Tralesinidase Alfa Enzyme Replacement Therapy (TA-ERT) for the Treatment of Sanfilippo Syndrome Type B (MPS IIIB)

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Conference Call
April 15, 2025

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Spruce Bio: Global Neuro Biopharma Company

Tralesinidase Alfa Enzyme Replacement Therapy (TA-ERT) for MPS IIIB

BLA-Ready Program

Expected BLA Filing anticipated in 1H 2026

- U.S. FDA Alignment on HS-NRE[1] as Valid Surrogate for Accelerated Approval
- Potential PRV Eligibility Upon U.S. FDA Approval[2]
- First-to-Market Potential | IP Exclusivity to 2037 | Orphan Drug Designations in US + EU
- Measured Investment Required for Launch | Commercial Team of ~10
- Fatal pediatric neurodegenerative genetic disorder with no approved therapies

Precision Psychiatry Program

Topline data anticipated in 1H 2026

- Tildacerfont + Cortibon (Companion Diagnostic) for Major Depressive Disorder (MDD)
- Development partner (HMNC Brain Health) funding Phase 2 study
- Topline data anticipated in 1H 2026

Novel mAb Pipeline

- CRH Antagonist mAb for Congenital Adrenal Hyperplasia
- GLP-1R Antagonist mAb for Post-Bariatric Hypoglycemia

1. Heparan sulfate non-reducing end.
2. Contingent upon reauthorization of Rare Pediatric Disease PRV Program and U.S. FDA approval.

Program Overview

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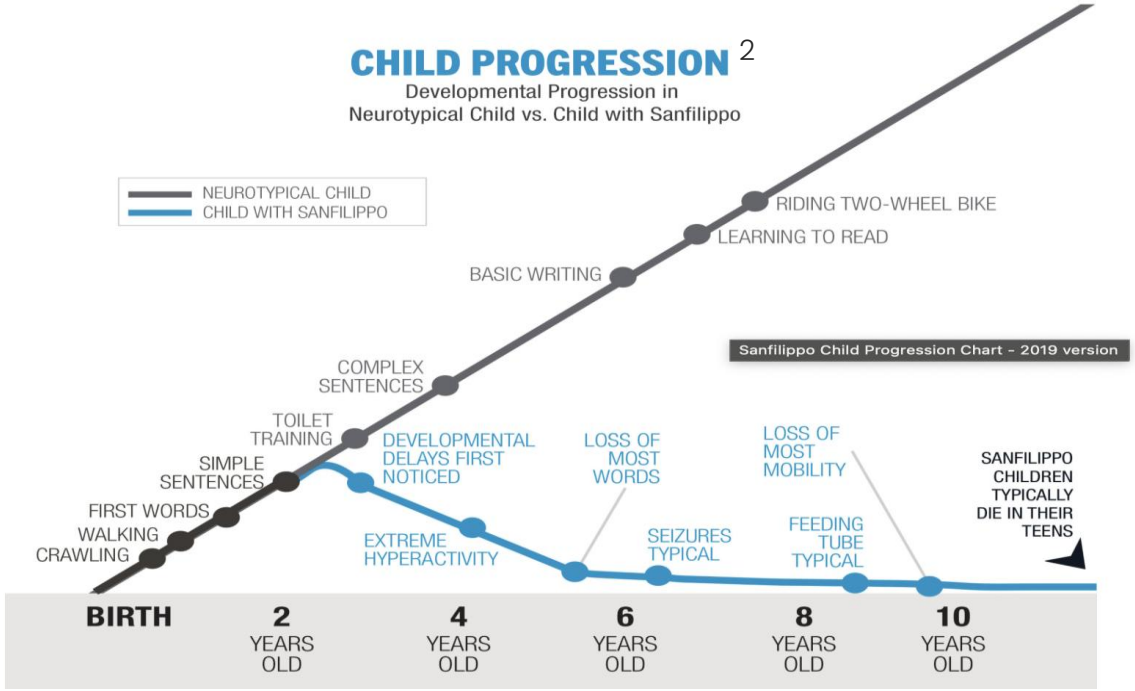
Mucopolysaccharidosis IIIB (MPS IIIB): Progressive Fatal Neurodegenerative Pediatric Disorder

- Autosomal recessive disorder affecting 1 in 200,000 newborns [1]
- A deficiency in alpha-N-acetylglucosaminidase (NAGLU) leads to lysosomal accumulation of Heparan Sulfate (HS)[2]
- HS buildup impairs neuronal development ultimately leading to neurodegeneration and death



Sources: 1. Disease modeling for Mucopolysaccharidosis type IIIB using patient derived induced pluripotent stem cells Huang et al. -Experimental Cell Research 2021; 2. https://curesanfilippofoundation.org

Well-Defined Regulatory Pathway to Approval for Tralesinidase Alfa

- HS-NRE is deemed to be a biomarker[1] reasonably likely to predict clinical benefit and serve as basis for accelerated approval (AA)
  - HS based AA in other MPS subtypes are being pursued (RARE,[2] DNLI[3], RGNX[4])

- Prior agreement with FDA on the tralesinidase program on:
  - Acceptability of HS based biomarker as the primary endpoint for BLA submission
  - The completed clinical and nonclinical studies are sufficient for BLA filing
  - The key design elements of a confirmatory trial (placebo-controlled 5-year study with a 2-year interim analysis in 14 patients) can be initiated prior to potential approval

- Potential Priority Review Voucher (PRV) eligibility upon approval[5]

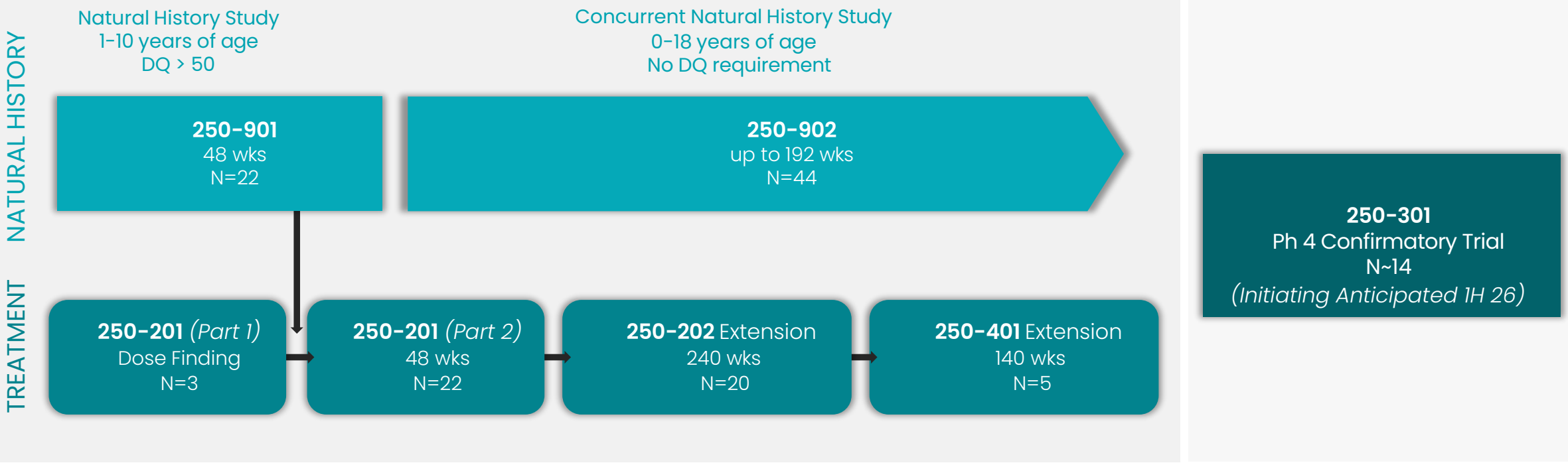
Sources: 1. Reagan-Udall Foundation Qualifying Biomarkers to Support Rare Disease Regulatory Pathways Workshop Feb 21, 2024; 2. Ultragenyx Pharmaceutical Inc. – Investor Relations https://ir.ultragenyx.com; 3. Denali Therapeutics Inc. – Investor Relations; https://investors.denalitherapeutics.com; 4. Regenxbio Inc. – Investor Relations https://www.regenxbio.com/investors; 5. Contingent upon reauthorization of Rare Pediatric Disease PRV Program.

Tralesinidase Alfa Anticipated Development Roadmap

No further clinical or non-clinical studies are required for BLA submission

COMPLETED STUDIES SUPPORTING A POTENTIAL ACCELERATED APPROVAL (AA[3])

PLANNED STUDY FOR FULL APPROVAL



Potential Accelerated Approval Based on Reduction in HS Biomarker[1, 2]

Confirmatory Trial Anticipated to Support Full Approval

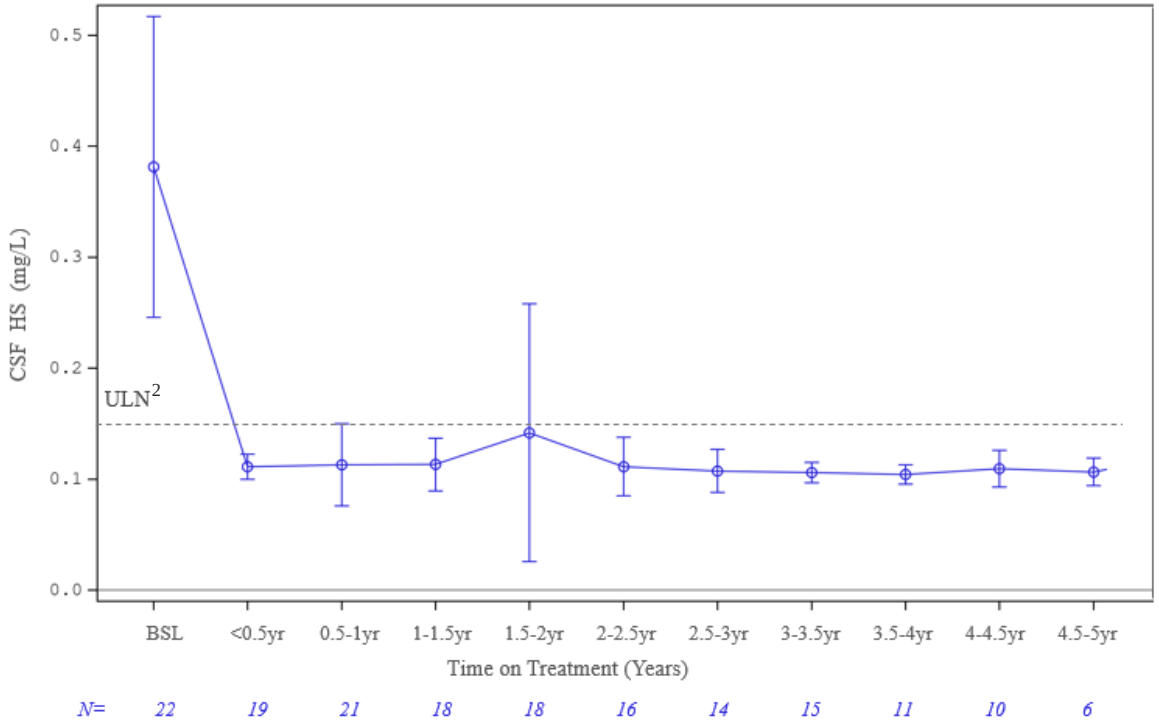
Sources: 1. Community consensus for Heparan sulfate as a biomarker to support accelerated approval in Neuronopathic Mucopolysaccharidoses Muenzer et al. -Molecular Genetics and Metabolism 2024 2. FDA Guidance to Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products 2019 3. Data from completed studies 250-201, 250-202 and 250-401 provide expected sufficient data for BLA filing in 2026.

Tralesinidase Alfa Was Shown to Significantly and Durably Normalize CSF HS and HS-NRE Levels

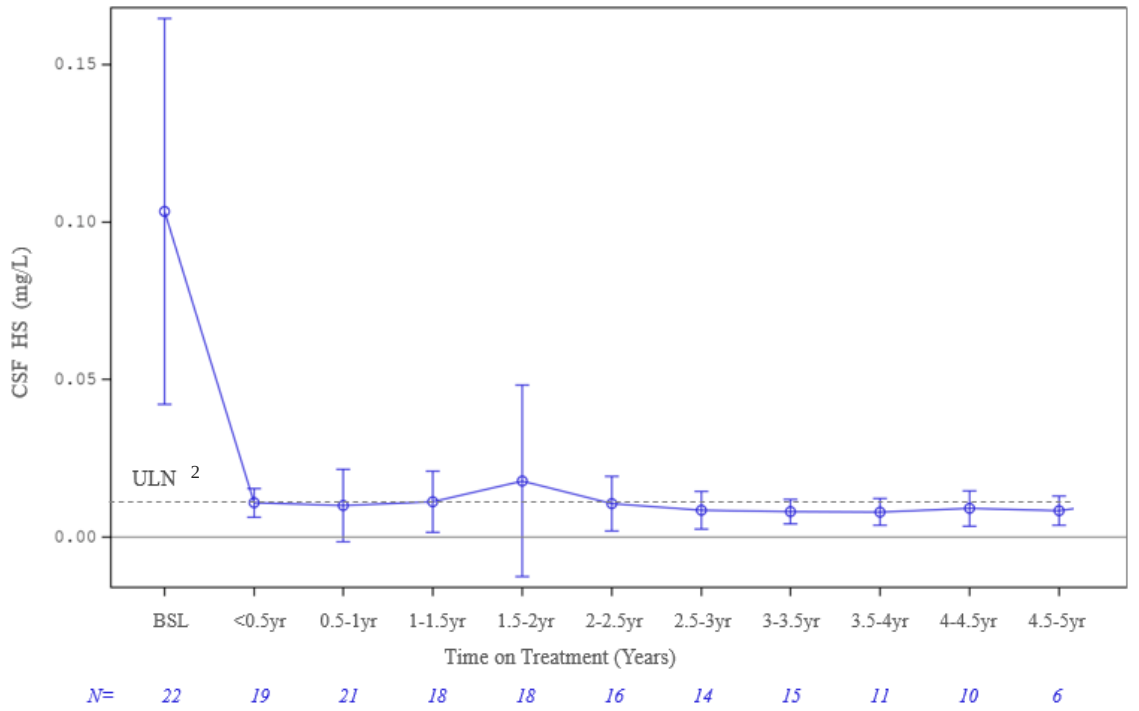
Normalization of pathogenic substrate in CSF is the goal of therapy

- Tralesinidase alfa is designed to target lysosomal delivery and correct NAGLU deficiency
- Tralesinidase alfa, 300 mg was ICV administered by a 10-minute infusion via an Ommaya reservoir weekly for 48 weeks and either weekly or every other week thereafter [2]

CSF HS Levels[1]



CSF HS-NRE Levels[1]

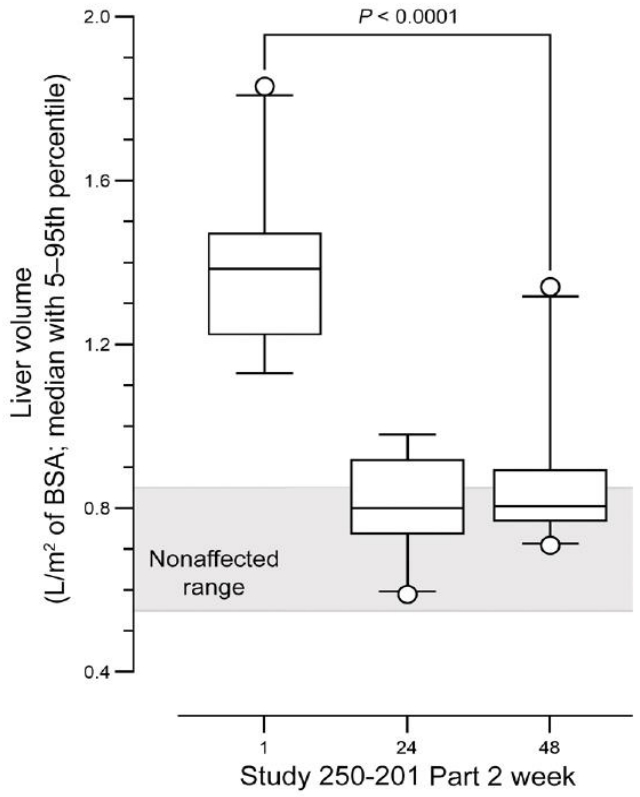


Sources: 1. Internal data on file; 2. J Clin Invest. 2023;133(2):e165076. https://www.jci.org/articles/view/165076

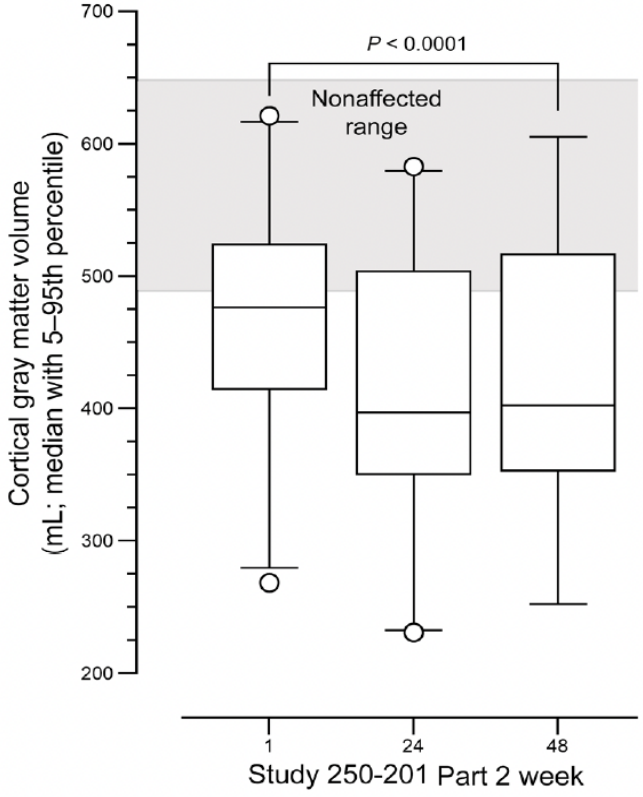
Tralesinidase Alfa Was Shown to Normalize Liver and Stabilize Cortical Grey Matter Volume

Reflective of tralesinidase alfa removal of HS deposits in target organs

Liver Volume [1]



Cortical Gray Matter Volume [1]



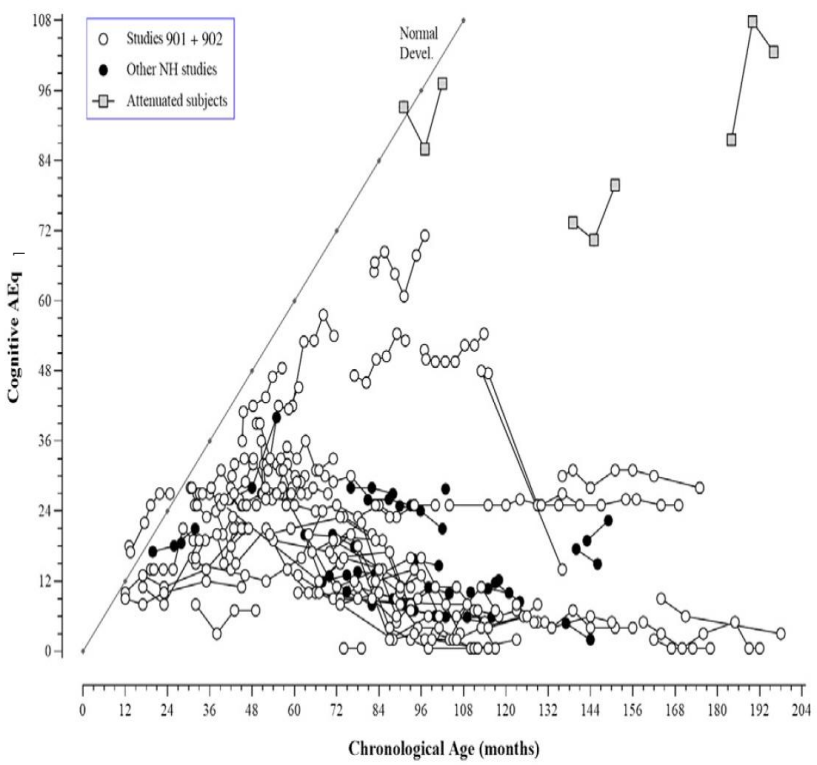
Tralesinidase alfa, 300 mg was ICV administered by a 10-minute infusion via an Ommaya reservoir weekly for 48 weeks

Source: 1. J Clin Invest. 2023;133(2):e165076. https://www.jci.org/articles/view/165076

Early Intervention with Tralesinidase Alfa Stabilizes Cognitive Decline in MPS IIIB

Alignment with U.S. FDA on Bayley's Cognition Raw Score as Primary Endpoint for Confirmatory Trial

Natural History:
Progressive Irreversible Cognitive Decline[2]



Bayley and Kaufman Assessments:
Most Benefit in Patients with Early Disease

	Early Disease	Late Disease
Baseline (N=22)	10	12
Stable Disease at Endpoint (%)	7/10 (70%)	3/12 (25%)

- *Tralesinidase alfa treatment was associated with stable cognitive function more frequently in patients with early disease, relative to patents with late disease*
  - Early and late disease groups based on baseline cognition score[3]
  - Disease stability: No meaningful loss of cognitive function[4] at endpoint evaluation

[1] Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) or the Kaufman Assessment Battery for Children, Second Edition (KABC-II) Cognition Age Equivalent Score (AEq); [2] J Pediatr. 2022 Oct;249:50-58.e2.; [3] Cognition BSID-III/KABC-11 AEq >40 months or Cognitive Disease Quotient>75 = early stage; [3] BSID-III/KABC-11 cognition AEq ≥6 change from baseline defined as stable disease ;[4] Data on file

Tralesinidase Alfa – Safety Profile and Immunogenicity[1]

- 22 patients enrolled in the 48-week initial study and extension studies lasting up to 6 years
- ~6,000 total infusions have been delivered in the 48-week initial study and its extensions
- Tralesinidase alfa was generally well tolerated with no discontinuations due to drug or device related adverse events and no deaths occurred in the study [1]
- Device-related adverse events occurred at 0.02 per infusion with serious adverse events occurring; at 0.01 per infusion [1]
- Hypersensitivity related adverse events reported at <0.01 per infusion and none were severe [1]
- Anti-drug and neutralizing antibodies occurred but did not affect CSF tralesinidase or CSF HS levels[2]

Source: [1] Internal data on file from 250-201 clinical study report; [2] J Pediatr. 2022 Oct;249:50-58.e2.

Financials and Commercial

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Financial Snapshot

Capital Structure and Summary Financials as of December 31, 2024

Capital Structure	Shares (M)
Common Shares Outstanding	42.2
Equity Awards Issued and Outstanding[1]	5.8
Common Stock Warrants[2]	12.7
Fully Diluted Shares Outstanding	60.7

Cash and Debt	000's
Cash & Cash Equivalents	$38,753
Debt[3]	$1,757

TA-ERT Exclusive Worldwide License Terms with BioMarin Pharmaceutical, Inc.

Term	
Milestones[4]	$125,500,000
Royalties on Worldwide Net Sales[5]	High-single digit to low-teens

1. Includes 3.5 million common stock options issued and outstanding, with a weighted-average exercise price of $3.27 per share, and 2.2 million restricted stock units outstanding (summation rounds up to 5.8 million equity awards issued and outstanding).
2. Common stock warrants issued in February 2023 in connection with private placement financing; 5-year term with strike price of $3.96 per share.
3. Term loan, gross balance as of December 31, 2024.
4. Up to $122.5 million in total milestones, including up to $25.5 million due upon the achievement of certain development and regulatory milestones and up to $100 million due upon the achievement of certain sales milestones.
5. Subject to the applicable royalty term and certain customary reductions and floors.

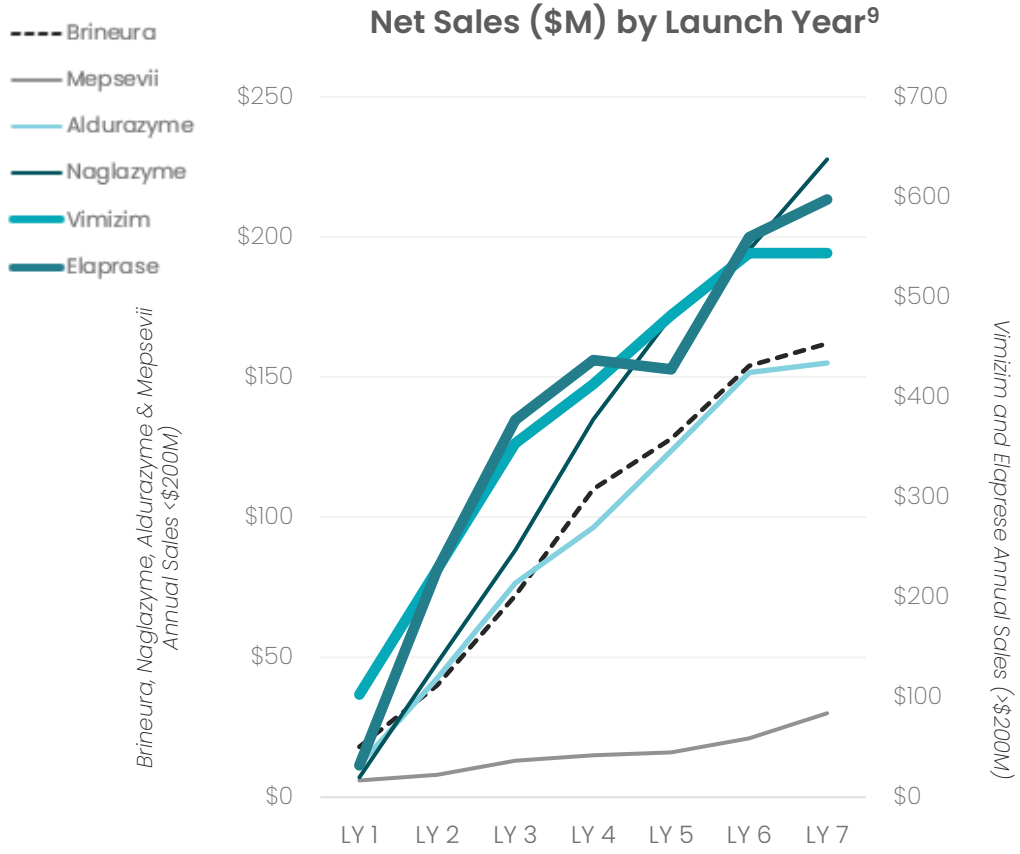
Market Benchmark: Enzyme Replacement in MPS Driving Robust Growth

Year-Over-Year Growth Reflective of Improved Diagnosis and Awareness Post-Launch

- **Consistent Growth Trajectories:** Patient-centric commercial strategy linking awareness, diagnosis, and reimbursement using a small field team has generated multiple high-value markets
- **Small patient numbers results in low overall payer burden:** Multiple approved MPS ERTs confirm long-term potential
- **Premium Pricing & Reimbursement:** High unmet need and measurable clinical benefit support favorable payer coverage and sustainable pricing models

Product	Indication[1]	Approval[1]	Incidence[2]	Annual Cost	2024 Annual Worldwide Net Sales
Brineura®	CLN2	2017	0.5 in 100K	$400–$500K[4]	$169M[5]
Vimizim®	MPS IVA	2014	1 in 200K	$450–$600K[3]	$740M[5]
Mepsevii®	MPS VII	2017	1 in 1M	$400–$600K[3]	$30M[6]
Aldurazyme®	MPS I	2003	1 in 100K	$200–$250K[3]	$311M[7]
Elaprase®	MPS II	2006	1 in 160K (males)*	$300–$400K[3]	$635M[8]
Naglazyme®	MPS VI	2005	1 in 250-600K	$400–$500K[3]	$480M[5]

**MPS II (Hunter Syndrome) exclusively affects males*



YoY sales trajectories MPS therapies, highlight earlier diagnosis and improved awareness contribute to strong market uptake.

Sources: 1. Approval Dates & Indications: U.S. Food and Drug Administration (FDA), *Drugs@FDA* Database (www.fda.gov); 2. National Organization for Rare Disorders (NORD); Christina L. Grant, Jaime López-Valdez, Deborah Marsden, Fatih Ezgü, Mucopolysaccharidosis type VII (Sly syndrome) - What do we know?, Molecular Genetics and Metabolism, Volume 141, Issue 3, 2024, 108145, ISSN 1096-7192,; 3. https://doi.org/10.1016/j.bbmt.2019.02.012; 4. https://www.fiercepharma.com/pharma/biomarin-picks-up-fda-approval-for-orphan-drug-brineura 5. Biomarin Pharmaceutical, Inc. 2024 Annual Report on Form 10-K (page 5); Evaluate Pharma; 6. Ultragenyx, Inc. 2024 Annual Report on Form 10-K (page 75); 7. https://www.sanofi.com/assets/dotcom/pressreleases/2025/2025-01-30-06-30-00-3017713-en.pdf; converted from 297 million EUR to $311 million as of 12/31/24; 8. Takeda Pharmaceutical Company Limited FY2024 Annual Securities Report; 91.6 Billion JPY converted to $635M as of 3/31/24; 9. Evaluate Pharma Uptake Reports (by product).

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