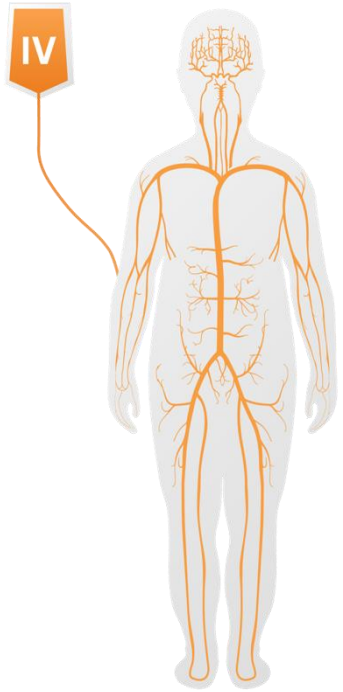
Our Fc-based TransportVehicle™ (TV) Is Designed & Engineered to Optimize Brain Delivery

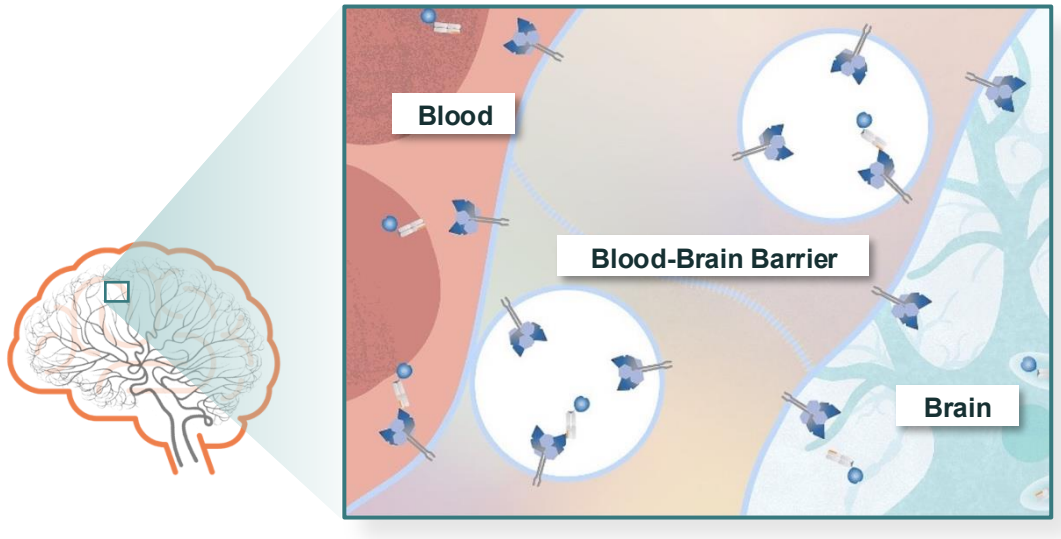
Treating the Whole Body, Including the Brain

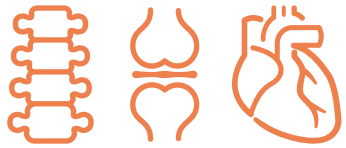


Transferrin receptor (TfR) is highly expressed at the blood–brain barrier for natural iron transport

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



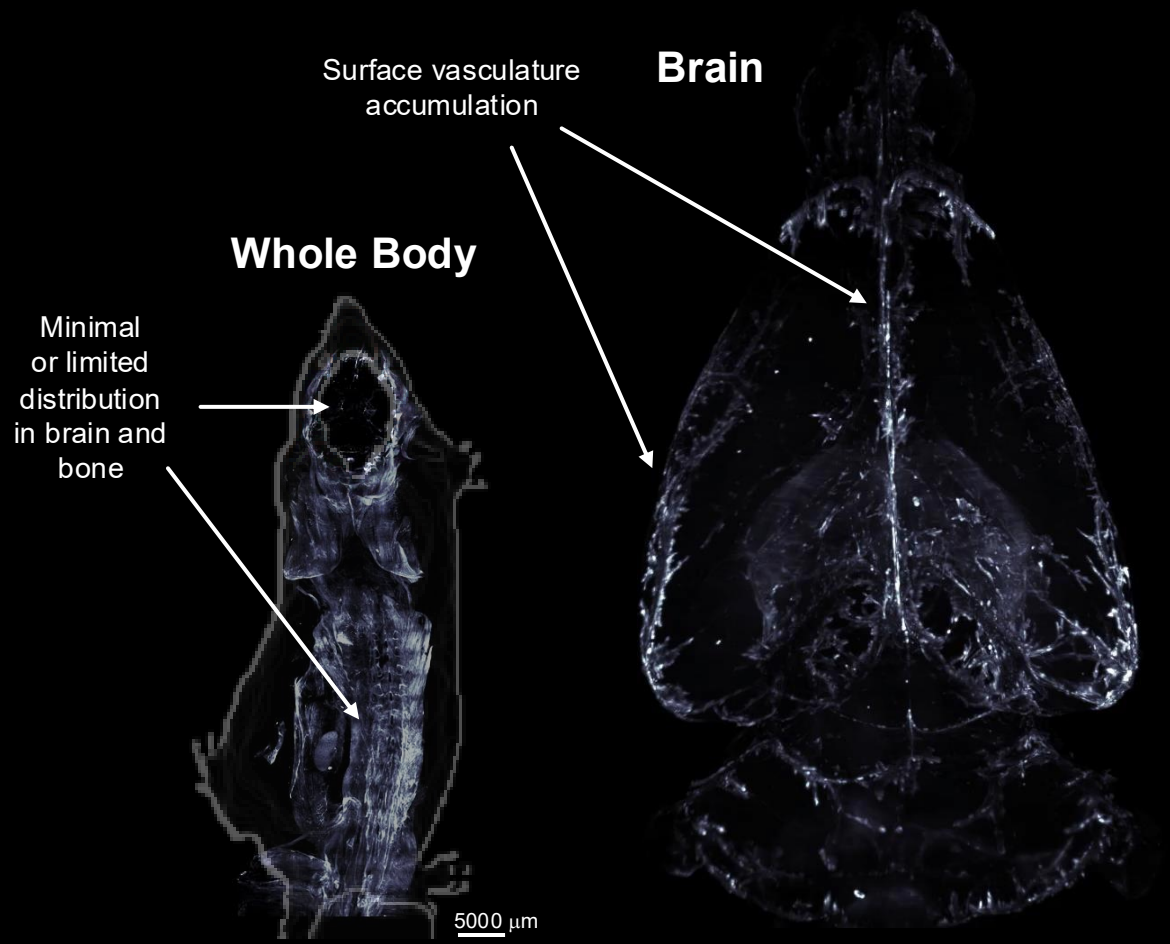




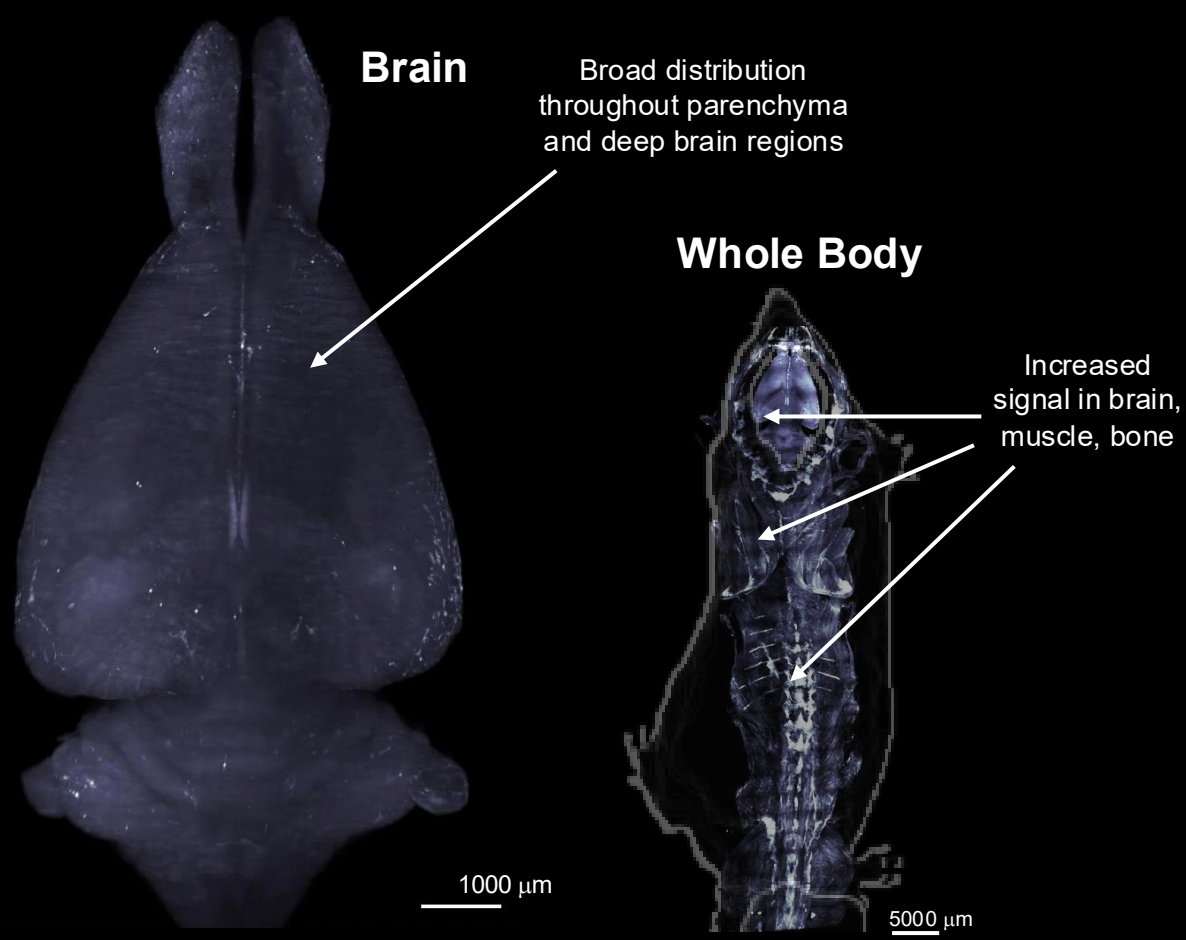
TfR may also facilitate delivery into tissues such as **bone**, **cartilage**, and the **heart**

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]
- 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]

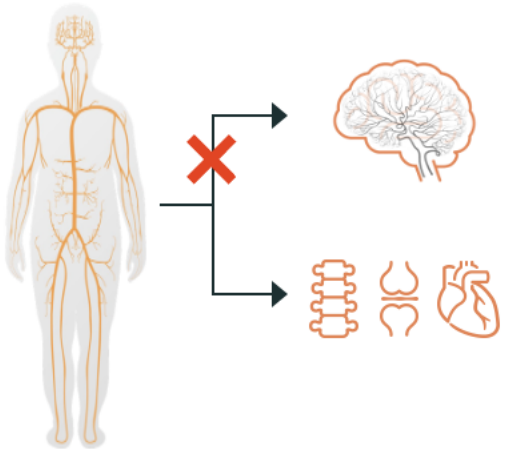
1. As of Oct 27, 2025; **2.** As of Nov 3, 2025; **3.** As of Dec 5, 2025. **BBB –** Blood-brain barrier; **Fc –** fragment crystallizable; **TfR –** Transferrin receptor; **NfL –** Neurofilament light chain

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**

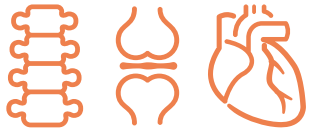


Traditional ERTs partially address somatic but not CNS symptoms

~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

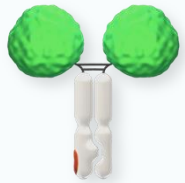
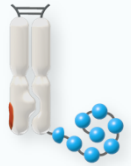
ETV – Enzyme transport vehicle; **LSDs** – Lysosomal storage disorders; **CNS** – Central nervous system; **ERTs** – Enzyme replacement therapies

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

Delivering the Next-Generation of TransportVehicle-Enabled ERT

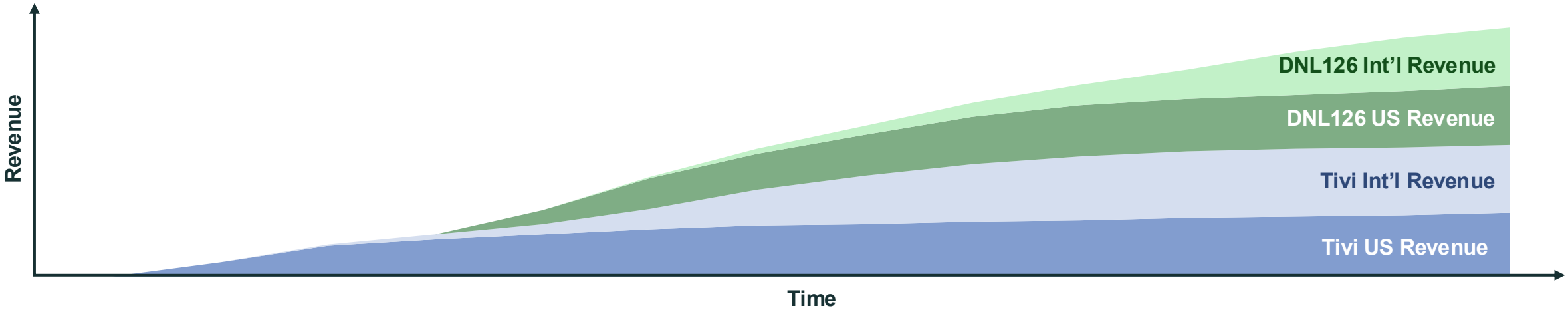
- Addressing neurologic and systemic disease
- Scalable commercial infrastructure
- Repeatable rare disease launch model
- Large, validated ~$9B ERT market[2]

	AVLAYAH™ (tividenofusp alfa-eknm)	Zafinofusp alfa (DNL126)	PTV:PGRN (DNL593)	ETV:GAA (DNL952)	ETV:GCase (DNL111)	ETV:IDUA (DNL622)
						
	MPS II Hunter syndrome	**MPS IIIA** Sanfilippo syndrome type IIIA	**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	U.S. accelerated approval Phase 2/3	Phase 1/2	Phase 1/2	Phase 1	IND-enabling	IND-enabling

WW – Worldwide; **IND** – Investigational New Drug; **GBA-PD** – Parkinson's Disease with GBA mutation; **GD** – Gaucher's Disease; **ERT –** enzyme replacement therapy

1. Excluding China and India; **2.** 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).

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

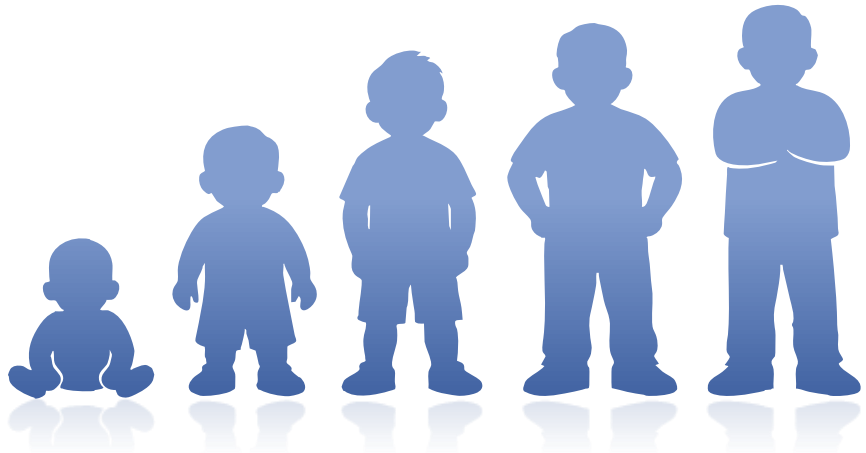
Genetic disorder caused by deficiency in the iduronate 2-sulfatase (IDS) enzyme[1]

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

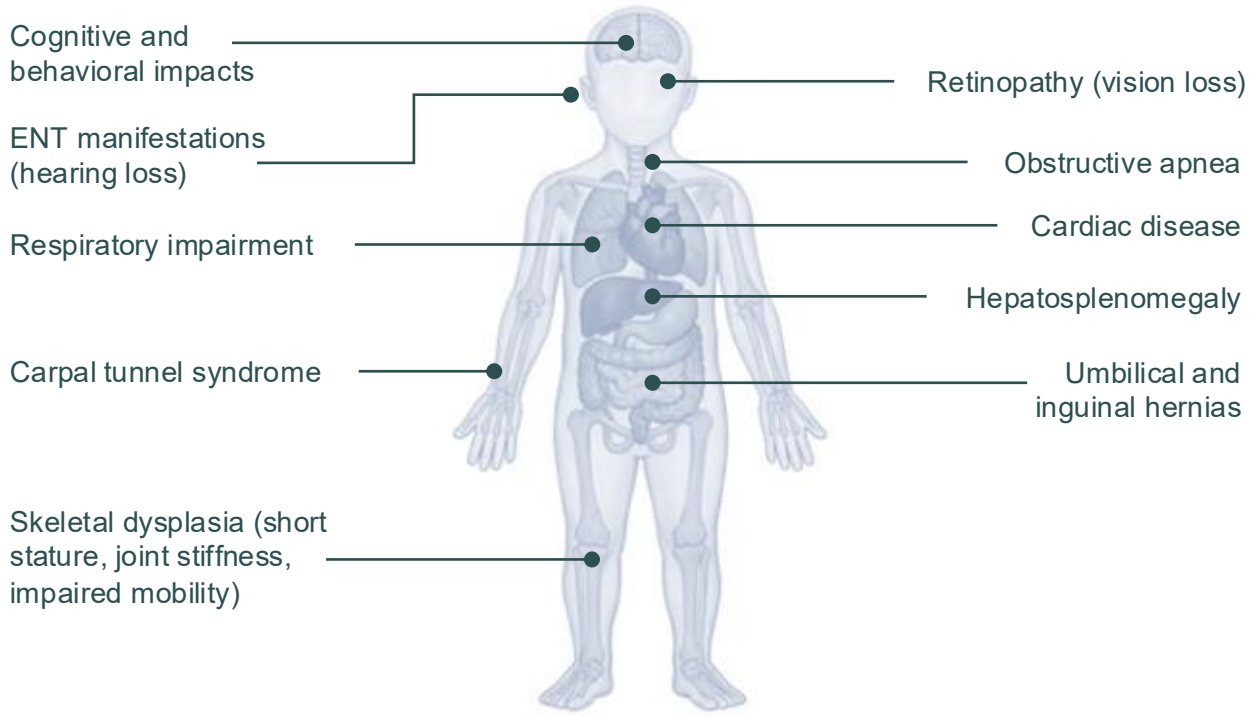
Progression[4] Rapid ← → Slow

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]

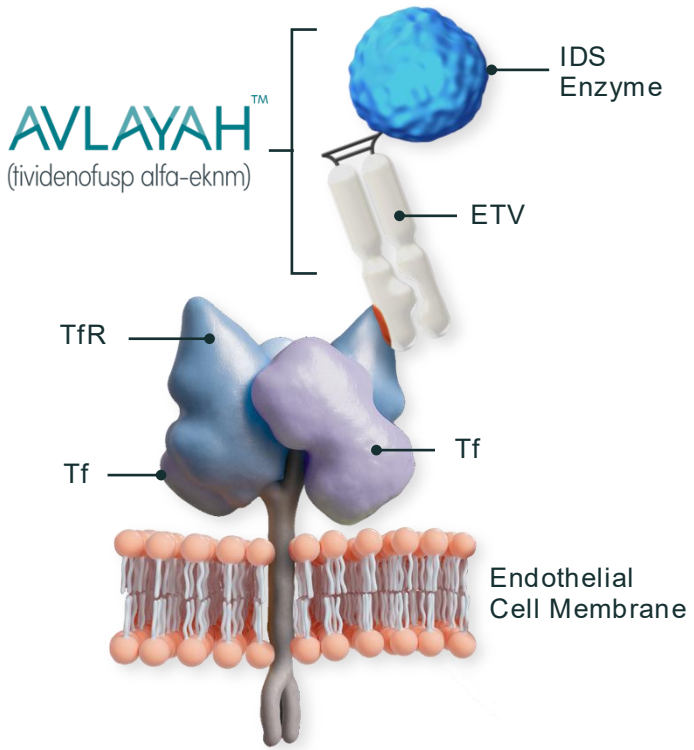
New therapies are needed to adequately address both the neurologic and peripheral manifestations of MPS II

BBB – Blood-brain barrier; **CNS** – Central nervous system; **ERT** – Enzyme replacement therapy; **GAG** – Glycosaminoglycan; **IV** – Intravenous; **MPS II** – Mucopolysaccharidosis type II;

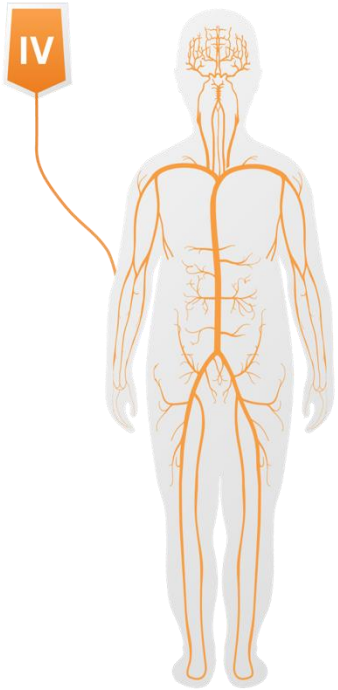
1. Al-Hertani W, et al. *Int J Mol Sci.* 2024;25(16):8573; **2.** Giugliani R, et al. *Int J Mol Sci*. 2021;22(20):10938; **3.** Bhalla A, et al. *Int J Mol Sci*. 2020;21(15):5188; **4.** Argueta C, et al. *Mol Genet Metab.* 2025;144(3):109055; **5.** Muenzer J, et al. *Mol Genet Metab*. 2025;146(4):109284; **6.** Muenzer J, et al. *Genet Med*. 2011;13(2):95-101; **7.** Muenzer J. *Mol Genet Metab*. 2014;111(2):63-72.

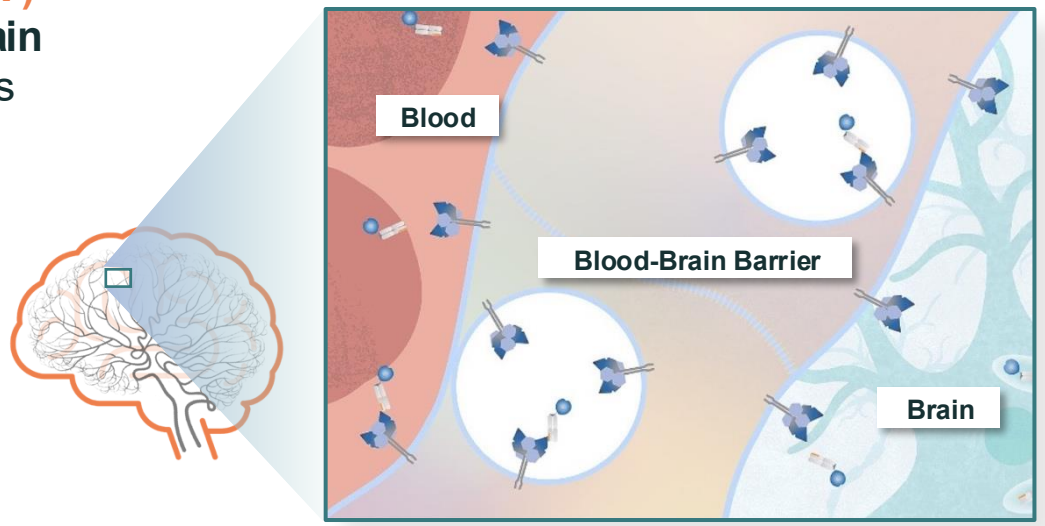
AVLAYAH™ Utilizes the Enzyme TransportVehicle™ (ETV) to Enable Delivery to the Brain and Periphery

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



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





Design of the TV is optimized to enable AVLAYAH™ to cross the blood-brain barrier

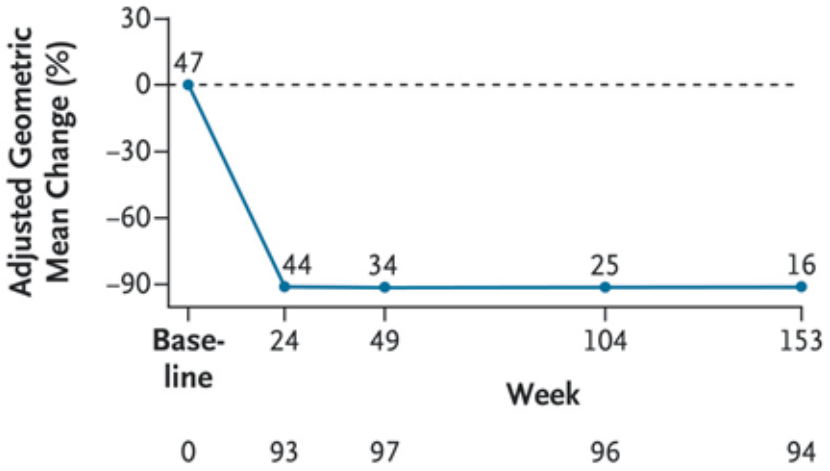
TfR binding may also facilitate delivery into other tissues

IDS – **I**duronate 2-sulfatase; **Tf** – Transferrin

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

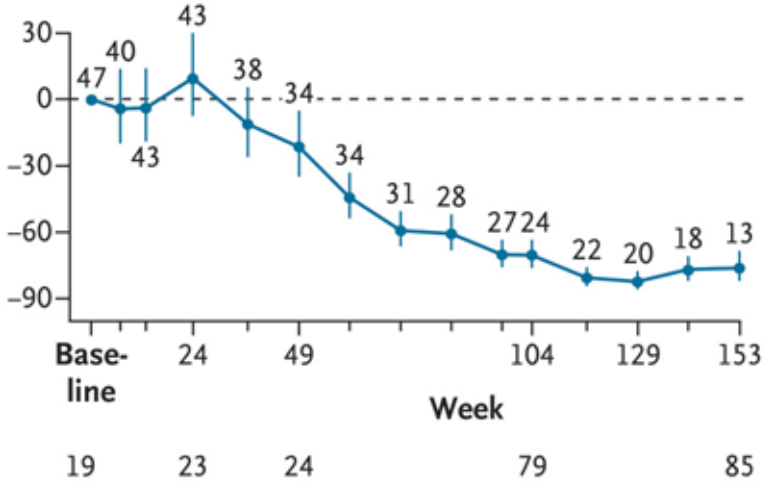
Normalization of CSF HS

Biomarker of CNS disease



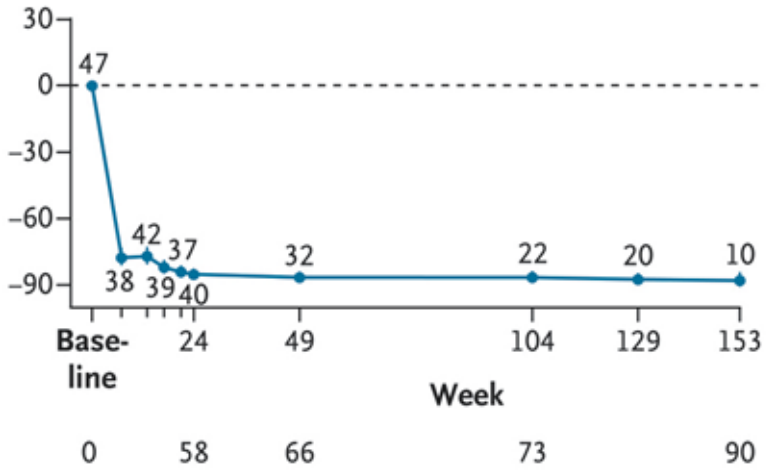
Normalization of NfL

Biomarker of neuronal damage



Normalization of Urine HS

Biomarker of peripheral disease



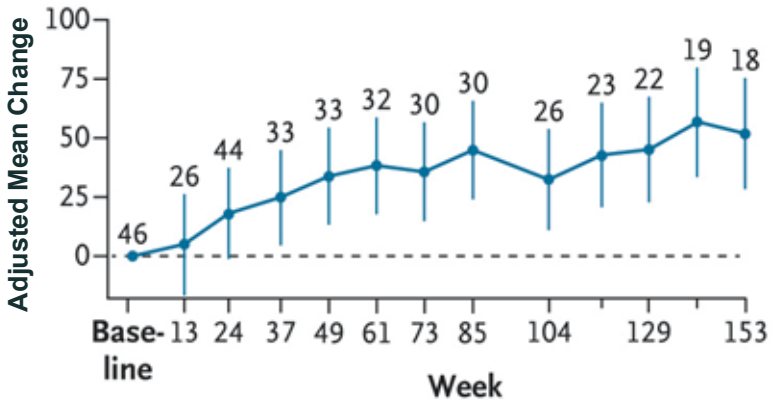
Treatment with tividenofusp alfa-eknm over a median duration of 2 years was associated with reductions in CNS and peripheral biomarkers of substrate accumulation and neuronal injury to levels within the range of unaffected children

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

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

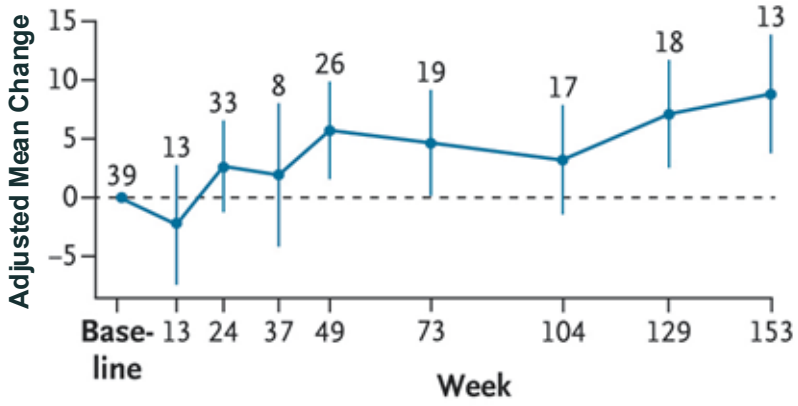
Improvement in Adaptive Behavior

Vineland-3



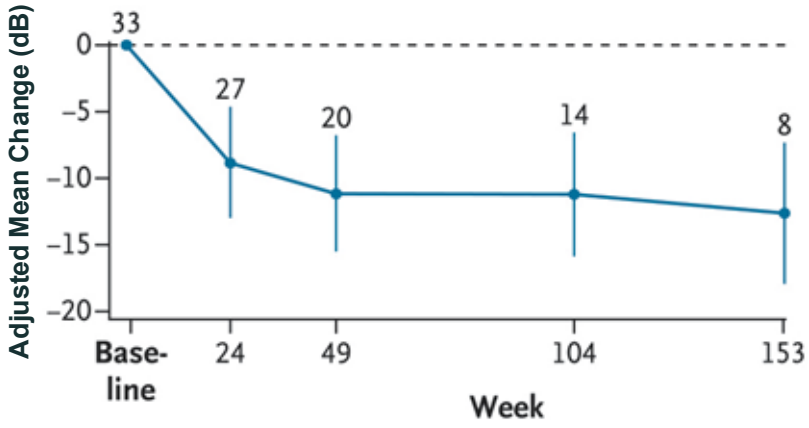
Improvement in Cognition

BSID-III



Improvement in Hearing

Auditory Brainstem Response (PTA)



While on tividenofusp alfa-eknm, 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*.

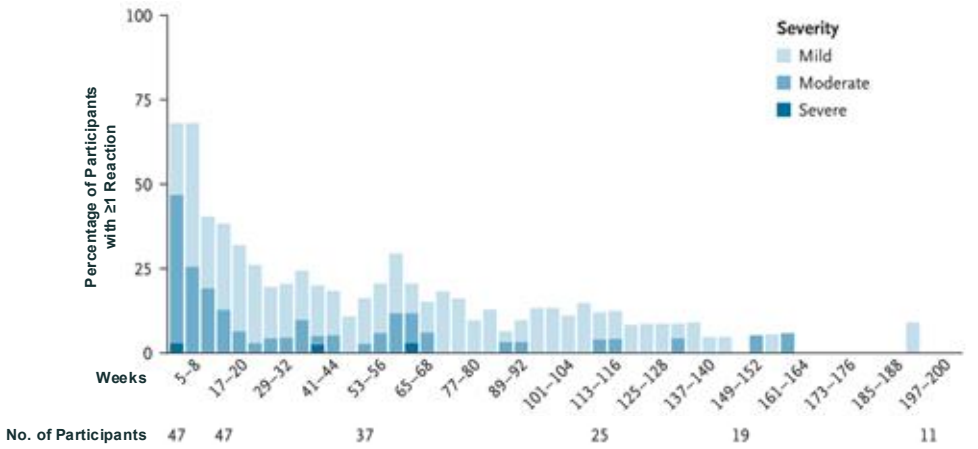
Tividenofusp alfa-eknm Phase 1/2 Results in MPS II: Safety

Summary of Adverse Events

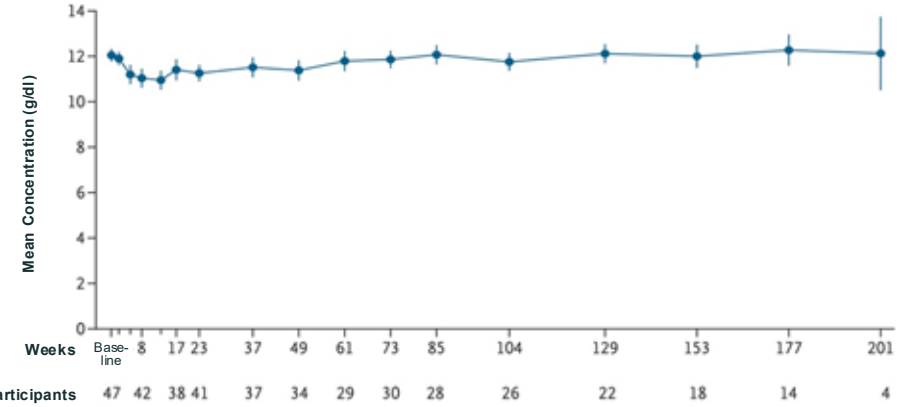
(Safety Analysis Population)

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

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

Select Highlights of AVLAYAH™ U.S. Prescribing Information

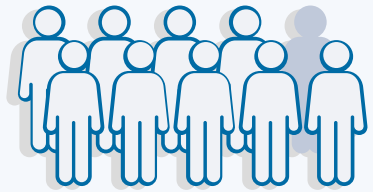
Indications and Usage	• AVLAYAH™ is indicated for the treatment of neurologic manifestations in patients with Hunter syndrome (MPS II) when initiated in presymptomatic or symptomatic pediatric patients weighing at least 5 kg prior to advanced neurologic impairment • AVLAYAH™ is not recommended for use in combination with other enzyme replacement therapies
Dosage and Administration	• Recommended AVLAYAH™ maintenance dosage is 15 mg/kg administered once weekly as an intravenous infusion over ~4 hours • AVLAYAH™ treatment should be initiated with a dose escalation regimen
Clinical Studies and Pharmacodynamics	• **CSF HS:** Treatment with AVLAYAH™ resulted in a significant 91% mean reduction of CSF HS from baseline with 93% of patients having CSF HS levels below the upper limit of normal (ULN) at Week 24 • **Urine GAGs:** At baseline, 4% of patients had total urine GAG levels below the ULN. After treatment with AVLAYAH™ 68% of patients had total urine GAG levels below the ULN at Week 24
Safety	• Boxed warning regarding hypersensitivity (including anaphylaxis) consistent with other approved ERTs • Infusion-Associated Reactions: Manage with monitoring and infusion rate adjustment; discontinue if severe • Anemia: Typically early onset and manageable with supportive care; monitor hemoglobin • Membranous Nephropathy: one case reported; monitor serum creatinine and urine protein to creatinine ratio

MPS II – Mucopolysaccharidoses Type II; **CSF** – Cerebrospinal fluid; **HS** – Heparan sulfate; **GAG** – Glycosaminoglycan; **ERTs** – Enzyme replacement therapies

Setting a New Bar for the Treatment of MPS II

AVLAYAH™
(tividenofusp alfa-eknm)

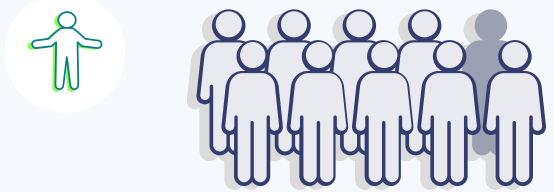
The first FDA-approved enzyme replacement therapy (ERT) to cross the **blood-brain barrier** to reach the brain in addition to the body



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

The most common adverse reaction was infusion-related reactions

* "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™ is Approved in the U.S. for ~375 Eligible Patients

Global MPS II Population

~2,000

Patients Worldwide Currently Receiving ERT Treatment for Hunter Syndrome in Addressable Markets[1]

~25%

Located in U.S.

U.S. MPS II Population

~500

Prevalent Patients

~30

Incident Patients per Year

~75%

Eligible per FDA Label

Current Eligible MPS II Population[2]

~375

Eligible Patients

Long term goal is to serve all patients with Hunter Syndrome globally, supported by the ongoing Phase 2/3 COMPASS Study

1. Source: EvaluatePharma (excluding China, India and Russia); 2. AVLAYAH is indicated for the treatment of neurologic manifestations of MPS II when initiated in presymptomatic or symptomatic pediatric patients weighing at least 5 kg prior to advanced neurologic impairment.

Strong Momentum with AVLAYAH ™ Launch

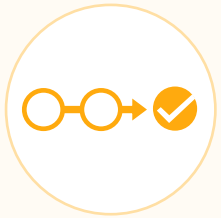
2026: Building the Foundation Across Key Stakeholders for Revenue Acceleration

Reach

Achieve broad patient reach through community-centered, high-touch engagement model

Switch

Activate and maintain switch to AVLAYAH



Access

Support seamless access for patients

Coverage

Drive fast coverage aligned to label

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

Healthcare Organization (HCO) Engagement

High awareness and motivating data translated into broad launch engagement across targeted treating HCOs

PRE-LAUNCH

HCP Awareness Prior to Launch

>80%

Physicians[1] aware of AVLAYAH™

AWARE

PRE-LAUNCH

Data Motivation

90%

View data as motivating to prescribe[1]

MOTIVATED

LAUNCH

Launch Reach

~80%

of HCOs* reached with launch messaging

ENGAGED

Pre-Launch Awareness[2] Helped Drive Strong Launch Engagement

> *I consider AVLAYAH™ mandatory for patients with MPS II because it crosses the BBB. Now all patients should be on AVLAYAH™.*
>
> — MPS II HCP

- HCPs recognize significant **unmet needs** across **brain and body**
- **No overall concerns** with safety profile
- Recognize the breadth and depth of neurologic manifestations

1. HCP insights from HCP Survey (N=35) conducted in Q4 2025
*Defined as HCOs with a valid MPS II pediatric patient claim in last 12 months and/or submitted an AVLAYAH™ Start Form since launch; 2. Based on scientific exchange

Patients and Caregivers are Aware of AVLAYAH™

Patient & Family Webinars

3 Launch Webinars

Focused on Clinical Data and Patient Access

REACHING

100+ Families

>25% of Eligible Patient Pool

Media Coverage

"This treatment is important to us — they have a chance now."

— Marie, MPS II Parent

"...the chance to start treatment feels like 'extra time' with her son."

— FOX6, Wisconsin

Positive Experience with Denali and AVLAYAH™

For the first time, it felt like Adam's world was opening up. We began to see changes in his speech and mobility that meant so much to our family. While his previous treatment helped his body, we always hoped for something that could address what was happening in his brain.

— Miriam, *MPS II Parent & Advocate*

When Cole started AVLAYAH™, all I hoped for was stability — a few more years with my son. But seeing him come alive, so aware of his environment, more active, trying to communicate, I have thrown away all my assumptions. I am allowing myself to look forward and dream of a better future for him.

— Kim, *MPS II Parent & Advocate*

The Denali team is doing a fantastic job navigating the access landscape.

— Terri Klein
CEO, National MPS Society

Today, [our son] is finally receiving a groundbreaking medication that we pray will help improve his quality of life and give him more time to be a kid. Happier, more comfortable, and more himself.

— AVLAYAH™ Caregiver
Facebook Post, Accessed on July 17, 2026

Exceptional Progress on Payer Coverage in the First Quarter After Launch, Exceeding Rare Disease Launch Analogs[1]

Commercial

of Covered Lives[2]

Medicaid

14

State Medicaid Programs list AVLAYAH™ as covered

Managed Medicaid coverage growing, with policies consistent with label

- Motivated and committed HCPs pushing through payer appeals
- Payer approvals across Commercial and Medicaid
- Strong uptake in payer policies at this phase in launch providing HCP confidence that patients can access AVLAYAH™

1. Analogs reflect selected rare disease launches from the five years preceding AVLAYAH's launch: olipudase alfa-rpcp, cipaglucosidase alfa-atga, and pegunigalsidase alfa-iwxj (ERTs); tofersen and delandistrogene moxeparvovec-rokl (rare disease non ERTs). Coverage is compared at the equivalent point post-launch. Data provided by MMIT; 2. Calculated based on the plans that represent 95% of lives within each segment (Commercial and Managed Medicaid).

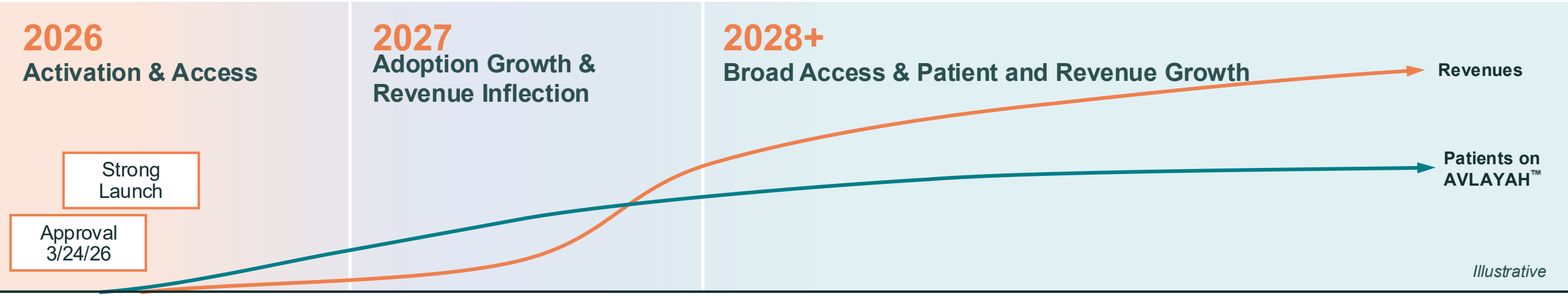
AVLAYAH™ U.S. Launch Dynamics

2026: Building the Foundation To Become the Standard of Care for MPS II Pediatric Patients*

$3.6M 2Q 2026 Net Revenue

>50% Commercial Lives Covered

~$10M to $12M Projected 3Q 2026 Net Revenue



* Pre-symptomatic or symptomatic neurologic manifestations; 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

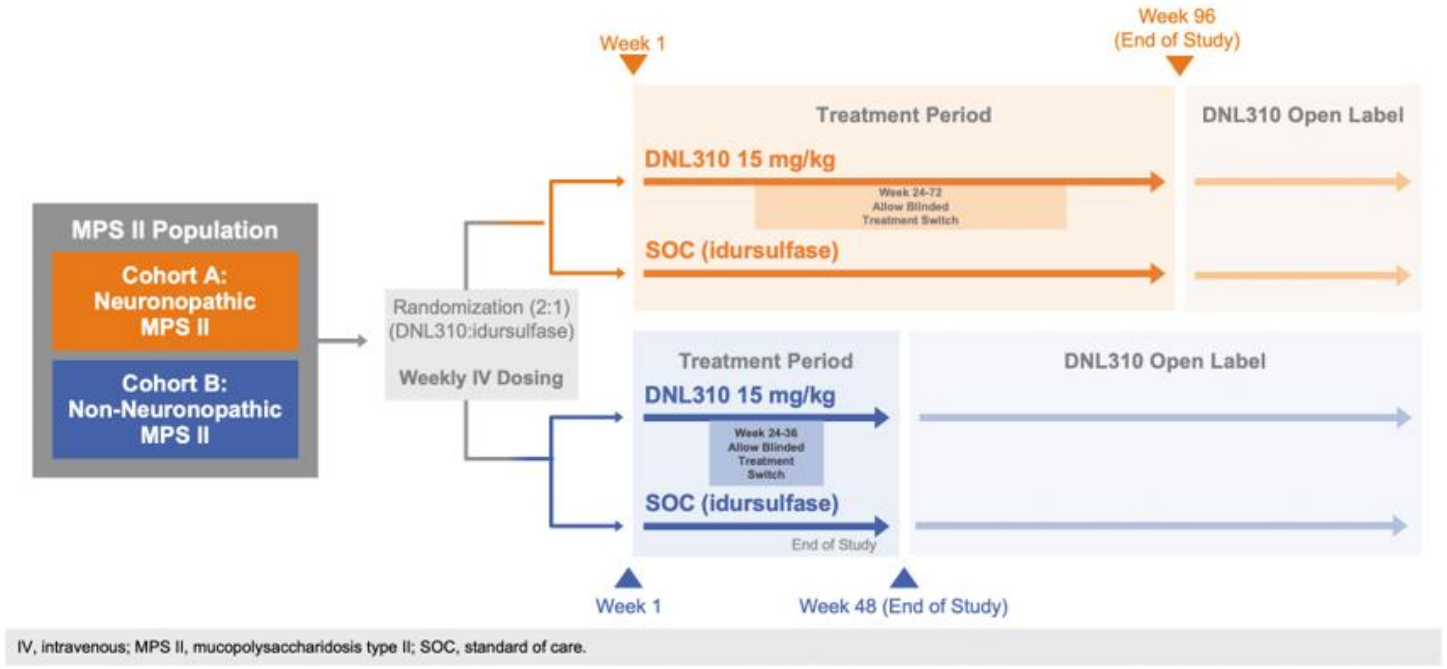
COMPASS

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



IV, intravenous; MPS II, mucopolysaccharidosis type II; SOC, standard of care.

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

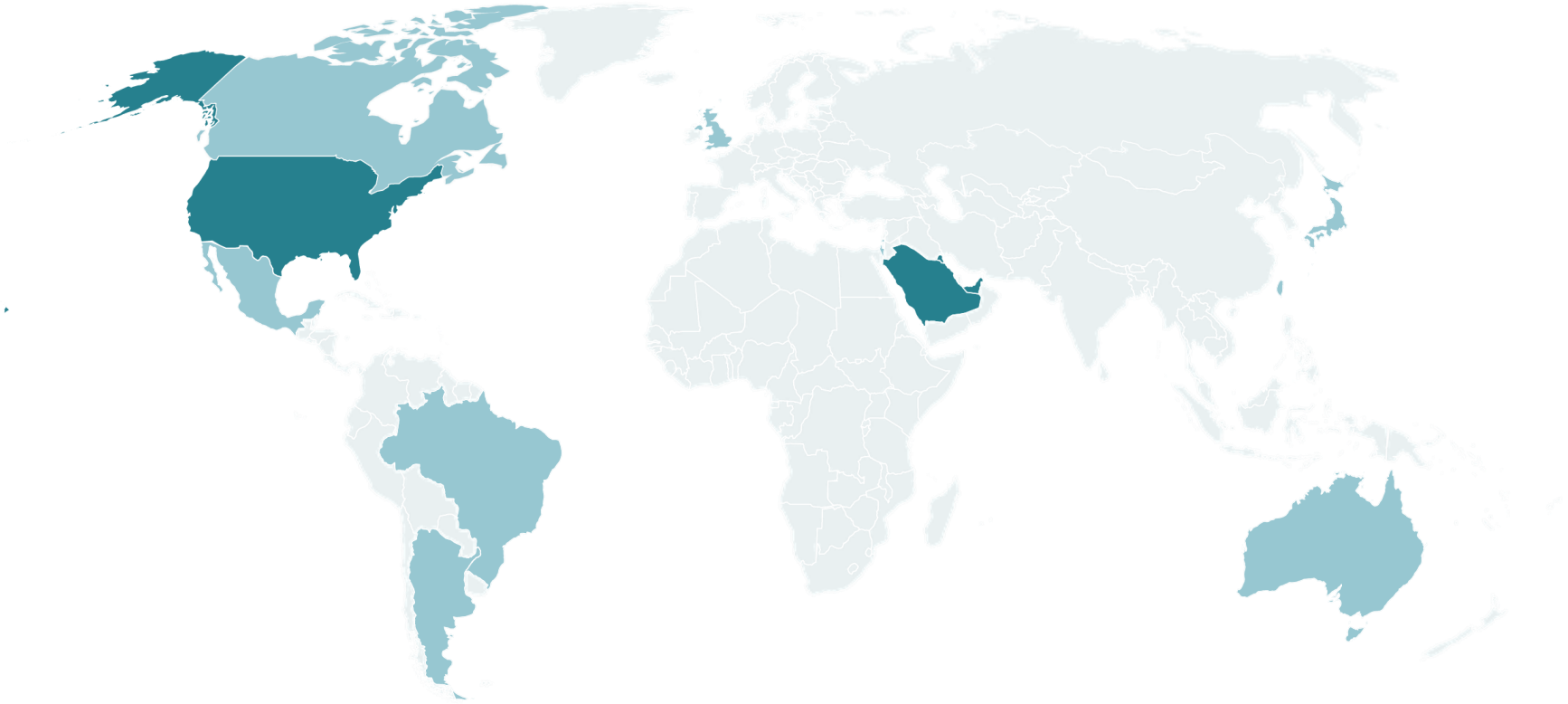
Key Endpoints

- **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

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

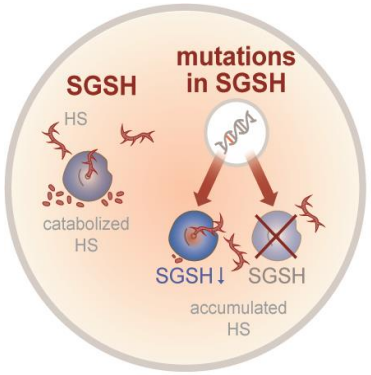
Note: Based on estimated worldwide split of idursulfase annual revenues of $650M to $700M, assuming we launch in ~90-95% of idursulfase geographies; **1.** COMPASS Phase 2/3 data not needed for regulatory filings; All strategies and tactics are subject to Legal review prior to implementation.

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

MPS IIIA Pathogenesis, Biomarkers, and Clinical Manifestations

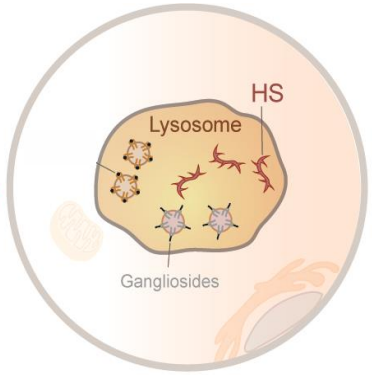
TARGET | **PATHWAY** | **CLINICAL**

Genetic Deficiency in SGSH Enzyme Activity



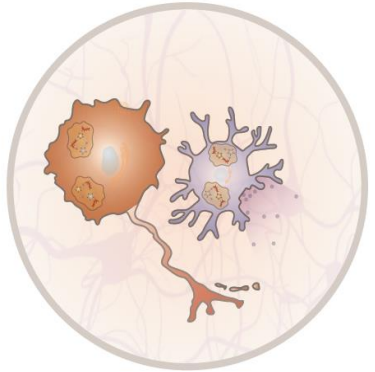
Accumulation of heparan sulfate

Lysosomal Dysfunction

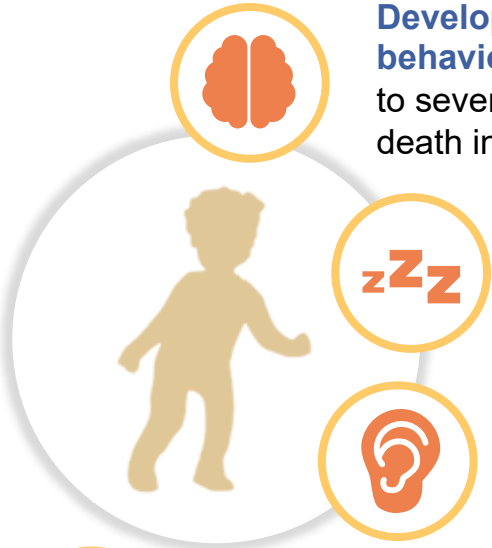


Accumulation of lysosomal lipids (e.g., GM3)

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]

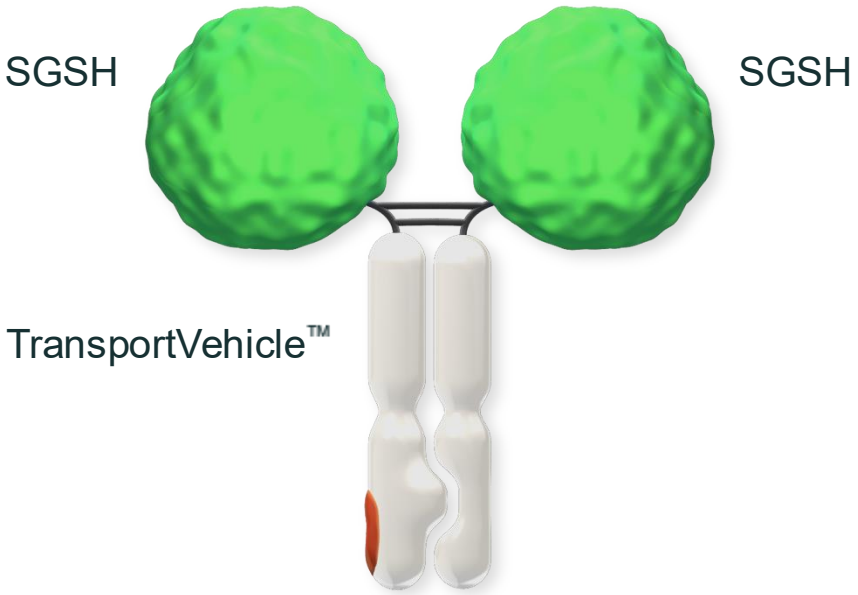
Somatic manifestations including diarrhea, hepatomegaly, and joint stiffness[3,6,7]

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



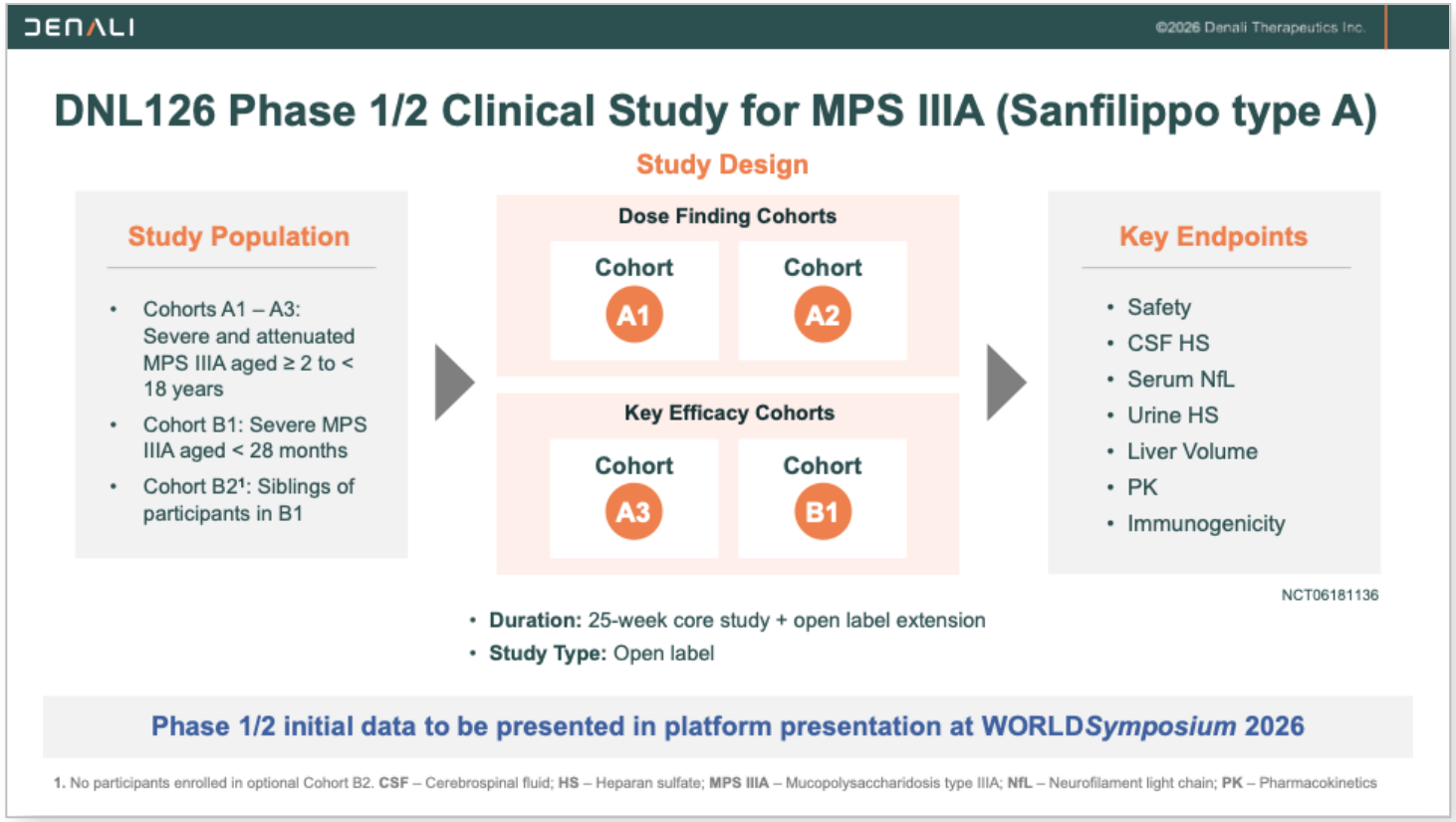
Program Status

- 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

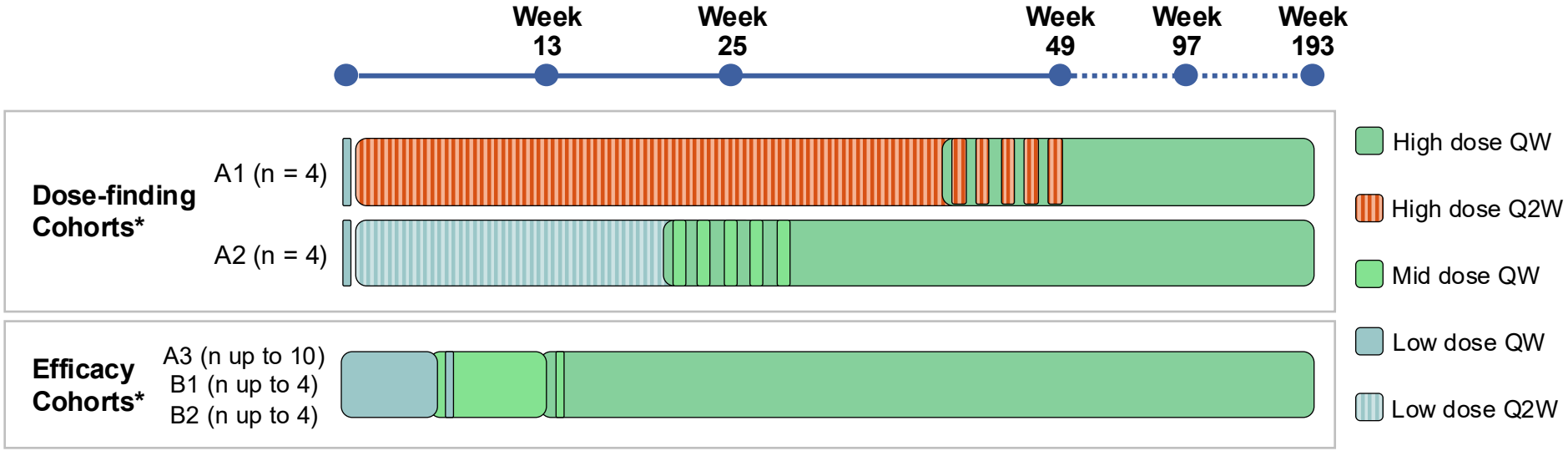
- At least 49 weeks of data for all participants (Cohorts A1-A3, B1; n=20)
- CSF HS reduction from baseline in key efficacy cohorts (n=12) – surrogate endpoint reasonably likely to predict clinical benefit
- Supportive data on central and peripheral biomarkers, clinical endpoints
- Long-term safety up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

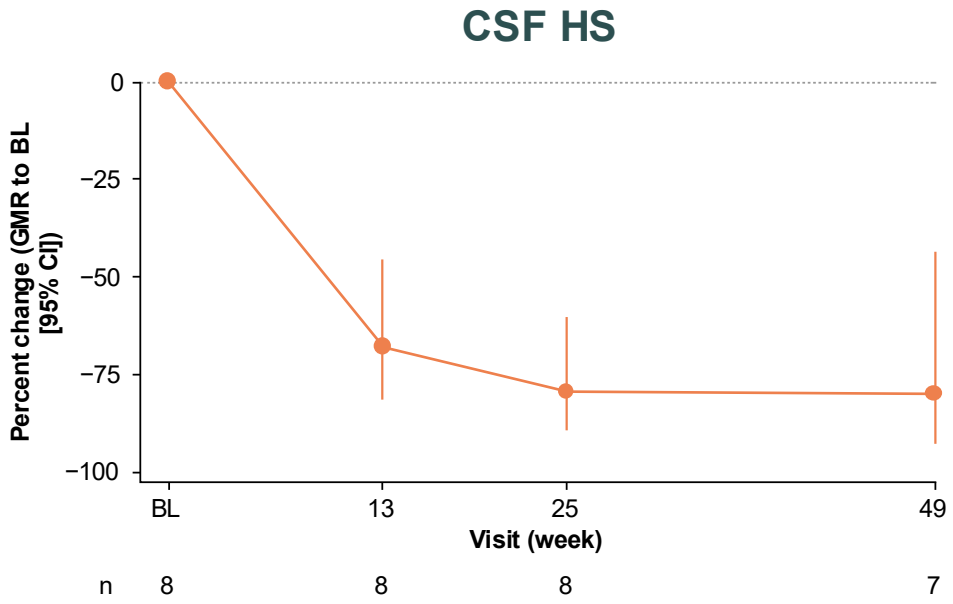
	Dose-finding Cohorts		Efficacy Cohorts*		
	Cohort A1 (n = 4)	Cohort A2 (n = 4)	Cohort A3 (n = 4)	Cohort B1 (n = 2)	All Cohorts (n = 14)
DNL126 Treatment Duration					
Completed up to Week 25	4 (100.0%)	4 (100.0%)	4 (100.0%)	1 (50.0%)	13 (92.9%)
Completed up to Week 49	4 (100.0%)	4 (100.0%)	0 (0.0%)	0 (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%)

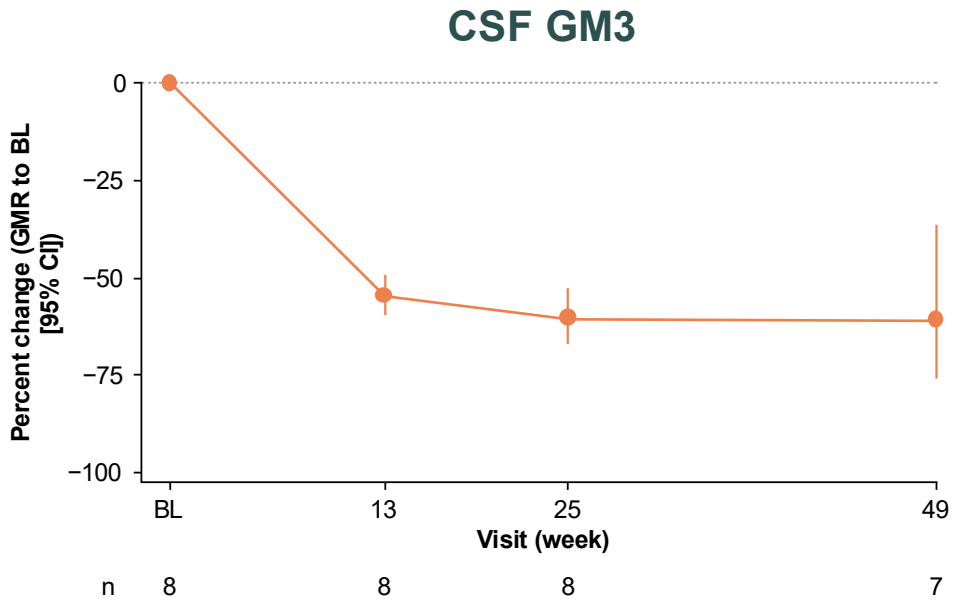
Study population includes a broad spectrum of pediatric ages and genotypes

*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

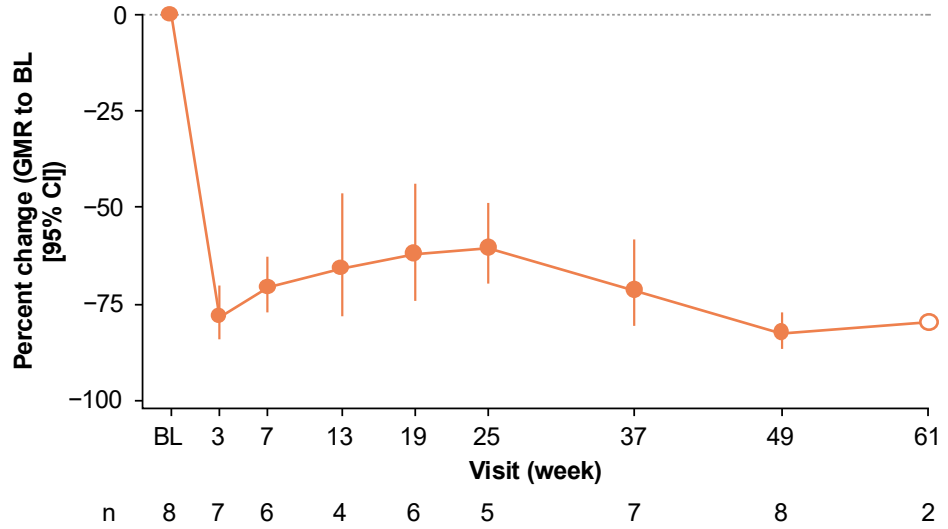
- Mean reduction of 80% in CSF HS with 3 of 7* participants within normal range**
- Mean reduction of 61% in GM3 with 6 of 7* participants within normal range***

*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)

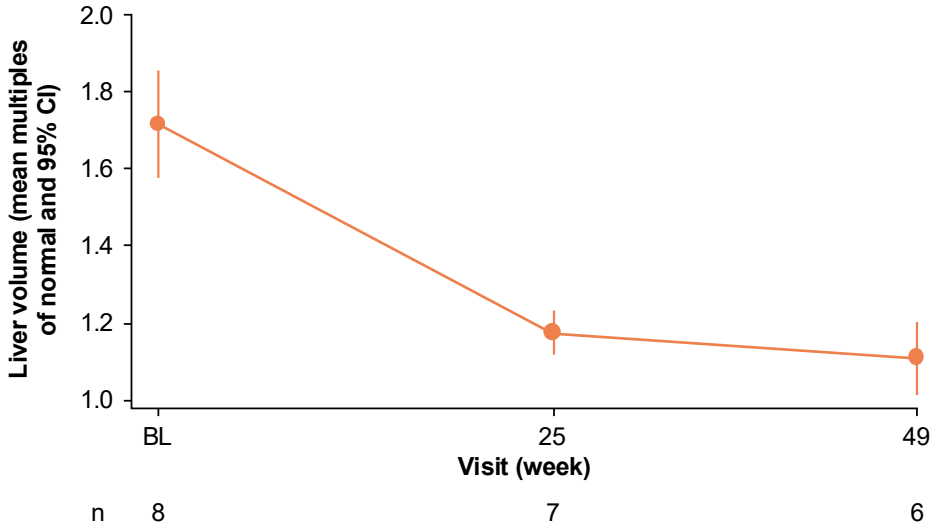
Peripheral Measures: Urine HS and Liver Volume

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

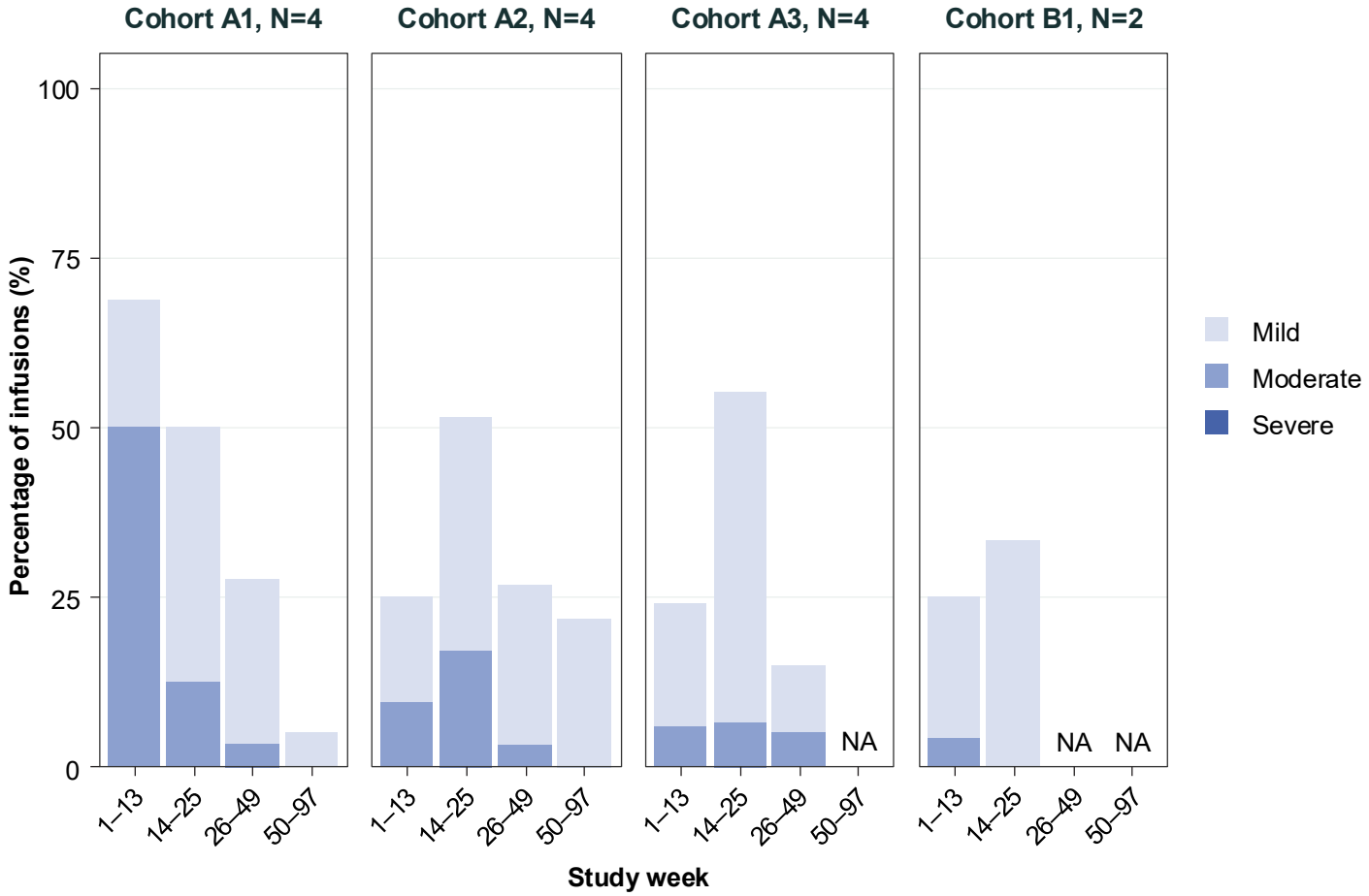
Preferred Term	All Cohorts (n = 14) [n (%)]
Infusion-Related Reaction	14 (100)
Upper Respiratory Infection	9 (64.3)
Vomiting	9 (64.3)
Nasal Congestion	7 (50.0)
Cough	6 (42.9)
Diarrhea	5 (35.7)
Ear Infection	5 (35.7)
Fall	5 (35.7)
Gastroenteritis	5 (35.7)
Irritability	5 (35.7)

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

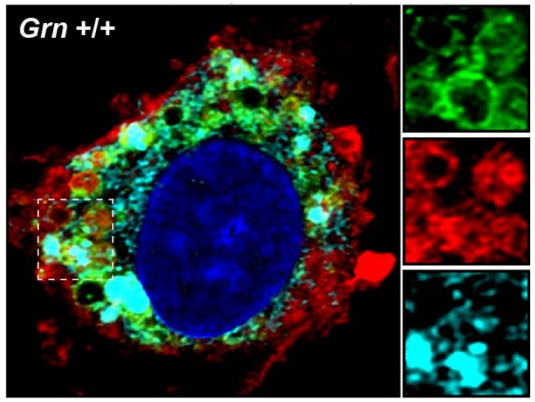
DNL593 (PTV:PGRN): Frontotemporal Dementia-Granulin (FTD-*GRN*)

DNL593 (PTV:PGRN) PGRN Replacement for FTD-*GRN*

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]



LAMP2
Lysosome Marker

BMP
Lipid critical for lysosome activity

PGRN
Localized to lysosome

DNL593 Phase 1/2 Clinical Study

Study Population

- **Part A:** Healthy volunteers aged ≥18 to ≤55 years
- **Part B:** *GRN* mutation carriers; symptomatic participants diagnosed with FTD-*GRN*; aged ≥ 8 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

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

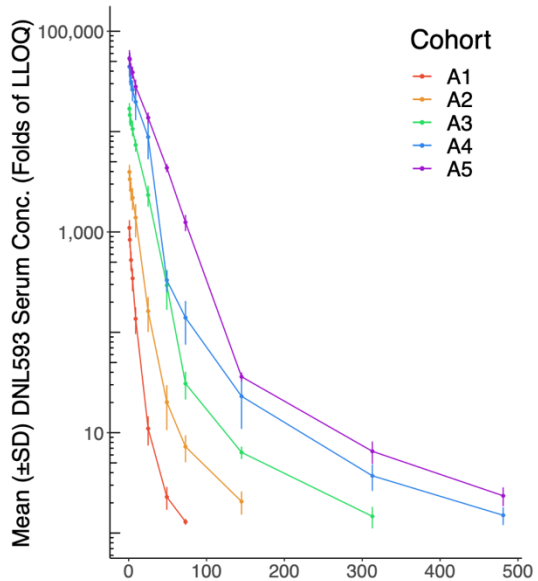
Strategic Path Forward

- Denali regained full ownership and control of the program from Takeda in 2Q 2026
- Phase 1/2 data now expected in 1H 2027 to allow for longer biomarker observation in OLE, including NfL
- We intend to explore a potential accelerated approval path based on biomarker data

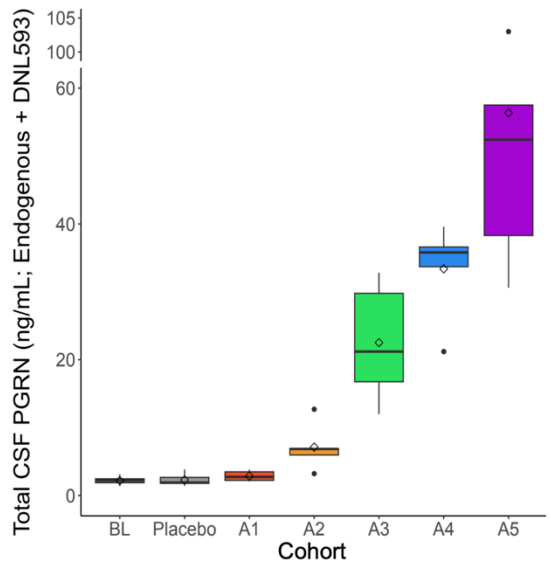
DNL593 (PTV:PGRN): Phase 1/2 Healthy Volunteer Data

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

HV SAD Serum PK



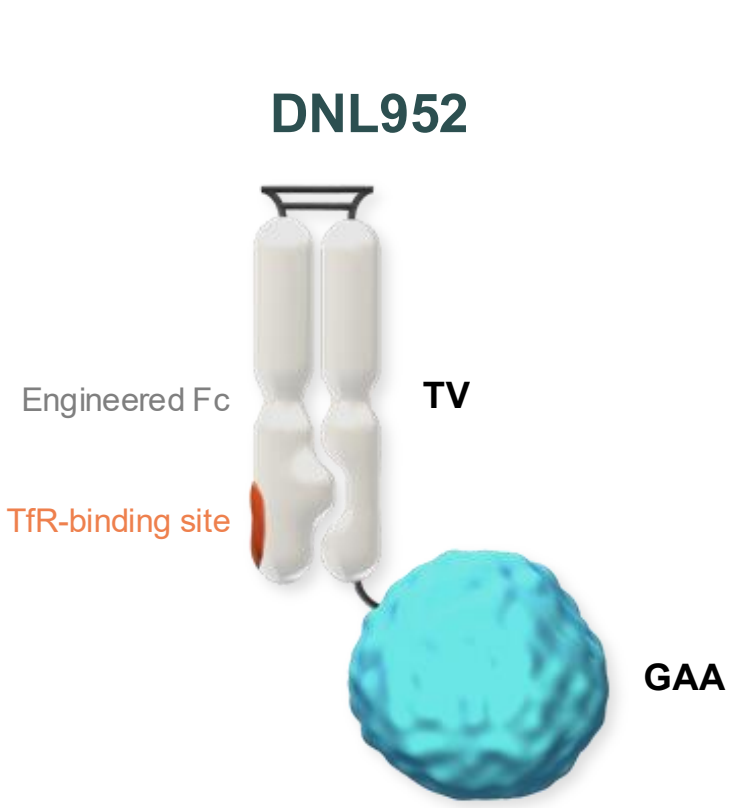
HV SAD CSF PGRN (24 hr)

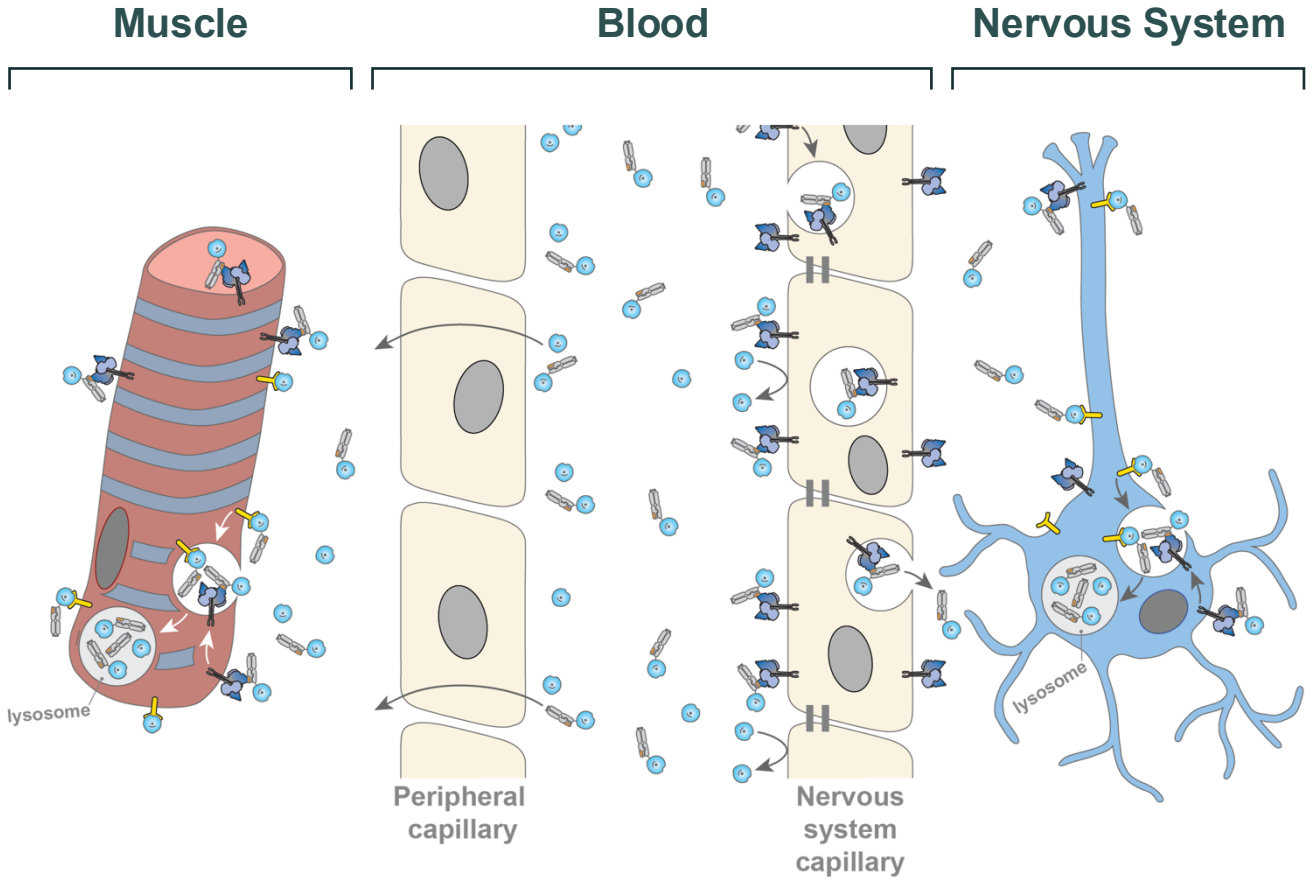


PTV:PGRN – Protein TransportVehicle:Progranulin; **FTD-*GRN*** – frontotemporal dementia granulin; **HVs** – healthy volunteers; **SAD** – single ascending dose; **CSF** – cerebrospinal fluid

DNL952 (ETV:GAA): Pompe Disease

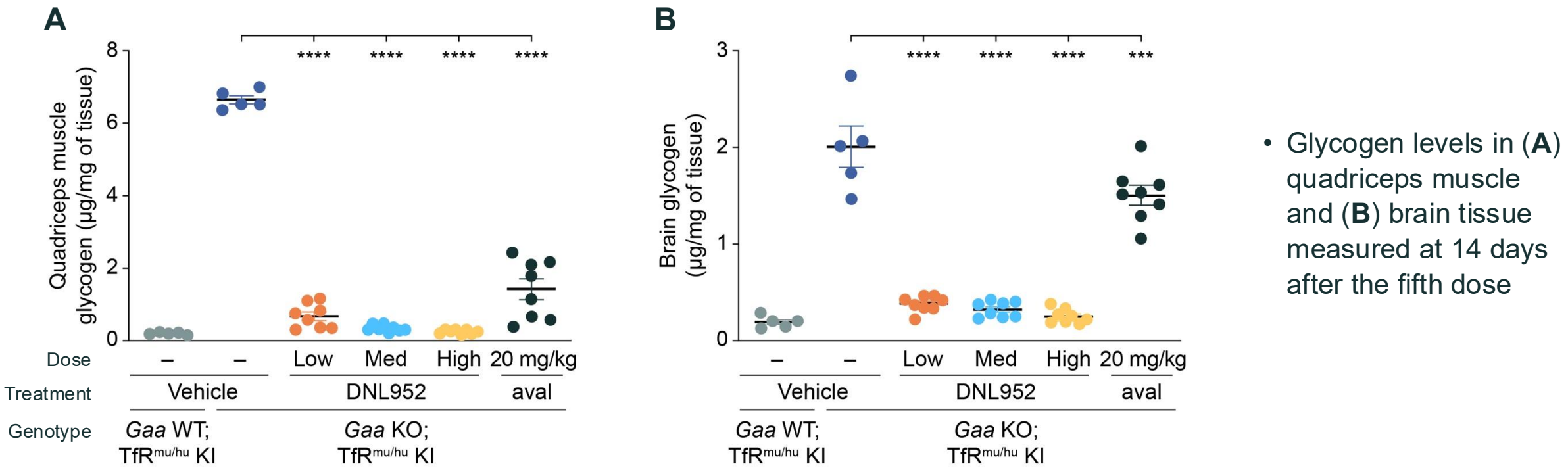
DNL952 is a Novel, Investigational ERT for Pompe Disease Designed to Improve GAA Delivery to Muscle and the Nervous System





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

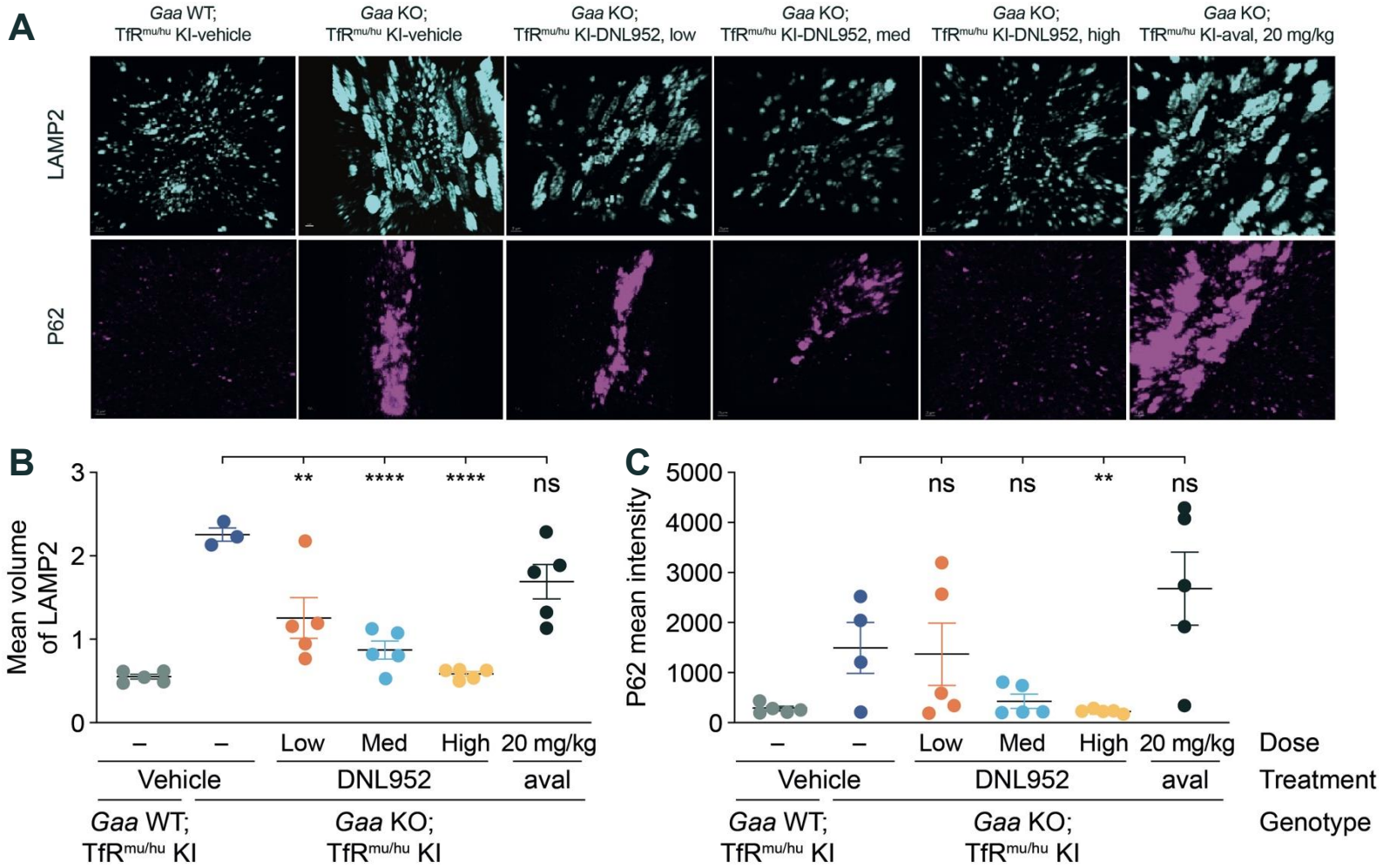


- Glycogen levels in (**A**) quadriceps muscle and (**B**) brain tissue measured at 14 days after the fifth dose

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

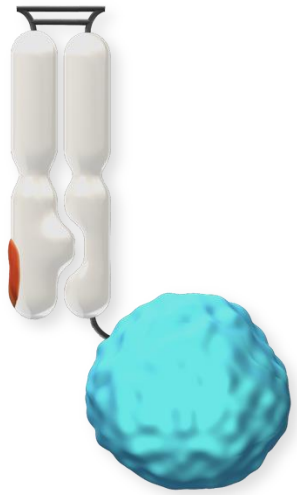
Improved pharmacodynamic response: Enhanced correction of glycogen & downstream pathology, including autophagy

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

Alzheimer's Disease Opportunity

Transformative Time for Alzheimer's Disease

New Opportunities for Success in Neurodegeneration

Biology

New insights into the underlying, multifaceted biology of neurodegeneration

Biomarkers

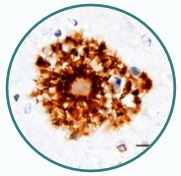
Enabling early diagnosis, monitoring of progression and treatment response

Blood-Brain Barrier

Validated technologies to address key challenge for biologics to reach the brain

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

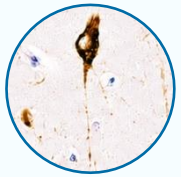
The Next Advances in AD May Depend on Better Brain Delivery



Amyloid-beta

Amyloid plaque

- Plaque clearance clinically validated
- Current limitations
  - Modest efficacy
  - ARIA safety risk

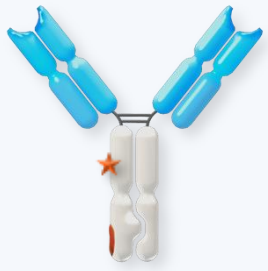


Tau

Neurofibrillary tangle

- Clinical benefit trend from tau reduction
- Current limitations
  - Uneven brain distribution
  - Intrathecal administration burden

TransportVehicle (TV) Opportunity

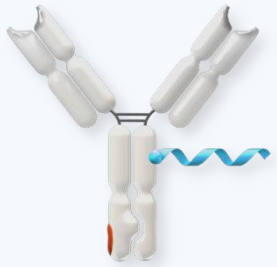


DNL921

(ATV:Abeta)

Potential best-in-class BBB-crossing anti-amyloid

- Improve plaque engagement
- Reduce ARIA potential
- Minimize peripheral immune activation



DNL628

(OTV:MAPT)

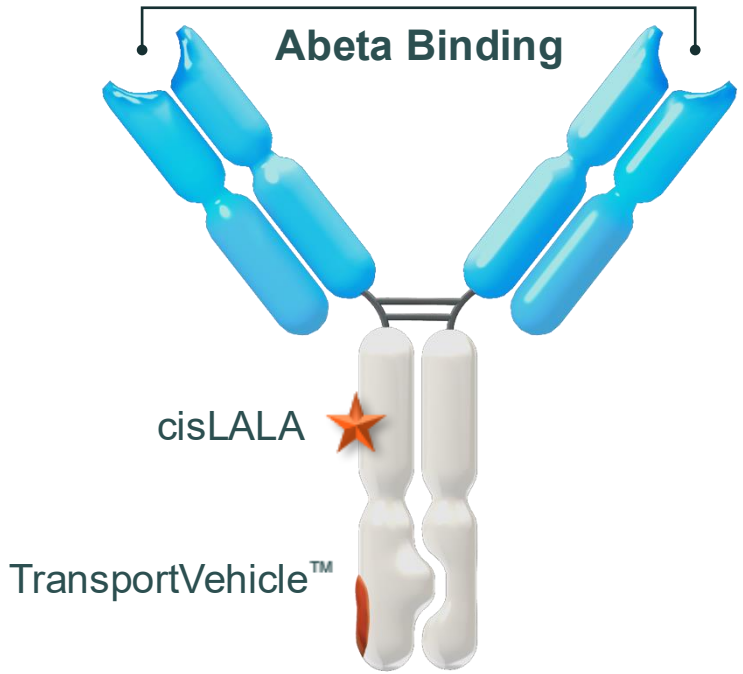
Potential first-in-class BBB-crossing tau ASO

- Broad, uniform brain distribution via the capillary network
- Systemic dosing without intrathecal administration

TV has the potential to transform brain delivery for the next generation of Alzheimer's therapies

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

ATV:Abeta



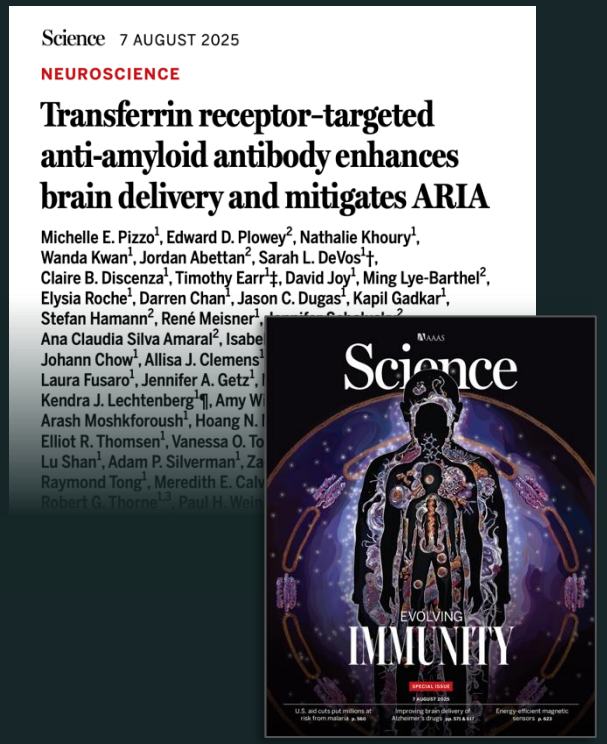
Program status: IND/CTA filing in 1H 2026

Key Characteristics

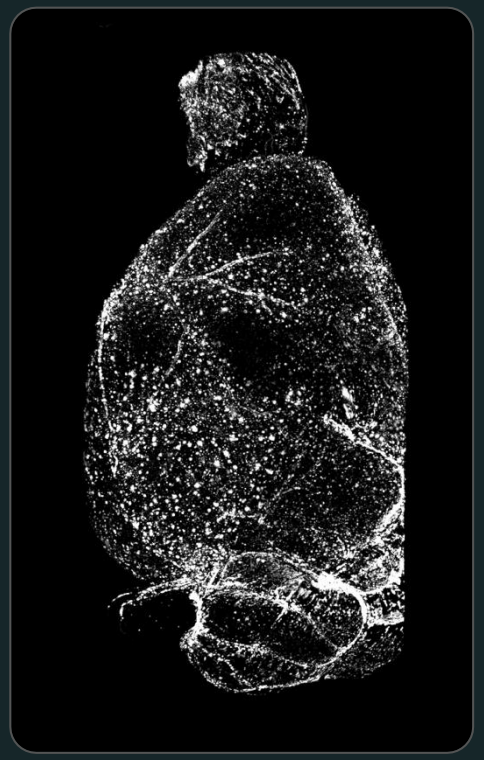
- TfR engagement tuned to maximize CNS biodistribution and target engagement while minimizing ARIA
- cisLALA architecture that is unique to TV allows molecule to safely retain effector function
- Designed to preferentially bind oligomeric Abeta and minimize monomer binding

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

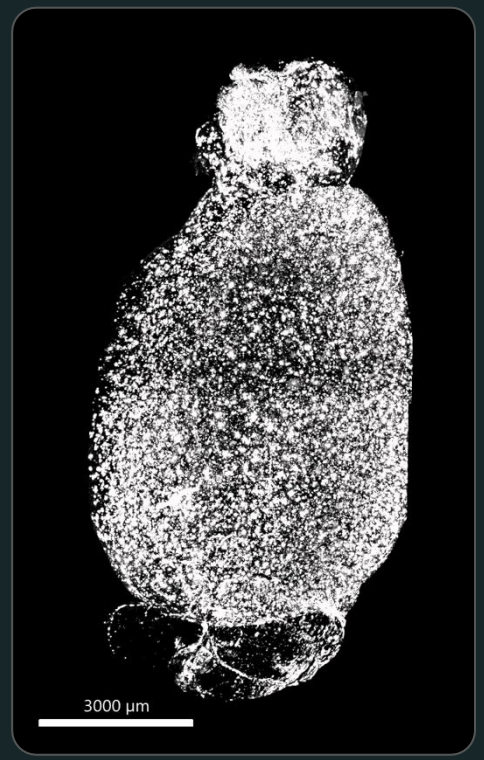
ATV:Abeta (DNL921) Exhibits Enhanced Target Engagement Compared to Standard Anti-Abeta in Mouse Model of AD



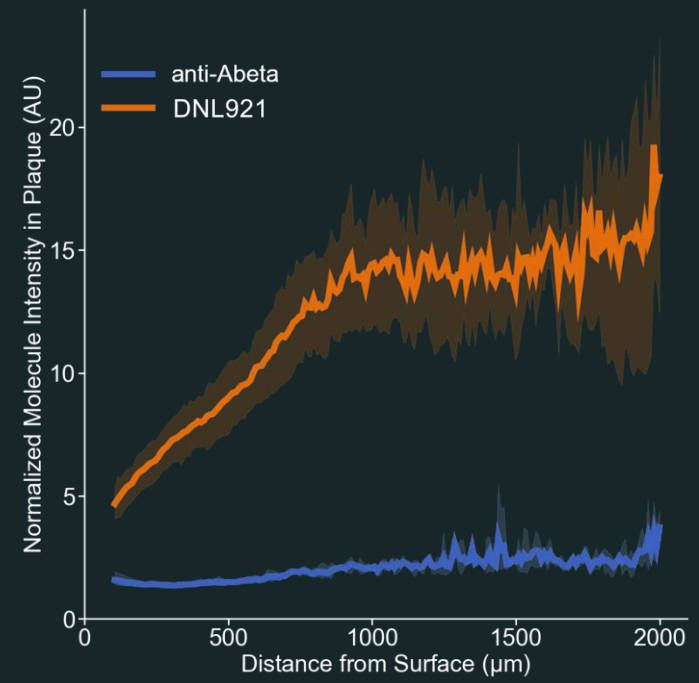
1st Generation Anti-Abeta



DNL921



Amyloid Plaque Target Engagement

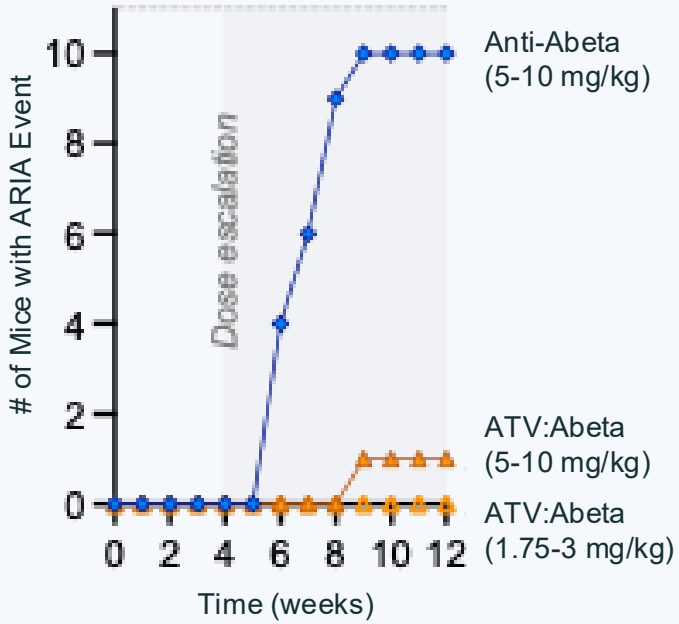


DNL921 (ATV:Abeta) is an investigational compound and has not been approved by any regulatory authority.
10 mg/kg, 24 hours post-dose, iDISCO-cleared hemibrain; signal represents amyloid plaque engagement; Source: Pizzo et al. *Science* 2025

ATV:Abeta Reduces ARIA Due to TfR-Mediated Capillary Delivery to Brain in Mouse Model of AD

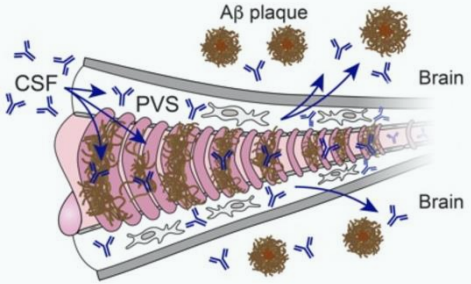
Incidence of MRI Lesions[1]

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

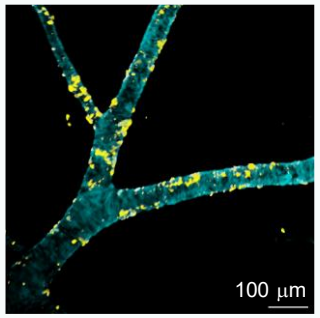


Route of Entry into Brain[2]

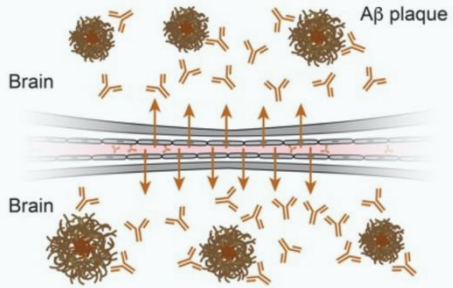
Conventional Anti-Abeta



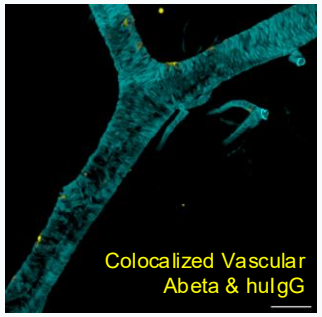
Artery / Arteriole Zone



ATV-Enabled Anti-Abeta



Microvessel (capillary) Zone



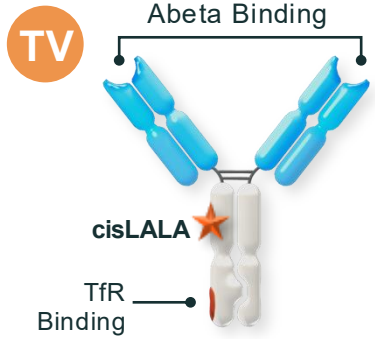
Bypassing arterial vascular plaque via TfR-mediated entry into the brain through capillaries and venules has the potential to improve amyloid-related imaging abnormalities (ARIA)

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

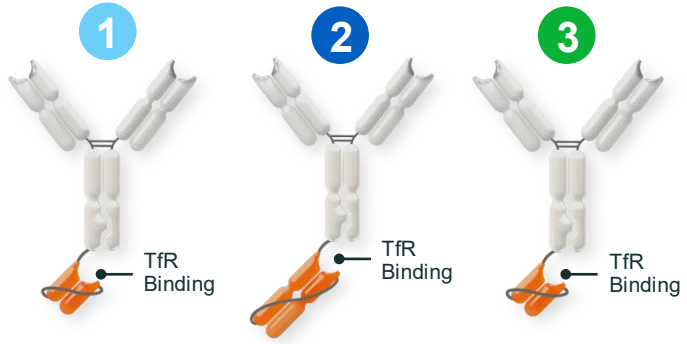
1. Data generated by Biogen; 2. Source: Pizzo et al. Science 2025; ARIA – Amyloid-related imaging abnormalities; TfR – Transferrin receptor

DNL921 Optimized for Robust Brain Delivery, Safety & Stability

DNL921 (ATV:Abeta)

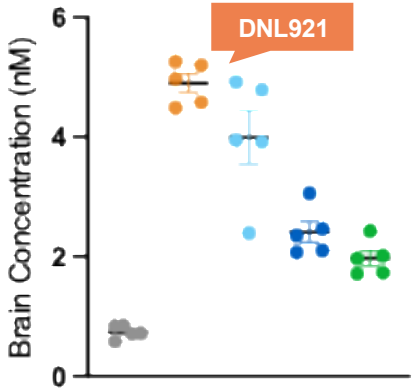


Fusion Molecules[1]

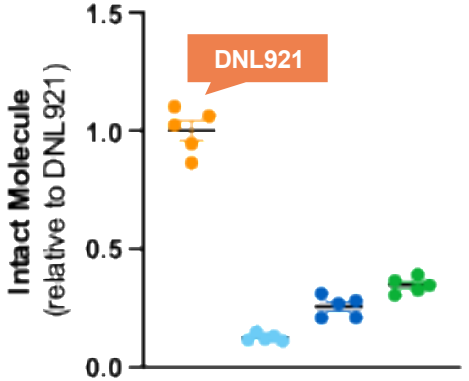


Molecule	Architecture	Epitope	Effector Function
Control	Control IgG	N/A	Full
DNL921	TV- TfR in Fc	Apical	Conditional
Molecule #1	C-term TfR	Protease	Full
Molecule #2	C-term TfR	Apical	Full
Molecule #3	C-term TfR	Apical	None

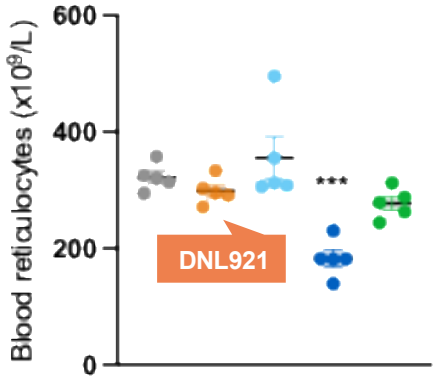
Brain Concentration[2]



Intact Molecule[2,3]



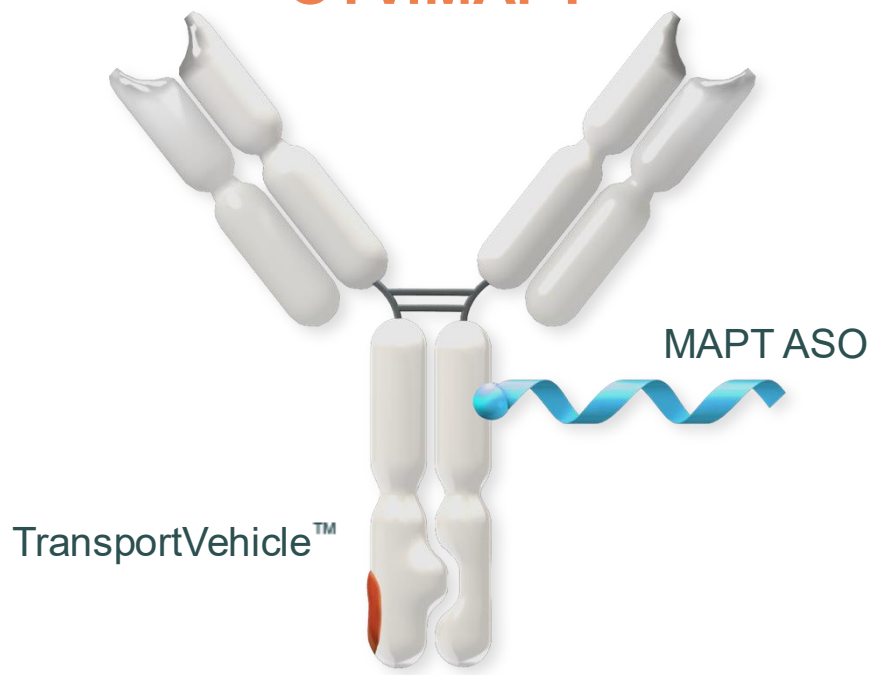
Immature Reticulocytes[2]



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

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

OTV:MAPT



Program status: First subject dosed in Phase 1b study

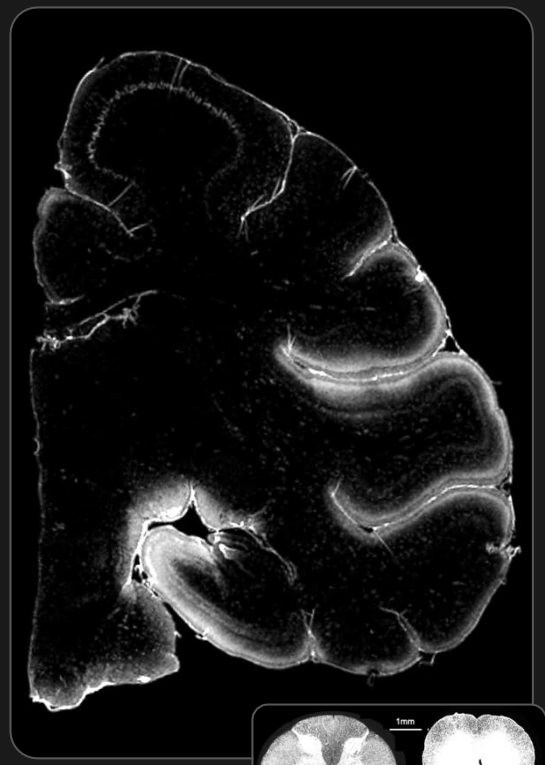
Key Characteristics

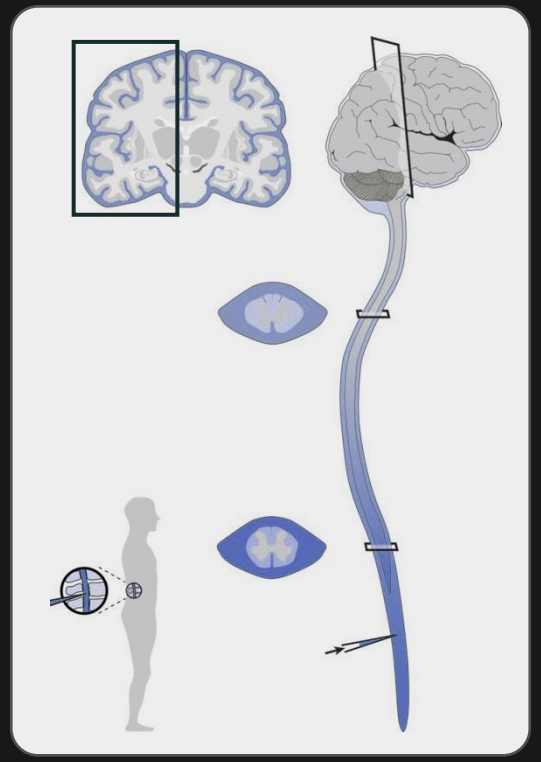
- TfR engagement optimized to maximize CNS uptake & biodistribution of oligo
- Biologic and oligo portion of molecule are engineered to improve exposure and safety
- Design principles can be readily applied to additional OTV programs

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

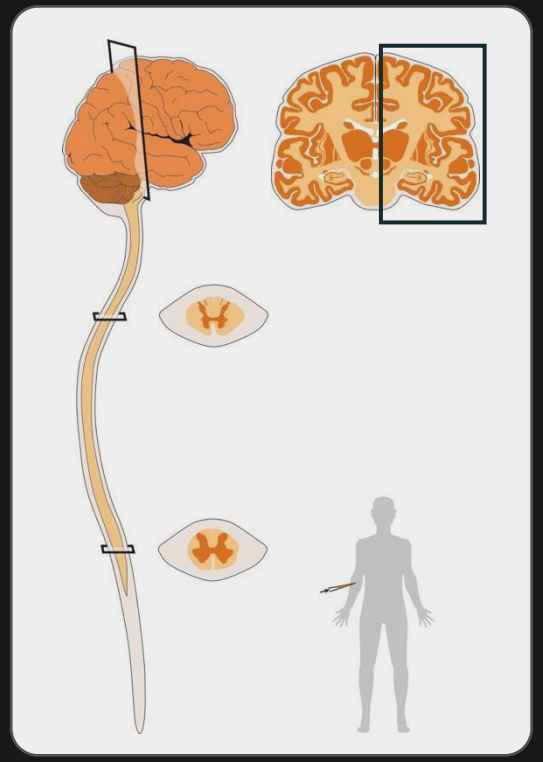
OTV Enhances Biodistribution of ASO Evenly Across Brain Regions

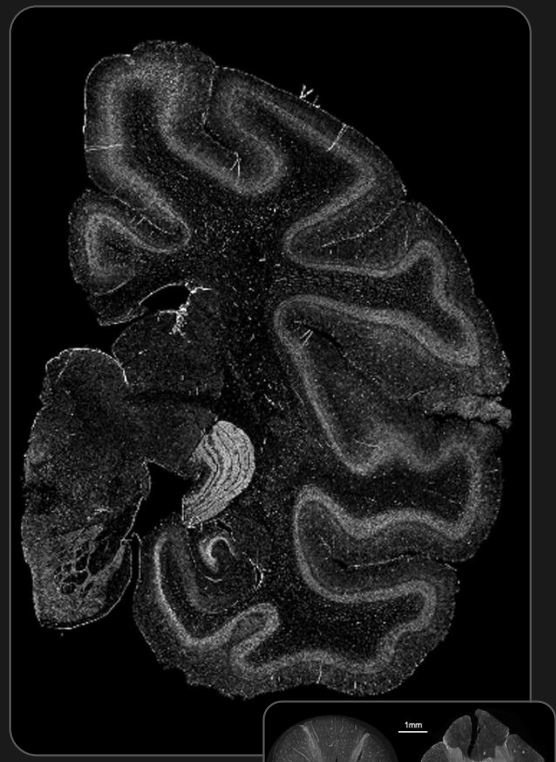
Limited biodistribution with intrathecal ASO





Widespread biodistribution with intravenous OTV:ASO

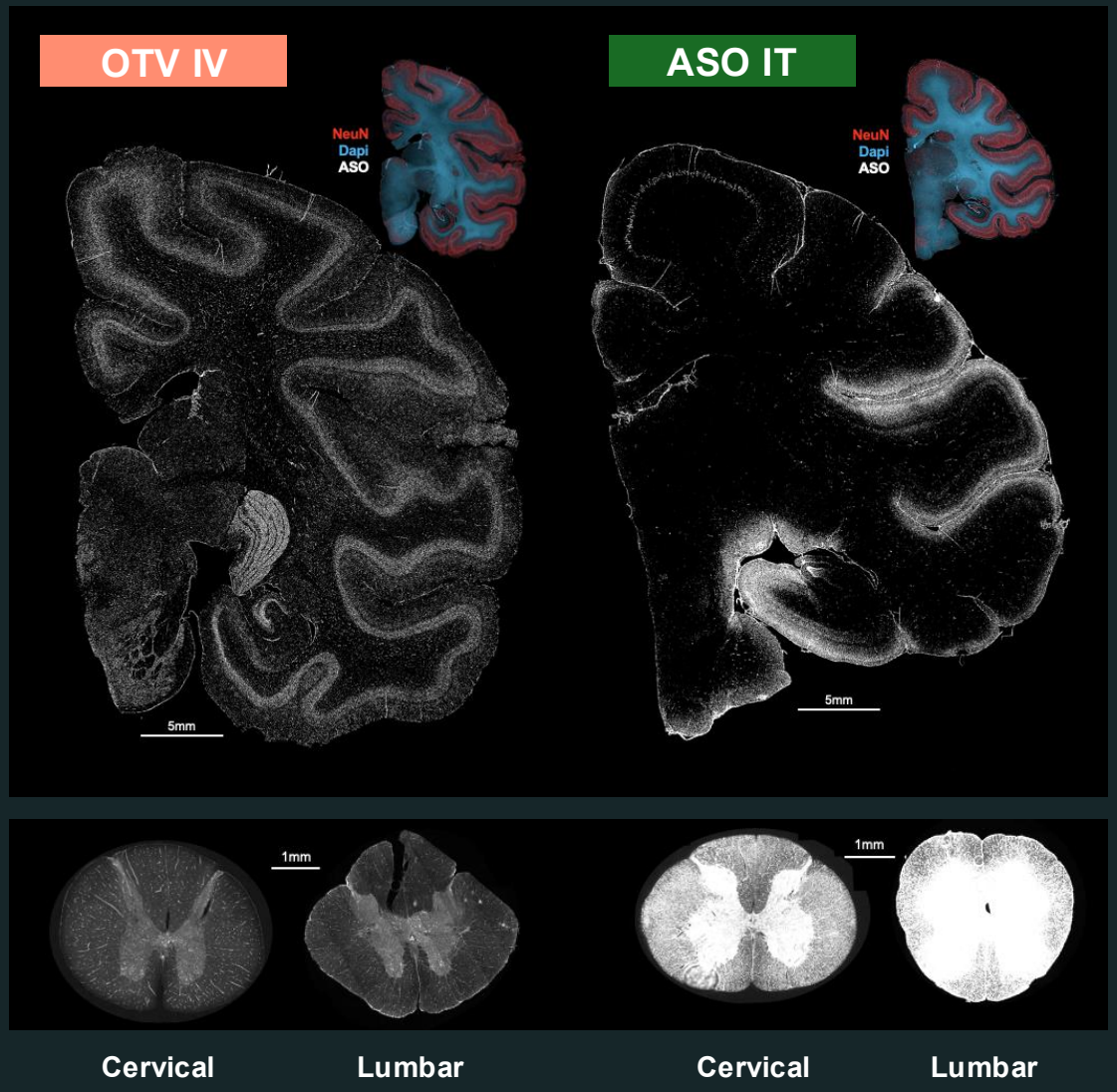




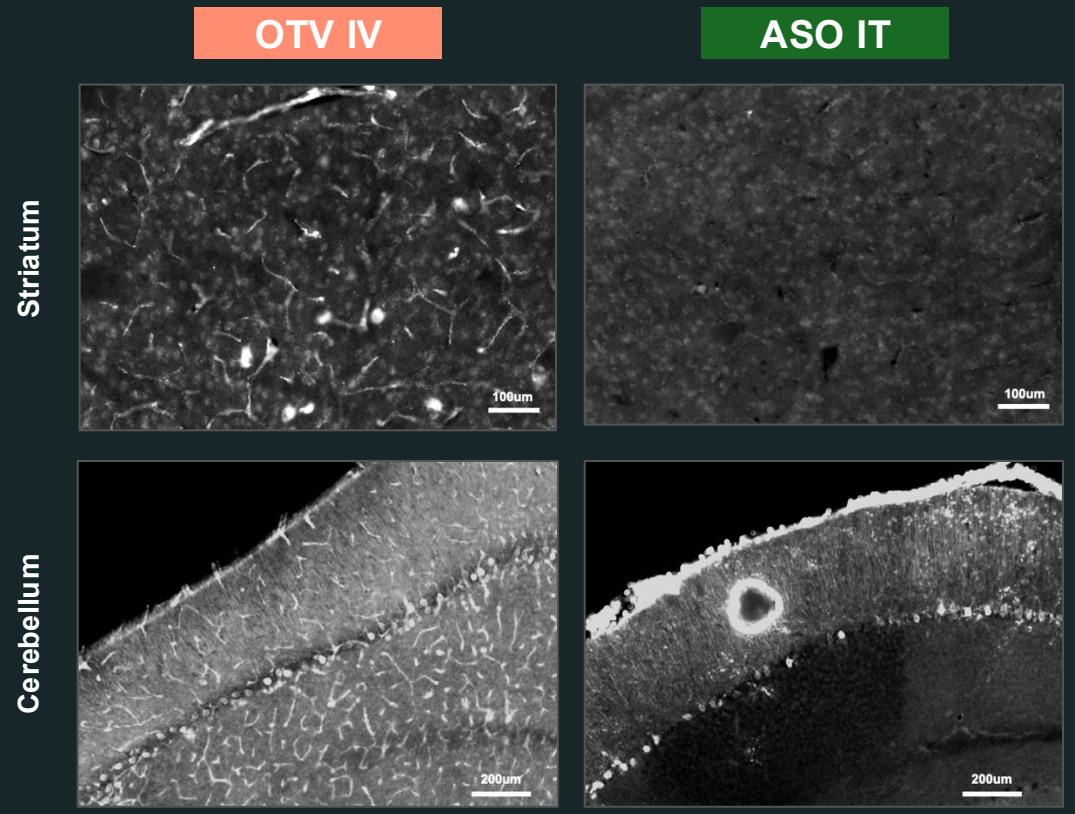
ASO Immunofluorescence hemibrain coronal section

Adapted from Barker et al. *Science Translational Medicine* 2024

OTV Eliminates Sharp ASO Gradient that Results from IT Dosing



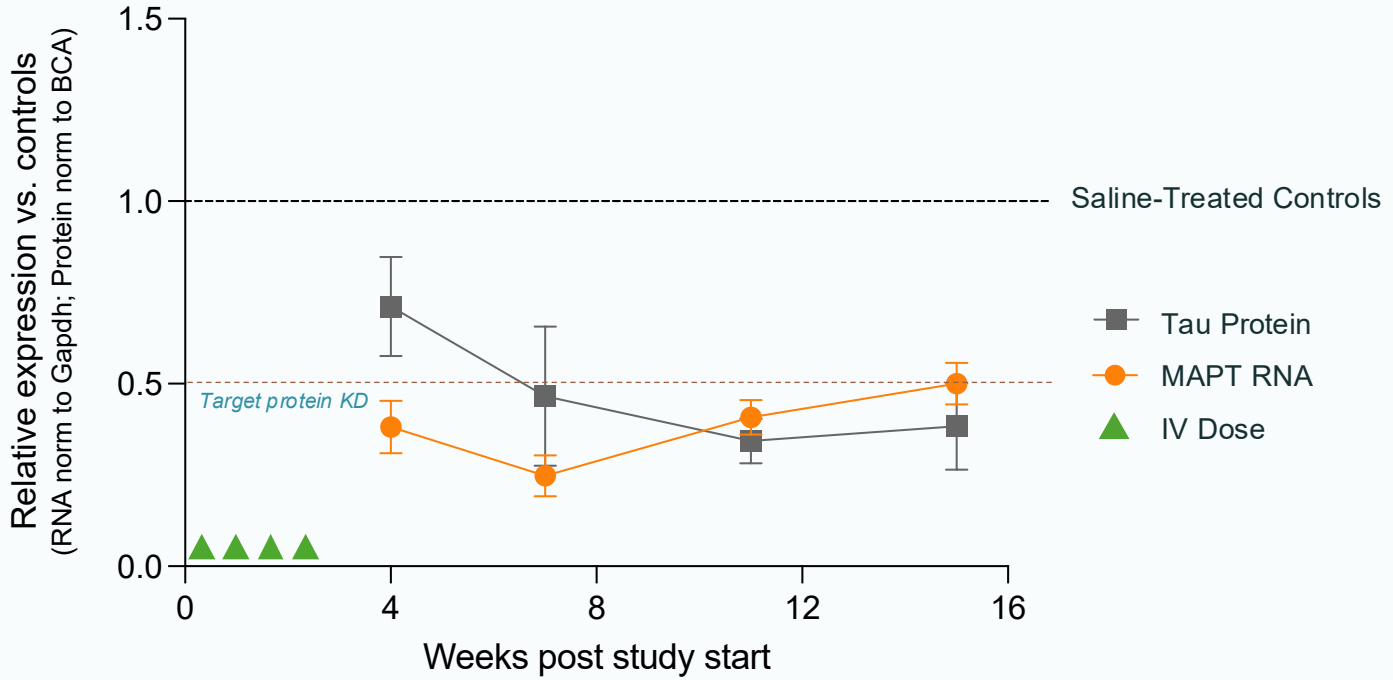
Enhanced ASO Deposition in Brain Regions that are Challenging to Target



Barker et al., *STM*, 2024

DNL628 Displays Robust and Sustained Knockdown in Mice Expressing Human Tau

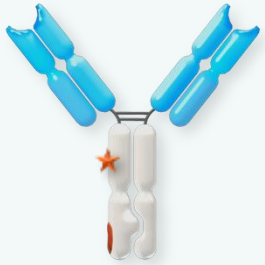
Brain MAPT RNA and Tau Protein Knockdown (KD) Persists for >12 Weeks After Dosing



Robust and sustained reduction in tau protein with DNL628

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

Initial Clinical Data from Both AD Programs Expected in 2027



DNL921 Phase 1/1b Clinical Study

Phase 1/1b → **Phase 3**

Study Population

SAD: Healthy Volunteers

MAD: Patients with biomarker confirmed Alzheimer's disease

Study Plan

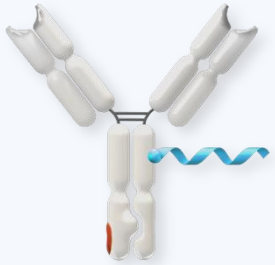
- SAD
- MAD Cohort A
- MAD Cohort B
- MAD Cohort C

Goals & Objectives

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

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

- Phase 1/1b study is ongoing
- Safety and clinical proof-of-concept data in 2027



DNL628 Phase 1b Clinical Study

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 study ongoing
- Clinical biomarker data expected in 1H 2027

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	• Data confirmed robust target engagement; study 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

Biomarker data from Phase2a BEACON study in LRRK2-PD expected in 1H 2027

Financial Update

Our Broad Therapeutic Portfolio

Lysosomal Storage Disorders

Molecule	Indication	Stage
tividenofusp alfa-eknm (ETV:IDS)	MPS II	FDA Approved Phase 2/3
zafinofusp alfa (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	Phase 1/1b
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

Capital to Execute

Strong Financial Foundation

$940M

Cash and investments as of Q2 2026

$195M PRV Sale

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

Near-term revenues

Launch of AVLAYAH™ and potential launch of DNL126 in 2027

Key Capital Allocation Priorities

Invest Strategically

- Successful launches of AVLAYAH™ and potentially zafinofusp alfa
- 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
- Drive low COGS and high margins from in-house manufacturing and commercial synergies

Maintain Capital Optionality

- Partnerships remain core to strategy
- Diversifying sources of capital

PRV – Priority Review Voucher

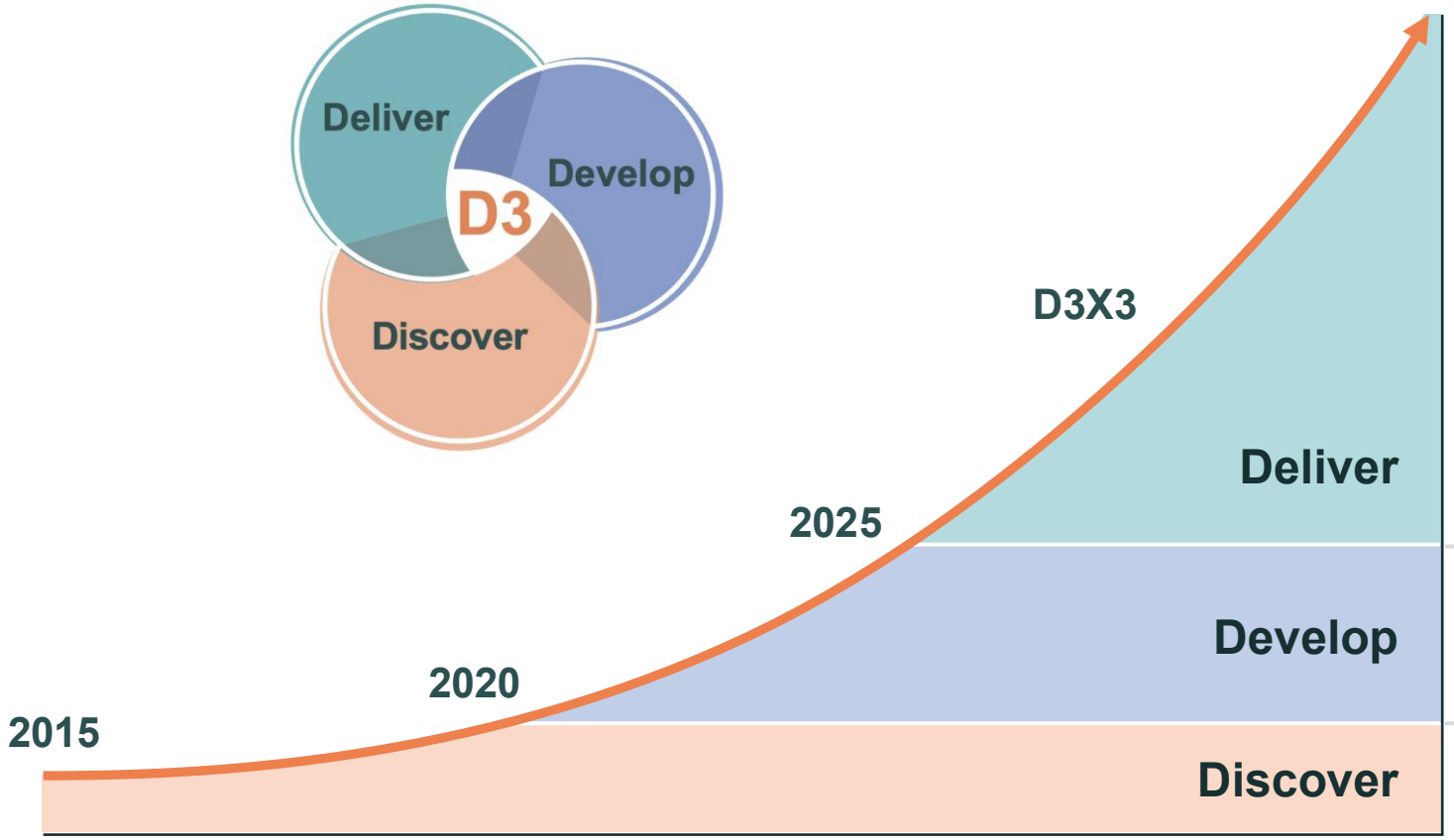
Q2 2026 Financial Summary

$ in millions	Three Months Ended June 30, 2026	Three Months Ended June 30, 2025
AVLAYAH Net Product Revenue	$3.6	$–
Total Revenue	**3.6**	–
Cost of Goods Sold	0.1	–
R&D Expense	97.0	102.7
SG&A	36.3	32.3
Amortization of Intangible Asset	0.7	–
Total Operating Expense	**134.1**	**135.0**
Loss from Operations	(130.5)	(135.0)
Interest and other income, net	3.0	10.8
Net Loss	**(127.6)**	**(124.1)**

$940M in cash, cash equivalents and marketable securities as of June 30, 2026, excluding $195M gross proceeds from the PRV sale[1]

1. The transaction closed and proceeds were received in July 2026.

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