



Redefining the Course of Neurodegenerative Conditions

Corporate Presentation

January 2026



Forward-Looking Statement

This presentation includes “forward-looking statements” within the meaning of, and made pursuant to the safe harbor provisions of, the Private Securities Litigation Reform Act of 1995, including, but not limited to: our expectations about timing and execution of anticipated milestones, including the progress of clinical studies and the availability of clinical data from such trials; timing of feedback from regulatory authorities; the potential of our product candidates versus other treatment options and clinical candidates; our expectations about cash runway; the ability of PBFT02 to treat FTD-*GRN* or FTD-*C9orf72*, and the potential development of other product candidates. These forward-looking statements may be accompanied by such words as “aim,” “anticipate,” “believe,” “could,” “estimate,” “expect,” “forecast,” “goal,” “intend,” “may,” “might,” “plan,” “potential,” “possible,” “will,” “would,” and other words and terms of similar meaning. These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including: our ability to develop and obtain regulatory approval for our product candidates; the timing and results of preclinical studies and clinical trials; risks associated with clinical trials, including our ability to adequately manage clinical activities, unexpected concerns that may arise from additional data or analysis obtained during clinical trials, the timing of and our ability to obtain and maintain regulatory approvals; our expectations about the willingness of healthcare professionals to use our product candidates, the timing, or amount, the occurrence of adverse safety events; the risk that positive results in a preclinical study or clinical trial may not be replicated in subsequent trials or success in early stage clinical trials may not be predictive of results in later stage clinical trials; failure to protect and enforce our intellectual property, and other proprietary rights; our dependence on collaborators and other third parties for the development and manufacture of product candidates and other aspects of our business, which are outside of our full control; the timing, or amount, of receipt of any potential future milestone and royalty payments; risks associated with current and potential delays, work stoppages, or supply chain disruptions; and the other risks and uncertainties that are described in the Risk Factors section in documents the company files from time to time with the Securities and Exchange Commission (SEC), and other reports as filed with the SEC. Passage Bio undertakes no obligation to publicly update any forward-looking statement, whether written or oral, that may be made from time to time, whether as a result of new information, future developments or otherwise.



Redefining the Course of Neurodegenerative Conditions



**Advancing clinical stage,
potential best-in-class, one-
time progranulin raising gene
therapy for FTD**



**Pursuing preclinical
development of differentiated
gene therapy approach in
Huntington's disease**



**Cash runway expected
into 1Q 2027***

* Based on cash, cash equivalents, and marketable securities as of December 31, 2025.

Validating the Therapeutic Potential of PBFT02

Urgent Patient Need in FTD-GRN

Genetic form of FTD
caused by *GRN* mutations,
which lead to progranulin
(PGRN) deficiency

No approved
disease-modifying
therapies

>>> Fast Track and
Orphan Drug Designation >>>

upl_{ix}FT-D

Promising data from initial clinical
study of PBFT02 in FTD-GRN

Differentiated, Potential Best-in-Class Profile

One-time, gene
replacement therapy

Proprietary
AAV1 construct

Nonsurgical injection
directly to cerebrospinal
fluid (CSF)

Durable, elevated CSF
PGRN levels*

* Based on interim data.

Significant Market Opportunity Addressing Neurodegenerative Diseases

Estimated Prevalence (US and EU)

CURRENT
CLINICAL
PROGRAM

~18K

FTD-GRN¹⁻³

CURRENT
CLINICAL
PROGRAM

~21K

FTD-C9orf72²⁻⁴

CURRENT
PRECLINICAL
PROGRAM

~70K

Huntington's disease⁵

1. Greaves CV, et al. *J Neurol* 2019; 266:2075-2086. 2. Galvin JE, et al. *Neurology* 2017; 89:2049-2056. 3. Onyike CU, et al. *Int Rev Psychiatry* 2013; 25:130-137.
4. Moore KM, et al. *Lancet Neurol* 2020; 19: 145-156. 5. Crowell et al. *Neuroepi*. 2021; 55:361-368.



PBFT02

Frontotemporal Dementia

Frontotemporal Dementia (FTD): A Devastating Adult Disease

OVERVIEW

- Fatal adult-onset neurodegenerative disease affecting the frontal and temporal lobes of the brain, characterized by a decline in behavior, language, and executive function
- One of the most common causes of early-onset dementia worldwide, disproportionately affecting individuals aged 40–65 years

CLINICAL SYMPTOMS

Disease progression is rapid and degenerative, including loss of speech, loss of expression, behavioral changes, and immobility



Loss of
inhibition



Apathy



Social
withdrawal



Hyperorality
(mouthing of objects)

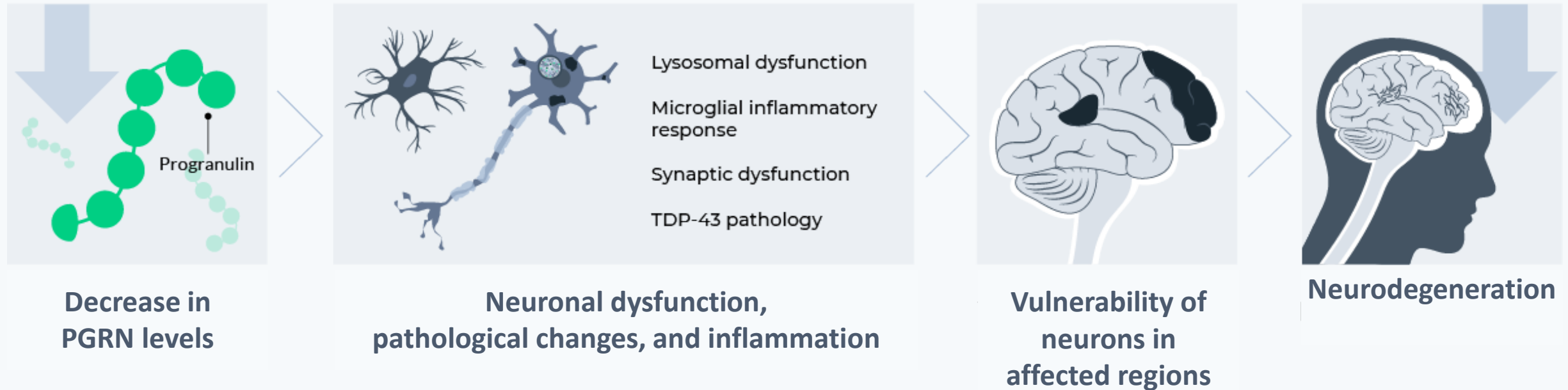


Ritualistic compulsive
behaviors

**On average,
people with
FTD live 8 years
after the onset
of symptoms**

Progranulin Deficiency is the Defining Characteristic of FTD-*GRN* and Leads to Neurodegeneration

Progranulin is critical to maintaining CNS cell homeostasis



Elevated PGRN Increases Potential for Improved Cellular Function

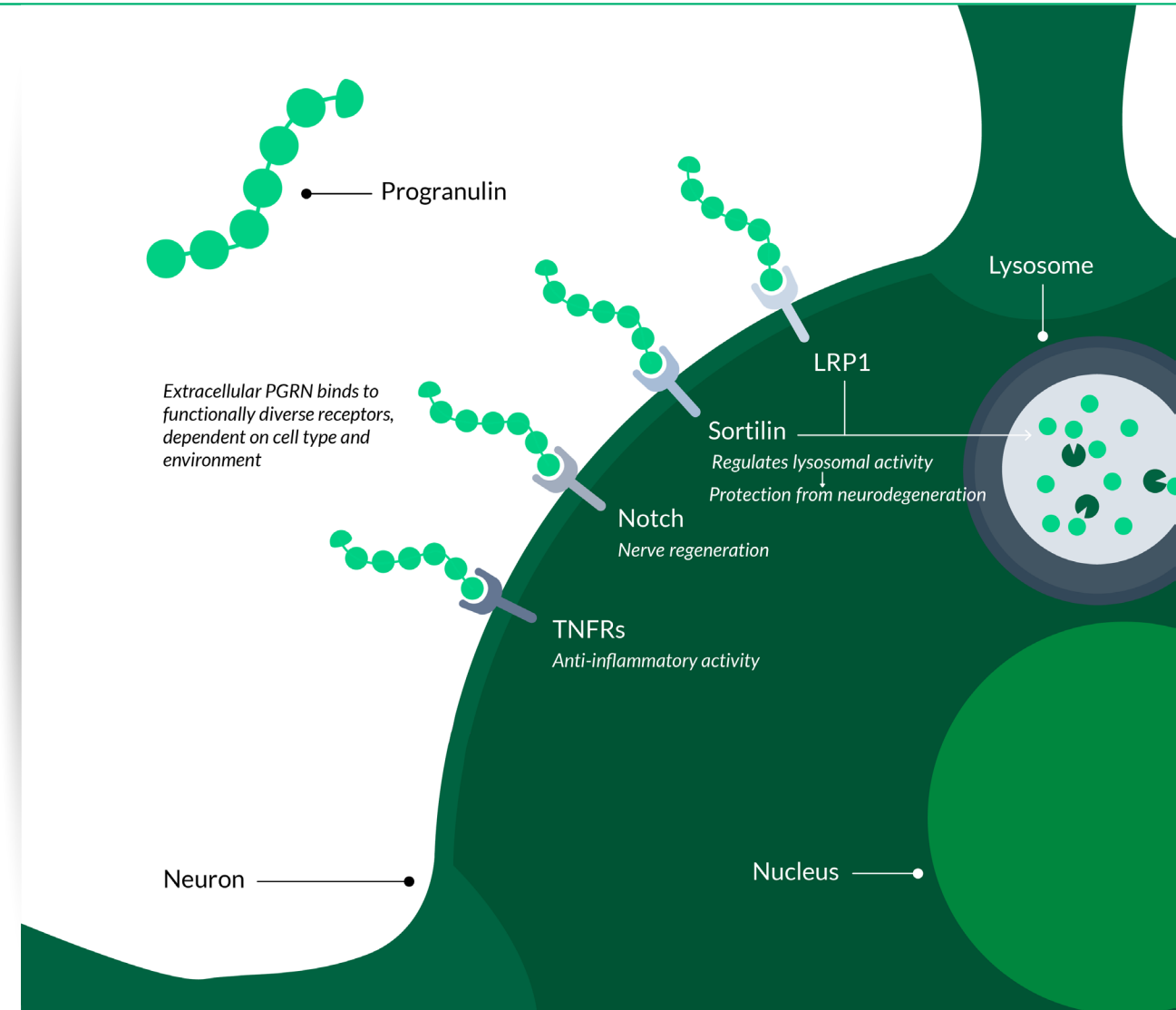
Progranulin is a secreted protein that binds to cell membrane receptors to affect multiple intracellular pathways

- Major role is regulating intracellular lysosomal activity
- Extracellular PGRN is endocytosed via multiple receptors

Driving elevated PGRN levels in the extracellular space increases the amount of PGRN available to enter target CNS cells

Able to leverage cross-correction mechanism: secreted PGRN can be taken up by non-transduced cells

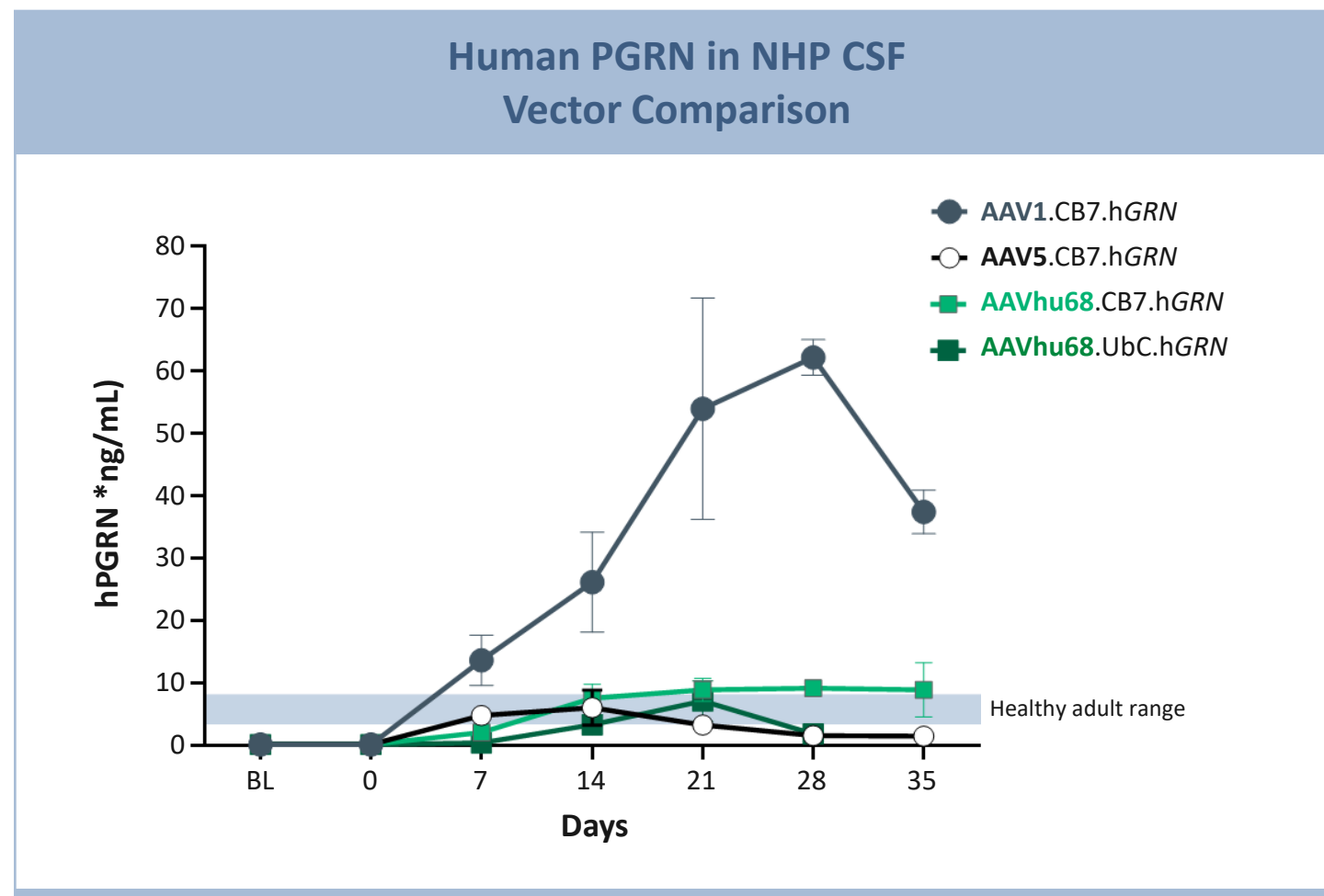
Paushter et al. *Acta Neuropathol.* 2018;136:1-17. Rhinn et al. *Trends Pharmacol Sci.* 2022; 43:641-652.



Preclinical NHP: AAV1 Achieved the Highest Levels of CSF PGRN

After ICM administration to NHPs:

- AAV1 capsid resulted in CSF hPGRN levels 5x higher than AAVhu68 (an AAV9 variant)
- Superior hPGRN response led to selection of AAV1 capsid for PBFT02



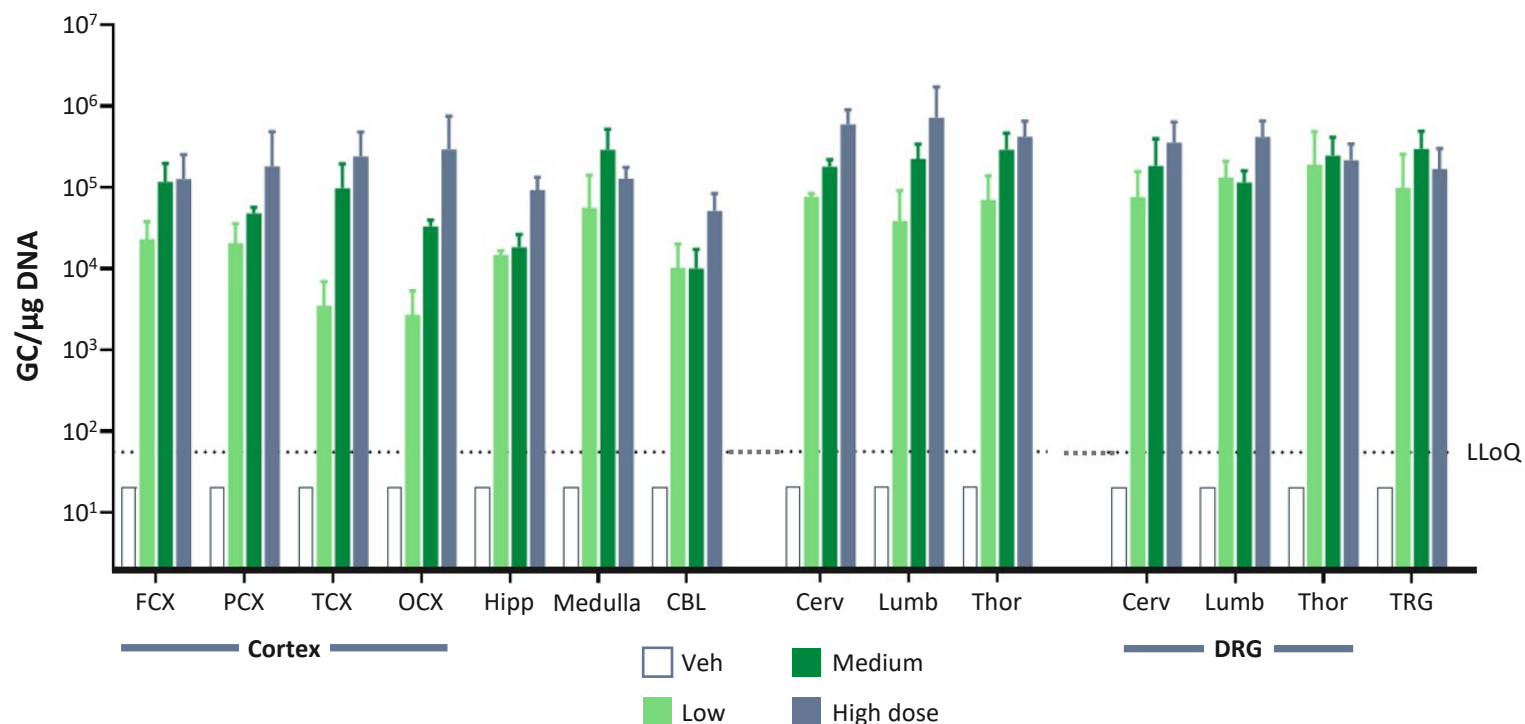
Rhesus macaques (n=2/gp) ICM-delivered AAV.hPGRN (3.3×10^{11} GC/g brain), day 0

*Size and duration of elevation muted by immune response to human PGRN. Shading: Healthy adult sample range for CSF PGRN, n = 61 (Passage Bio data)

CSF, cerebrospinal fluid; GC, genome copies; ICM, intra-cisterna magna; NHP, non-human primate. Reference: Hinderer et al., *Ann Clin Trans Neurol.* 2020; 7:1843-1853.

Preclinical NHP: ICM Administration of PBFT02 Led to Broad Distribution of Vector Throughout Brain/Spinal Cord

Vector Biodistribution in NHPs 90 Days Post-ICM PBFT02



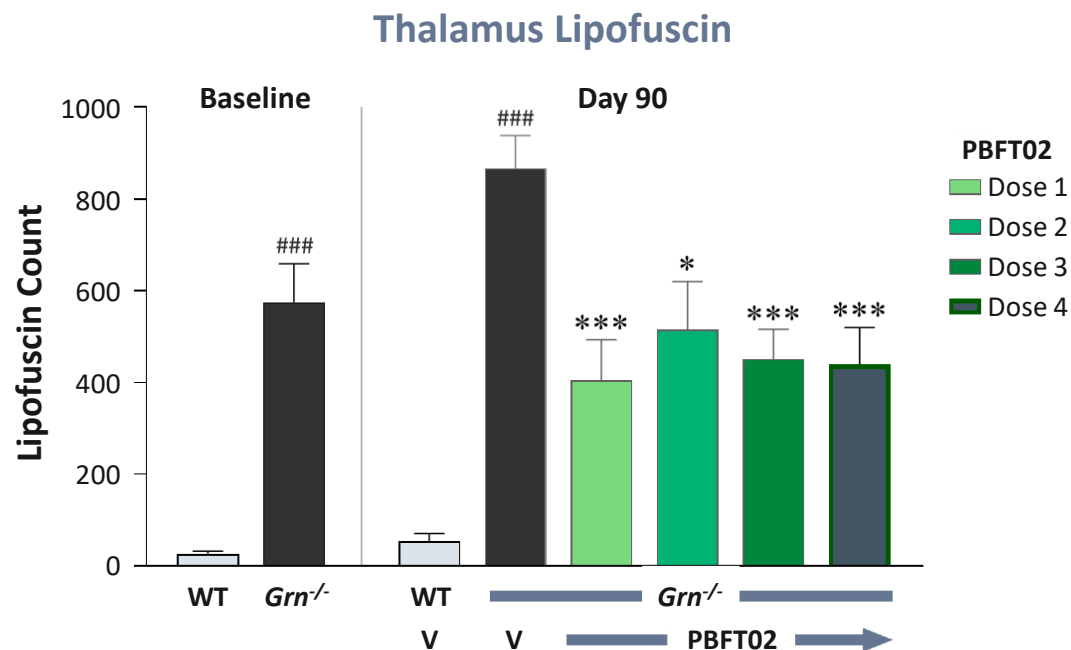
- Robust, dose-dependent vector delivery to cortical and sub-cortical brain regions affected in FTD
- NHP low dose, equivalent to clinical Dose 1 of PBFT02 in upliFT-D study, resulted in ~10⁴ GC/μg DNA in all sampled areas throughout the brain

n=3/gp. Data are mean +/- SEM.

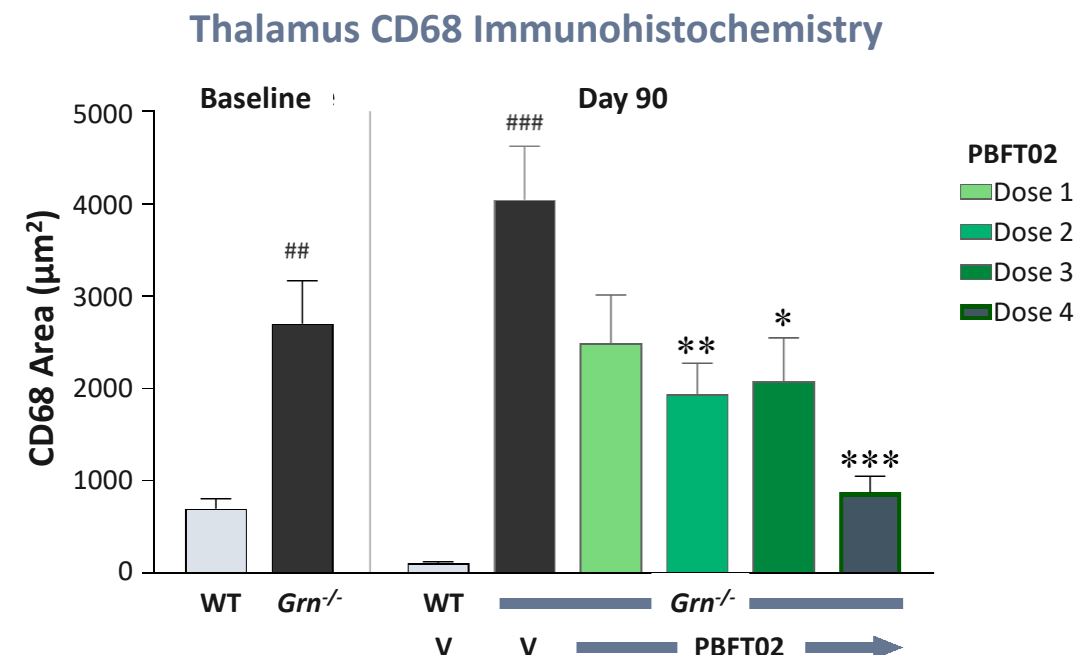
CBL, cerebellum; Cerv, cervical; DRG, dorsal root ganglion; FCX, frontal cortex; GC, genome copies; Hipp, hippocampus; ICM, intra-cisterna magna; LLoQ, lower limit of quantitation; Lumb, lumbar; OCX, occipital cortex; PCX, parietal cortex; TCX, temporal cortex; Thor, thoracic; TRG, trigeminal root ganglion; Veh, vehicle

Preclinical Grn^{-/-} Mice: Expression of hPGRN Improved Lysosomal Dysfunction and Neuroinflammation in the Brain

PBFT02 Reduced Lipofuscin Deposition at All Doses, Suggesting Improved Lysosomal Dysfunction



Dose-Dependent Elevations in CSF PGRN after PBFT02 Led to Progressive Reductions in Microglial Activation



Greatest pathological benefit was associated with the highest PGRN levels in the CSF

Lipofuscin deposition and microglial activation are hallmark pathologies seen in FTD; Improvements in both measures were seen in cerebral cortex, thalamus, and hippocampus after PBFT02 administration

Grn^{-/-} and WT mice (n=14-15/gp) ICV-administered PBFT02 or vehicle (V). Baseline controls were untreated mice on Day 1. Bars: mean +/- SEM.

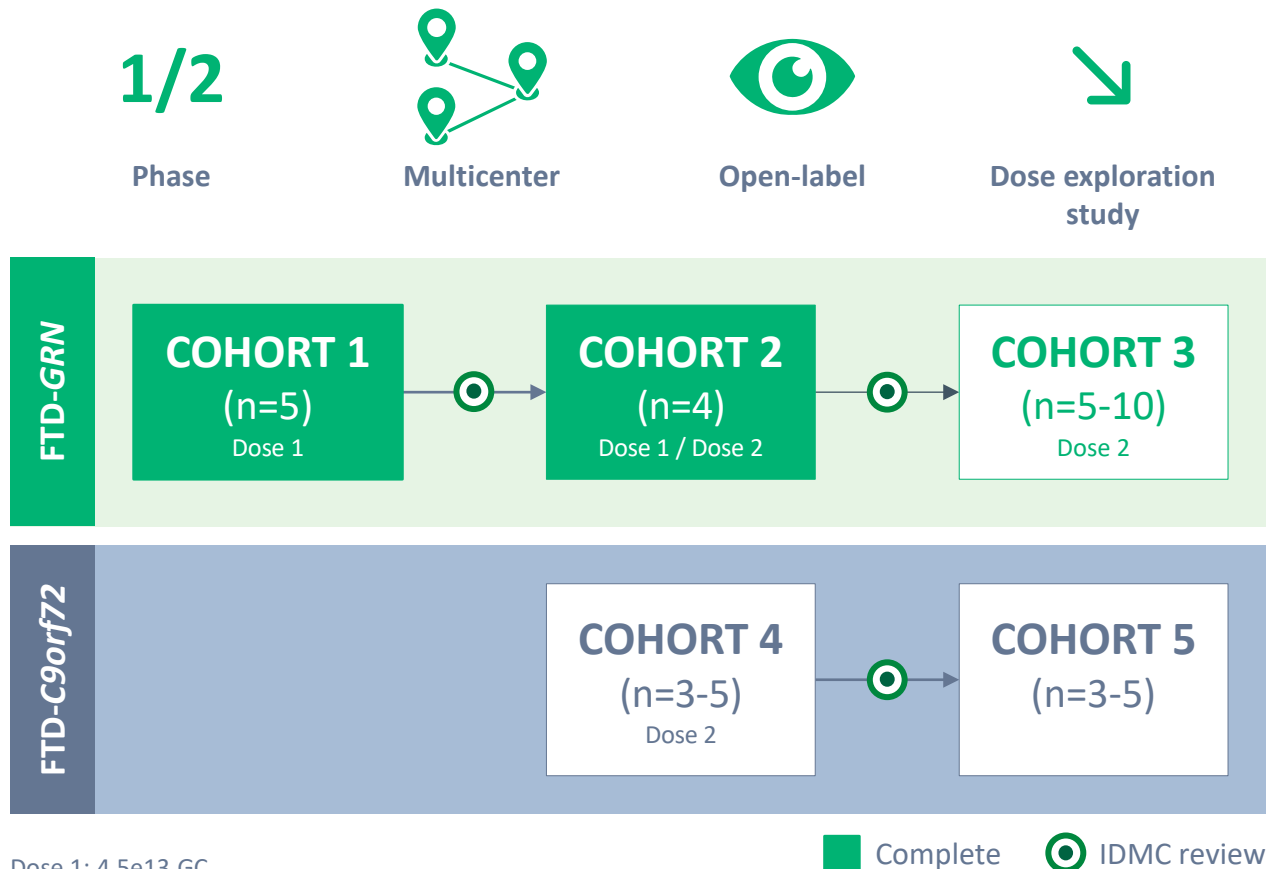
$p < 0.01$, ### $p < 0.005$ vs WT control; * $p < 0.05$, *** $p < 0.005$ vs Grn^{-/-} + V, one-way ANOVA followed by Tukey's multiple comparisons test.

Grn, granulin gene; ICV, Intra-cerebroventricular; PGRN, progranulin; WT, wildtype

upliFT-D: Global Phase 1/2 Trial with PBFT02

Currently enrolling patients in Cohort 3 and Cohort 4

TRIAL DESIGN



Dose 1: 4.5e13 GC
Dose 2: 2.2e13 GC

DURATION

2 years; with additional 3 years of follow-up for safety and durability of effect

PRIMARY ENDPOINTS

Safety and tolerability

SECONDARY ENDPOINTS

Biomarkers

- Progranulin (CSF, plasma)
- vMRI
- Retinal nerve fiber layer and retinal lipofuscin deposits via OCT
- NfL (CSF, plasma)

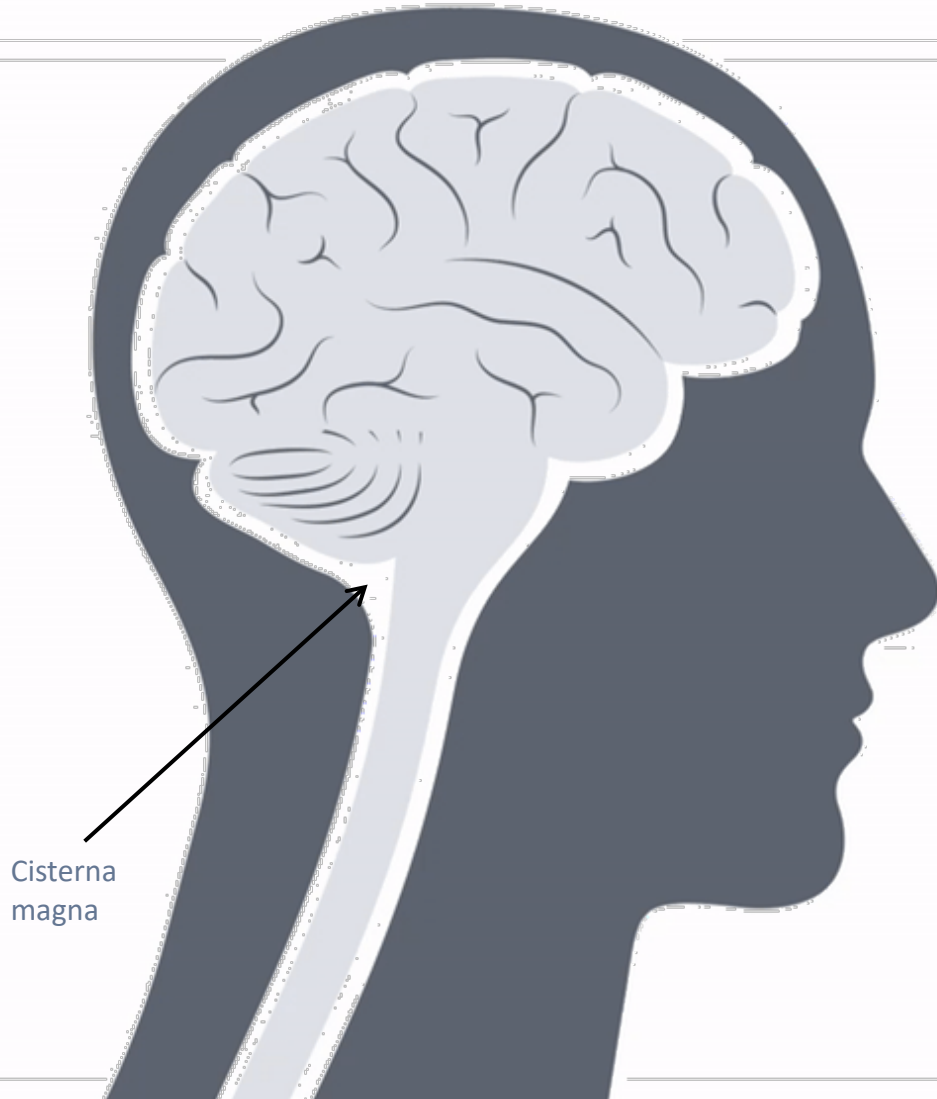
Clinical

- CDR + NACC FTLD sum of boxes

EXPLORATORY BIOMARKERS

- Cathepsin D (CSF)
- GFAP (CSF, plasma)
- LAMP 1 (CSF)
- Lys-GL1 (CSF)

Intra-Cisterna Magna (ICM) Administration



Directly deliver vector into the CSF via a single injection

- Allows for broad CNS biodistribution¹
- Lower doses compared to IV systemic delivery
- Reduced impact of neutralizing antibodies

Brief (<60 min), non-surgical, CT-guided procedure for precise delivery to the cisterna magna

Procedure avoids penetration of brain tissue

1. Hinderer et. al, *Hum Gene Ther.* 2018; 29:15-24.

Key Baseline Demographics for FTD-*GRN* Participants*

Dose 1 (n=7); Dose 2 (n=1)

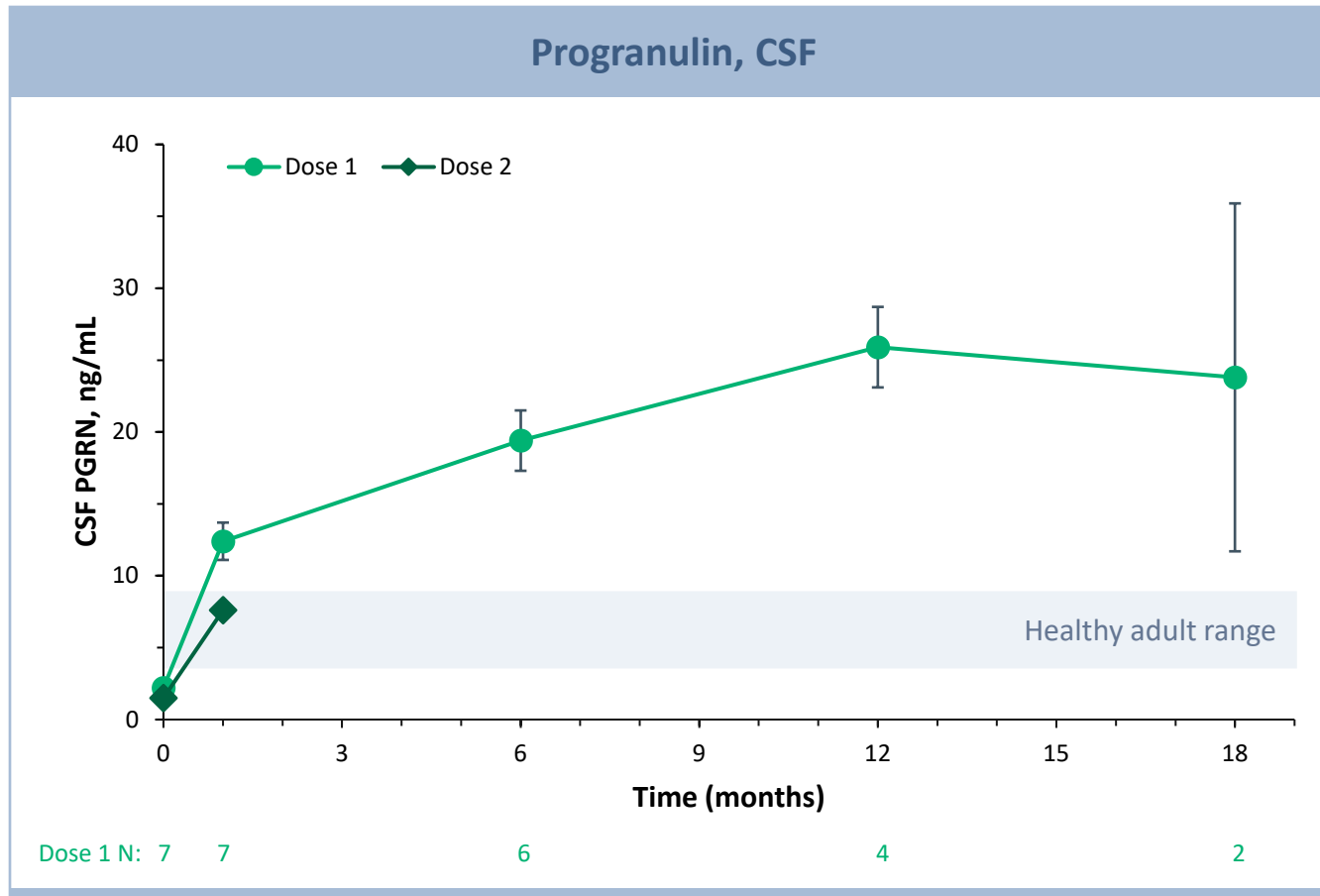
(n=8)	Mean / % / n	Range
Age (yrs)	64.4	51–72
Sex	M: 50% F: 50%	
FTD-<i>GRN</i> phenotype (n)	bvFTD: 5 PPA: 3	
Disease duration at baseline (yrs)	2.9	1 –5
PGRN, CSF (ng/mL)	2.1	1.5 –2.9
PGRN, plasma (ng/mL)	36.6	22.4 –89.0
NfL, plasma (pg/mL)	51.9	12.4 –111
Clinical Dementia Rating Scale¹, Global (%)	1: 50% 2: 50%	
Clinical Dementia Rating Scale¹, Sum of Boxes	10.3	5–17

*Data as of June 15, 2025

1. CDR[®] +NACC FTLD.

bvFTD, behavioral variant; PPA, primary progressive aphasia.

PBFT02 Generated Robust, Durable Increases in CSF PGRN in FTD-GRN Patients



First **Dose 2** patient (Patient 8) increased from 1.5 ng/mL at baseline to 7.6 ng/mL at M1, approaching the upper healthy adult range

Data as of June 15, 2025. Mean +/- SEM

Shading: Healthy adult sample range for CSF PGRN (range: 3.28 – 8.15 ng/mL, mean: 4.76 ng/mL, n = 61) (Passage Bio data)

Dose 1: 4.5e13 GC; Dose 2: 2.2e13 GC

CSF, cerebrospinal fluid; M, month.

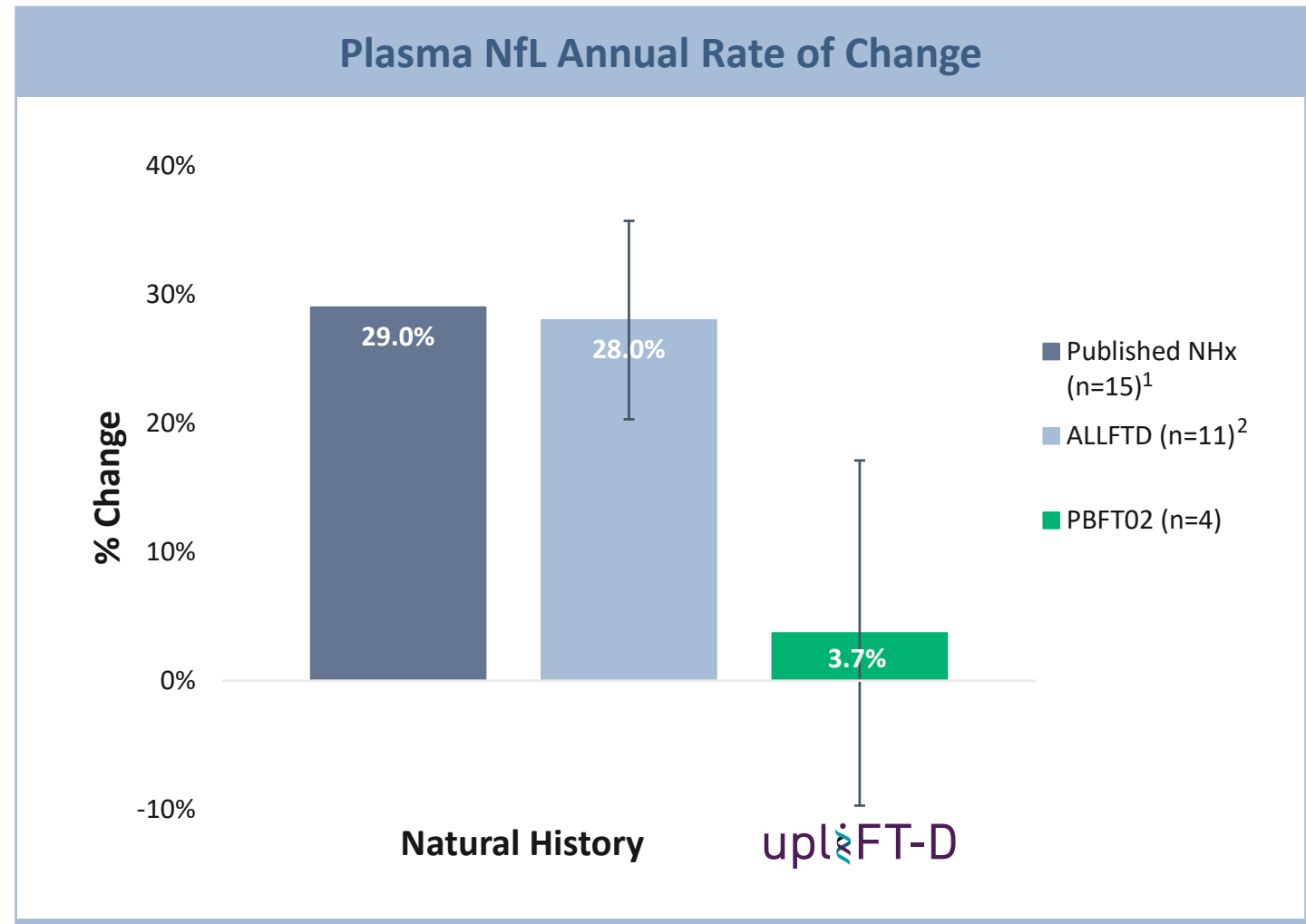
Plasma NfL Showed Early Evidence of Improvement in a Disease Progression Biomarker vs. Natural History

- Plasma NfL is the only FTD-GRN disease progression biomarker with longitudinal natural history data available^{1,3}
- PBFT02-treated patients with 12 months follow-up (n=4) had a reduced annual rate of change in plasma NfL compared to published natural history data

Data as of June 15, 2025. Mean +/- SEM

PBFT02 patients (n=4, Dose 1): Baseline plasma NfL (neurofilament light chain) range: 39.6 to 45.6 pg/mL. Average time since diagnosis 2.3 years.

1. Published natural history. Chart (left): 15 symptomatic, untreated FTD-GRN patients; mean years since diagnosis: 2.9; Note (right): 65 healthy adults. (Saracino et al, *J Neurol Neurosurg Psych* 2021; 92:1278-1288). **2.** Passage Bio analysis of ALLFTD natural history sample comprised of individuals with a pathogenic GRN mutation and a CDR+NACC FTLD global score between 0.5 and 2, inclusive. **3.** van der Ende et al, *Lancet Neurol* 2019; 18:1103-11.



Note: Annual rate of increase in plasma NfL in a healthy adult sample reported to be ~4%¹.

PBFT02 Interim Safety Profile

Data as of June 15, 2025

PBFT02 was generally well tolerated

- SAEs related to PBFT02 all asymptomatic; all occurred at Dose 1
 - Venous sinus thrombosis (2)
 - LFT increase (1)
- No SAEs related to PBFT02 at Dose 2
- No evidence of thrombotic microangiopathy
- No evidence of dorsal root ganglion (DRG) toxicity in any patient
- No complications from ICM procedure

	N	Events
TEAE considered related to PBFT02	7	26
Serious TEAE unrelated to PBFT02	1	1
Serious TEAE related to PBFT02	2	3

SAE, serious adverse event; LFT, liver function test; ICM, intracisterna magna; TEAE, treatment emergent adverse event.

PBFT02 Offers Best-in-Class Therapeutic Potential

	PBFT02		
Product Candidate	AAV1 gene therapy delivering <i>GRN</i>	AAV9 gene therapy delivering <i>GRN</i>	AAV9 gene therapy delivering <i>GRN</i>
Stage of Development	Phase 1/2	Phase 1/2	Phase 1/2
Route of Administration	ICM (non-surgical, 1 hour procedure)	ICM	Intrathalamic (neurosurgery, lengthy procedure)
CSF PGRN Level at 12m ¹	26 ng/mL (mean; n=4)	~4-8 ng/mL (n=7 higher dose) ²	—
Durability of CSF PGRN Elevation ¹	Durable at 18 m (n=2)	Declining from 2 to 12 m (n=7 higher dose) ²	—

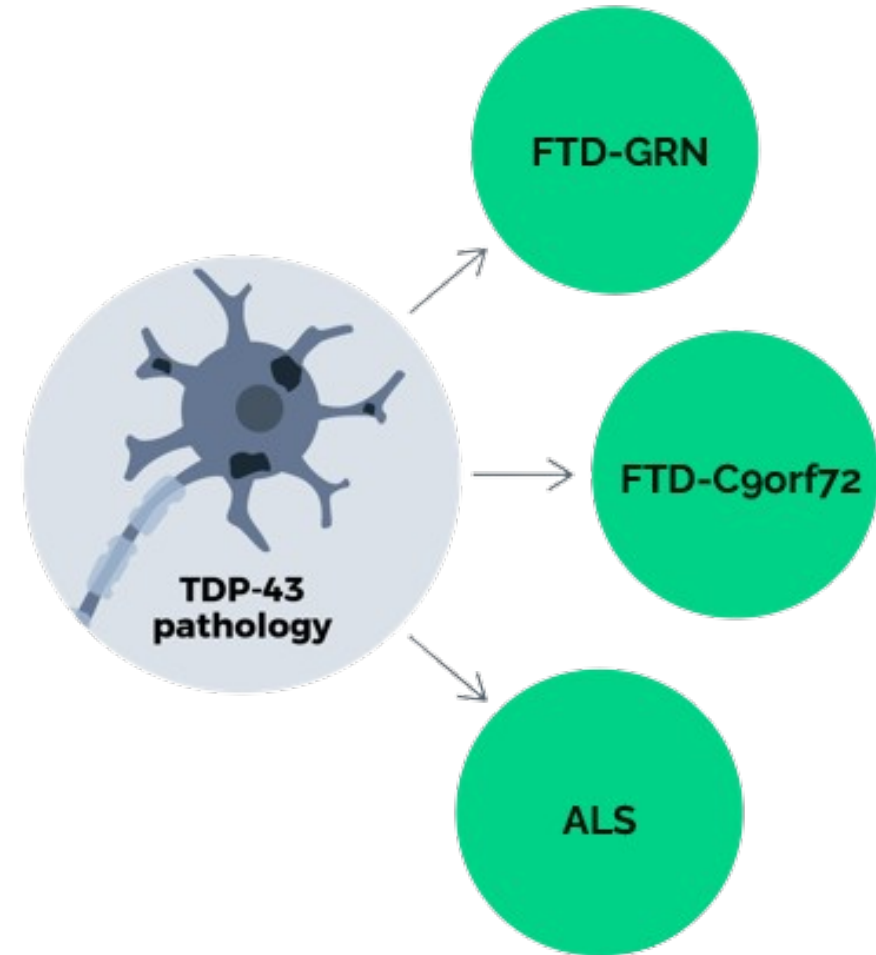
PBFT02 uniquely positioned to offer a one-time therapy capable of achieving highest progranulin levels

1. Clinical evidence based on public disclosure. Results are derived from different clinical trials at different points in time. No head-to-head trials have been conducted among the results shown. Comparing the results from different trials may be unreliable due to different protocol designs, trial design, patient selection and populations, number of patients, trial endpoints, trial objectives and other parameters that may not be the same between trials. 2. Lilly/Prevail AD/PD Mar 2024 presentation and abstract.

PBFT02 has Potential to Correct Underlying Pathology in FTD-GRN, FTD-C9orf72 and ALS

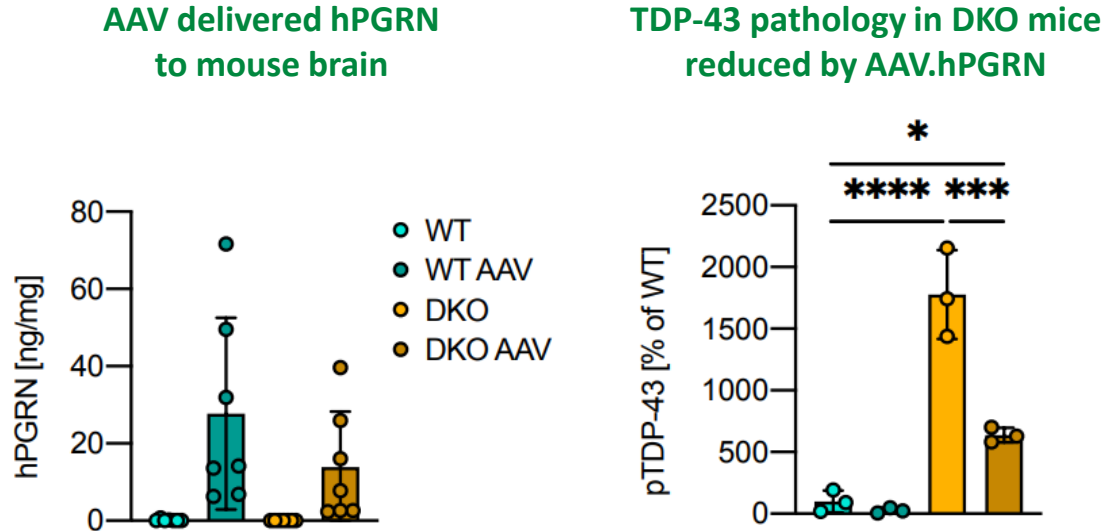
TDP-43 pathology is a hallmark of multiple neurodegenerative diseases¹

- TDP-43 mislocalizes from nucleus to cytoplasm
- Forms inclusion bodies associated with neurodegeneration



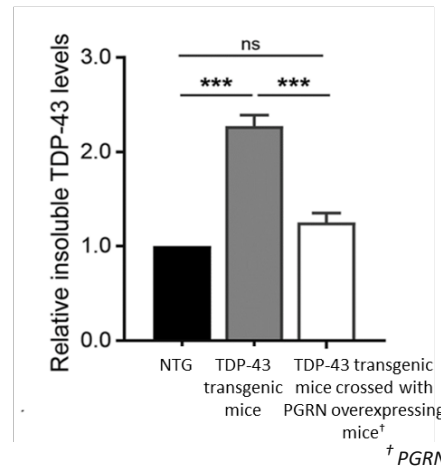
Elevated PGRN Ameliorates TDP-43 Pathology in Preclinical Models

TDP-43 pathology due to lysosomal dysfunction (*GRN*/*TMEM106* double knockout, DKO) reduced by AAV.hPGRN¹

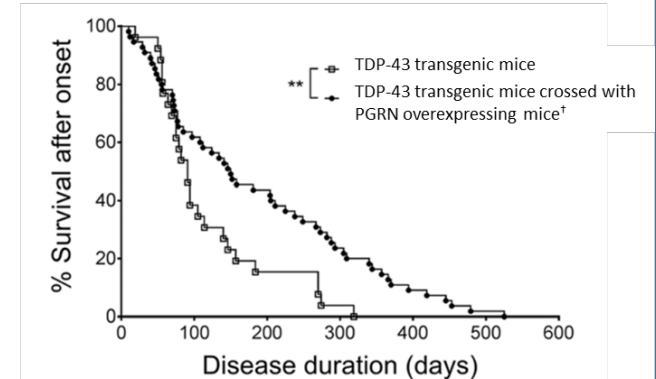


Elevated PGRN ameliorated TDP-43 pathology and disease course in a preclinical model²

Elevated PGRN reduced insoluble TDP-43 in mouse spinal cord



Elevated PGRN extended survival of TDP-43 mutant mice



- Elevated PGRN also prevented degeneration of large axon fibers in TDP-43 mice
- PGRN neuroprotection from pleiotropic effect, not single pathway

1. Reich et al. *Sci Transl Med.* 2024; 16(750); 2. Beel et al. *Mol Neurodegen.* 2018; 13:55.; Laird et al. *PLoS One* 2010; 5:e13368.

DKO, double gene knockout; *GRN*, granulin gene; PGRN, progranulin; TDP-43, transactive response DNA binding protein 43 kDa

PBFT02: Summary of Approach

- AAV delivery of functional GRN gene to **express new PGRN, increasing levels both intra- and extra-cellularly**
 - Preserves all natural pathways to properly traffic PGRN intracellularly where it is needed
- ICM route of administration enables **low doses of AAV and broad CNS biodistribution**
 - Non-surgical, brief procedure (< 60 minutes)
- Promise of a **one-time therapy** for patients
 - Durable elevation of CSF PGRN¹

1. Interim data from upliFT-D as of June 15, 2025.





Huntington's Disease Preclinical Program

Huntington's Disease: A Fatal Neurodegenerative Disease with No Disease-Modifying Therapy

OVERVIEW

- Fatal, monogenic, autosomal dominant neurodegenerative disease
- Caused by trinucleotide (CAG) expansion in the huntingtin (*HTT*) gene resulting in mutant huntingtin (mHTT) protein expression
- More than 200,000 people estimated to be at risk in the US¹

CLINICAL SYMPTOMS

- Symptom onset typically occurs between 30–50 years old
- Characterized by progressive motor, cognitive, and behavioral deterioration, due to neuronal dysfunction then degeneration



**Motor
deterioration**



**Cognitive
deterioration**



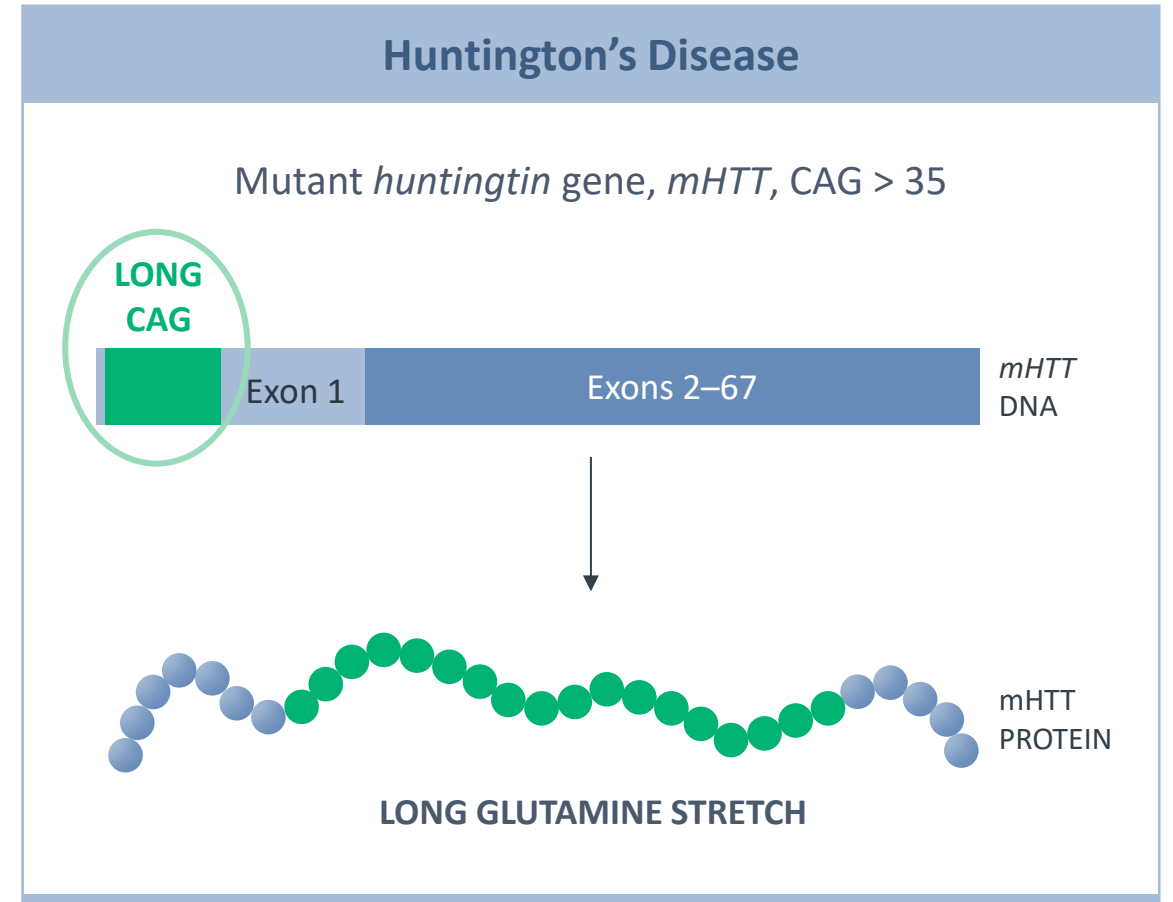
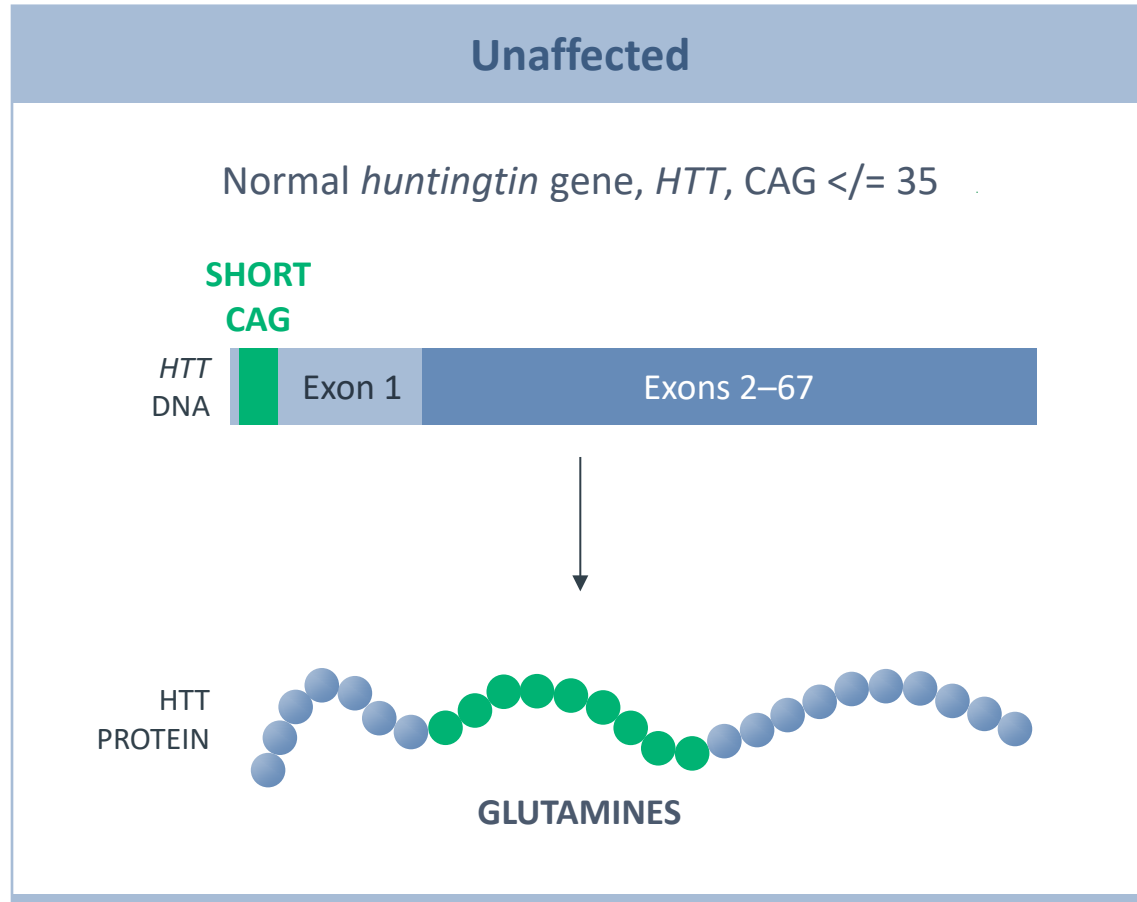
**Behavioral
deterioration**

**Average life
expectancy
after symptom
onset is
15–20 years**

1. HDSA; Fisher and Hayden Mov Disord. 29:105-14, 2014.

HD Is Caused By A Mutation In *Huntingtin* (*HTT*) Gene: A Stretch Of CAG Nucleotides Is Expanded

CAG repeat expansion leads to production of mutant huntingtin protein (mHTT)



DNA Repair (DR) Proteins Play a Key Role in CAG Repeat Expansion

In Huntington's disease (HD), the CAG repeat in the *HTT* gene can elongate over time, termed *somatic instability*

- CAG expansion above a certain threshold leads to neurodegeneration
- Longer CAG repeats associated with worse disease pathology
- CAG expansion occurs at different rates in different neurons, and is fastest in the caudate and putamen brain regions which degenerate first

MSH3, a DR protein, is a key driver of somatic instability

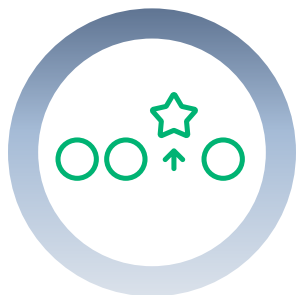
- In the presence of certain CAG motifs, MSH3 can erroneously incorporate CAGs into DNA, leading to CAG expansion
- In HD: certain genetic variants altering MSH3 function are associated with delayed onset and slowed progression¹
- In HD mice: MSH3 is essential for CAG expansion, and MSH3 knock-down reduced somatic instability and HTT pathology^{2,3}

1. Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium, *Nat Genet.* 2025; 57:1426-36.

2. Dragileva E et. al, *Neurobio Dis.* 2009; 33:37-47. 3. Mouro Pinto et. al, *Nat Genet.* 2025; 57:314-322.

Our Approach: Decrease MSH3 to Reduce Somatic Instability in the *HTT* Gene

Program Status



Developing a differentiated approach to decrease MSH3 expression via AAV delivery of a miRNA



Plan to utilize an optimized intraparenchymal delivery approach

- One-time delivery
- Direct delivery to critical brain regions
- Reduced total procedure time
- Limited peripheral exposure to reduce safety risks



Proof-of-concept studies completed, with additional preclinical studies ongoing

**Expect to
declare a clinical
candidate in
2H 2026**



Looking Ahead

Critical Manufacturing Milestones Achieved to Enable Late-Stage Development of PBFT02

Functional Potency Assay

Developed assay and reached alignment with FDA on suitability of assay for PBFT02 release



Robust Manufacturing Process

Completed development of high-productivity, suspension-based manufacturing process

Single production lot estimated to yield >1,000 doses¹ with >70% full capsids



Process Comparability Plan

Aligned with the FDA on an analytical approach to establish comparability of suspension-based process



1. Estimated yield based on Dose 2.

Plan to Initiate Discussions with the FDA on a Registrational Study Design in 1H 2026

Rationale for a single-arm registrational study

1

FTD-*GRN* is a rapidly progressing disease with no approved disease-modifying therapies and a substantial unmet clinical need

2

Multiple recent gene therapy precedents demonstrate FDA receptivity to a single-arm registrational approach

3

Existing, well-structured FTD natural history studies with >300 FTD-*GRN* patients

Upcoming Milestones and Corporate Updates

	TIMING	MILESTONE
●	1H 2026	Report updated interim safety and biomarker data from Dose 2 in FTD patients
●	1H 2026	Seek regulatory feedback on registrational trial design in FTD-GRN
●	2H 2026	Declare clinical candidate for Huntington's disease

BALANCE SHEET

- Cash balance of ~\$46 million as of 12/31/25*
- Cash runway into 1Q 2027

* Based on cash, cash equivalents and marketable securities.



Redefining the Course of Neurodegenerative Conditions



**Advancing clinical stage,
potential best-in-class, one-
time progranulin raising gene
therapy for FTD**



**Pursuing preclinical
development of differentiated
gene therapy approach in
Huntington's disease**



**Cash runway expected
into 1Q 2027***

* Based on cash, cash equivalents and marketable securities as of December 31, 2025.



Thank you!

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Focused Pipeline Addressing Rare and Prevalent Neurodegenerative Indications



1. Greaves CV, et al. *J Neurol* 2019; 266:2075-2086. 2. Galvin JE, et al. *Neurology* 2017; 89:2049-2056. 3. Onyike CU, et al. *Int Rev Psychiatry* 2013; 25:130-137. 4. Moore KM, et al. *Lancet Neurol* 2020; 19: 145–156. 5. Brown et al. *Neuroepi* 2021; 55:342-353. 6. CDC ALS Registry Dashboard. 7. Sheng J, et al. *Gene* 2014; 141-145. 8. Alz Assoc. 2023 Alzheimer’s Disease Facts and Figures. *Alzheimers Dement* 2023;19. 9. Crowell et al. *Neuroepi*. 2021; 55:361-368.

Demonstrated Leadership

Deep experience in rare disease, CNS disorders and genetic medicines

LEADERSHIP TEAM



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Chief Executive Officer



Kathleen Borthwick
Chief Financial Officer



Sue Browne, Ph.D.
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Eden Fucci
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Karl Whitney, Ph.D.
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