



Passage Bio

Corporate Presentation

May 2025

Nasdaq: PASG

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REDEFINING THE COURSE OF NEURODEGENERATIVE CONDITIONS



Advancing potential best-in-class, one-time progranulin raising FTD-GRN gene therapy



Exploring benefits of elevated progranulin in multiple adult neurodegenerative diseases



Established suspension-based PBFT02 manufacturing process to support late-stage development



Strong cash position with runway expected to the end of 1Q 2027*

* Based on cash, cash equivalents and marketable securities as of March 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[®]FT-D

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

Differentiated, Potential Best-in-Class Profile

One-time, gene
replacement therapy

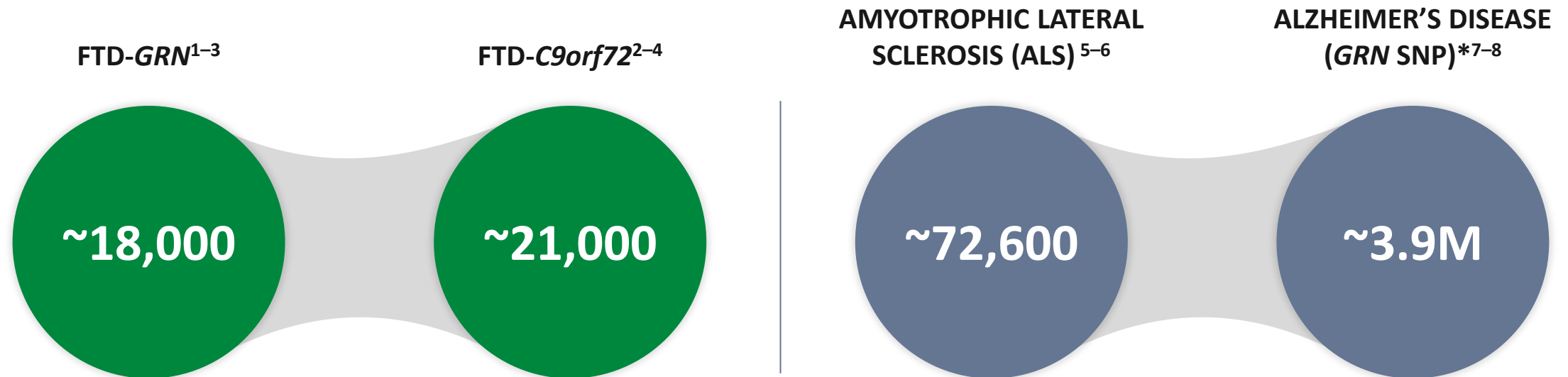
Proprietary AAV1
construct

Nonsurgical injection
directly to cerebrospinal
fluid (CSF)

Durable, elevated CSF
PGRN levels*

Significant Market Opportunity for PBFT02 Across Multiple Neurodegenerative Diseases

Estimated Prevalence (US and EU)

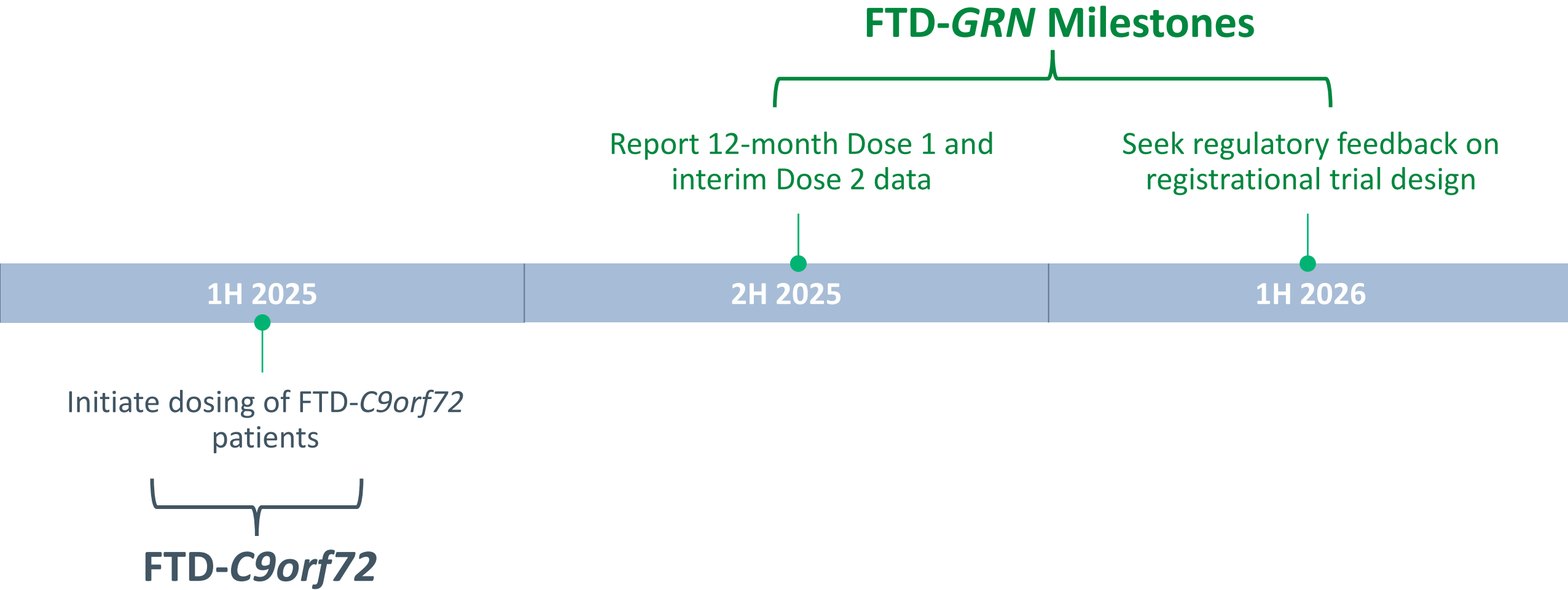


Current clinical programs

* rs5848 single nucleotide polymorphism (SNP)

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.

Anticipated Upcoming Milestones and Data Readouts





PBFT02

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)

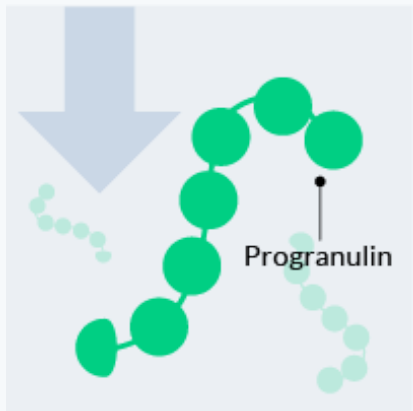


Ritualistic compulsive
behaviors

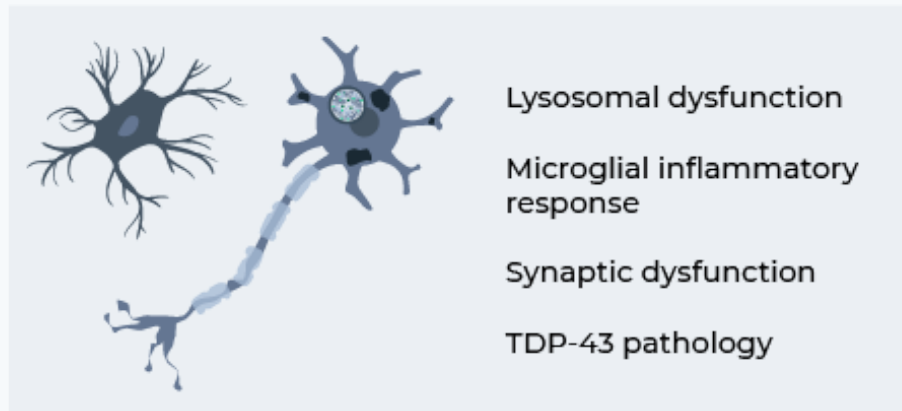
On average,
people with FTD
live 8 years after
the onset of
symptoms

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

Progranulin is critical to maintaining CNS cell homeostasis



Decrease in PGRN levels



Neuronal dysfunction, pathological changes, and inflammation



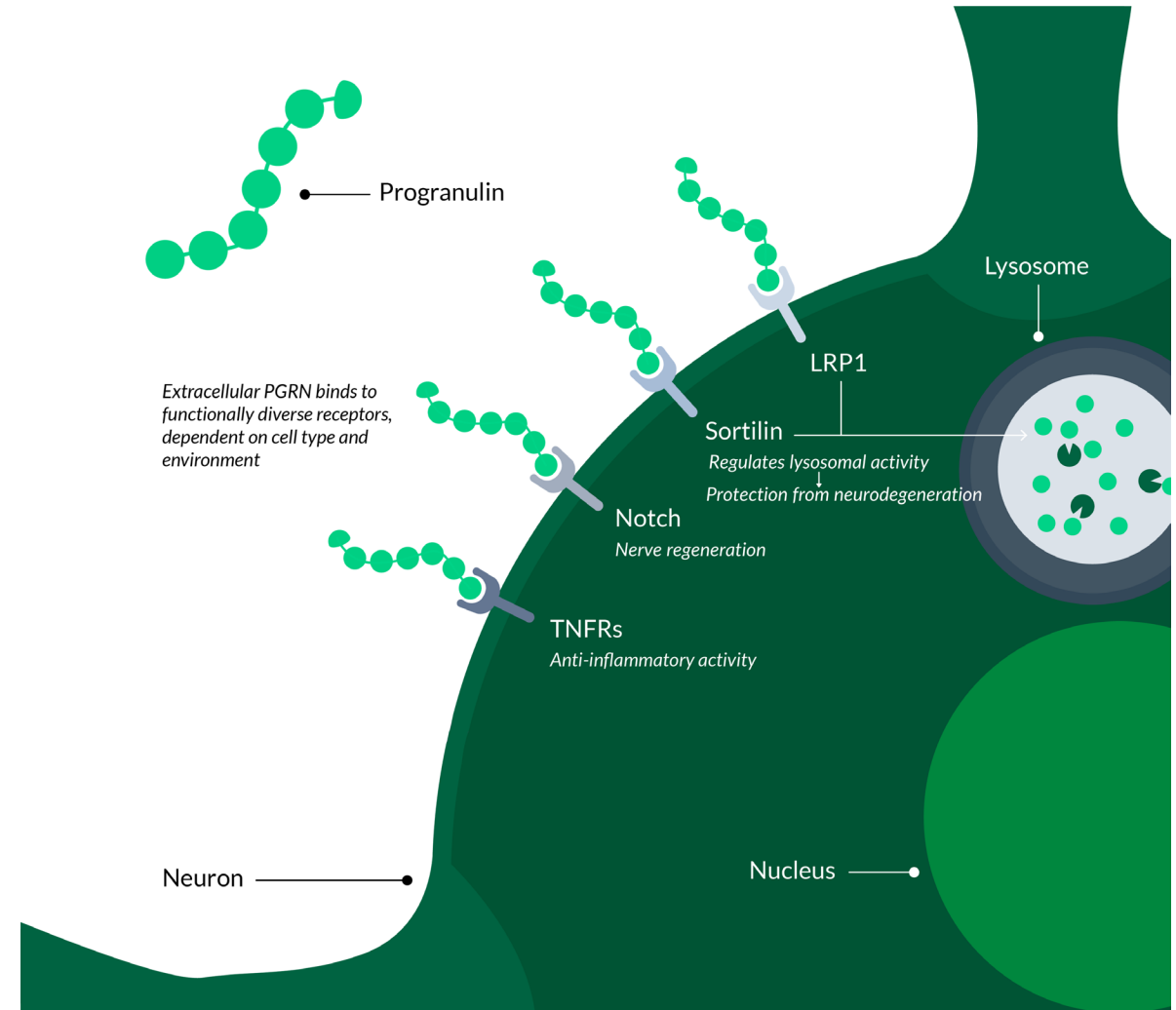
Vulnerability of neurons in affected regions



Neurodegeneration

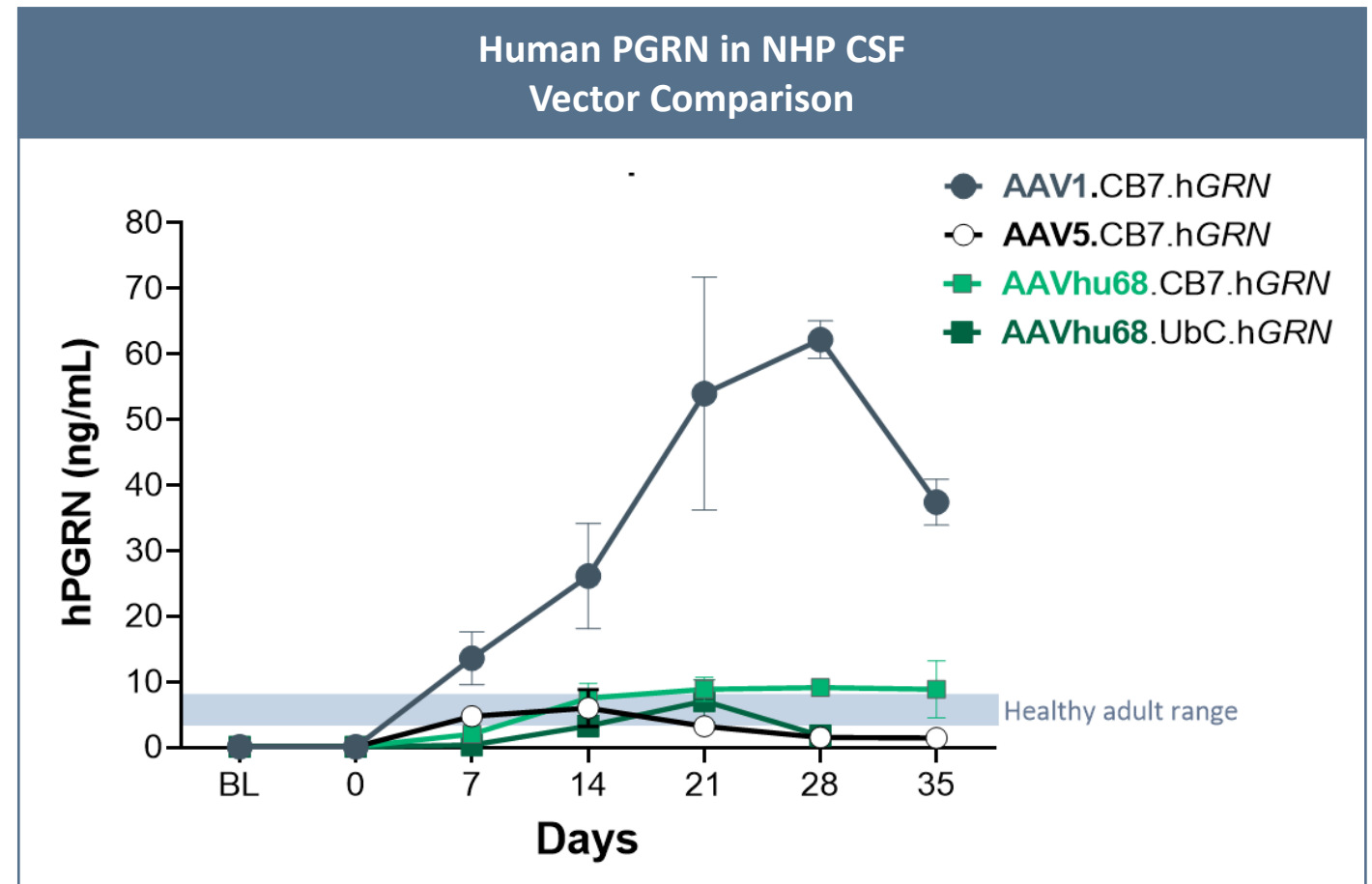
Elevated PGRN Increases Potential for Improved Cellular Function

- 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



Preclinical NHP: AAV1 Achieved the Highest Levels of CSF PGRN

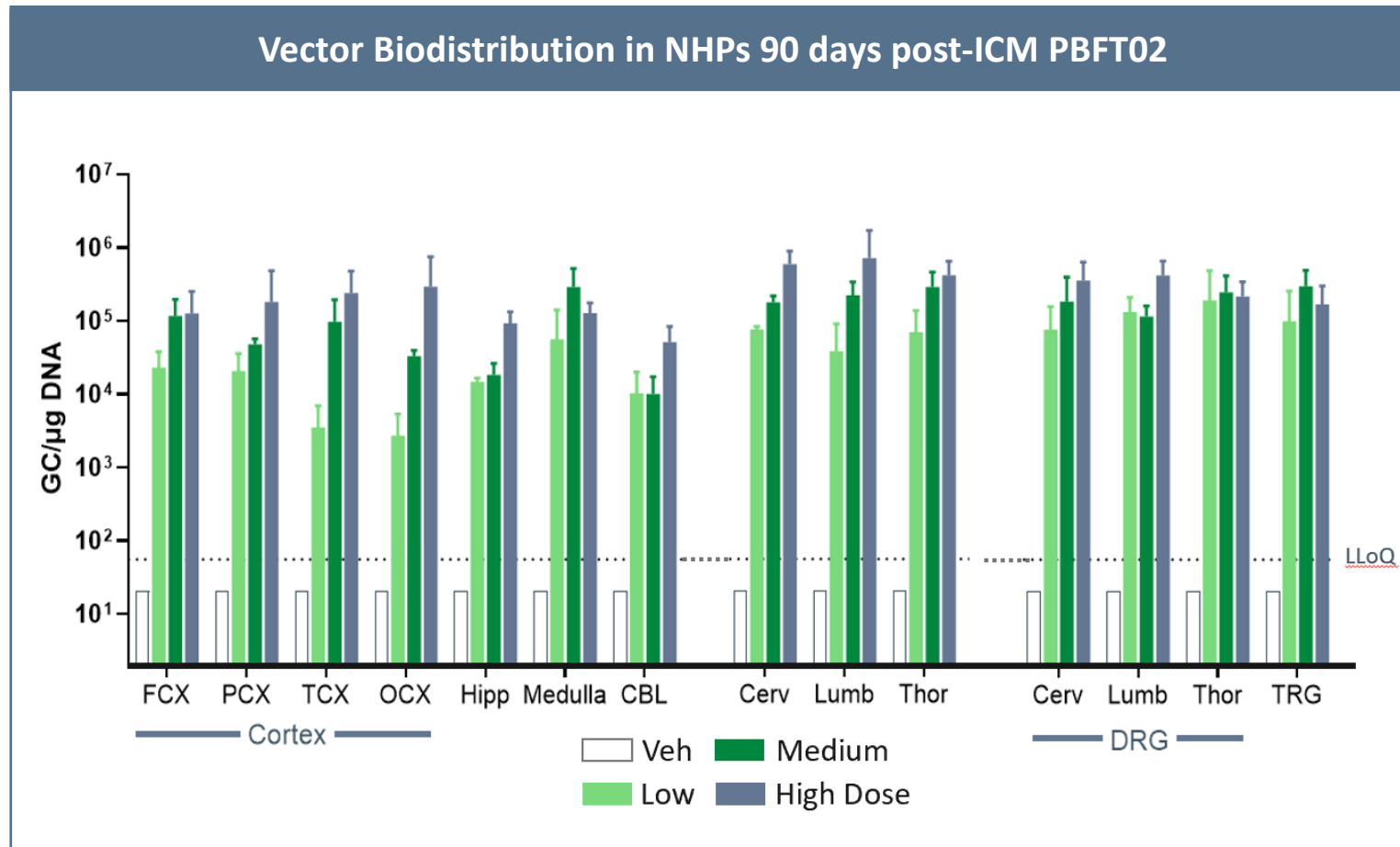
- AAV1 resulted in superior CSF hPGRN levels, 5x higher than AAV5 and AAVhu68 (an AAV9 variant) vectors, after ICM administration



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

11 *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



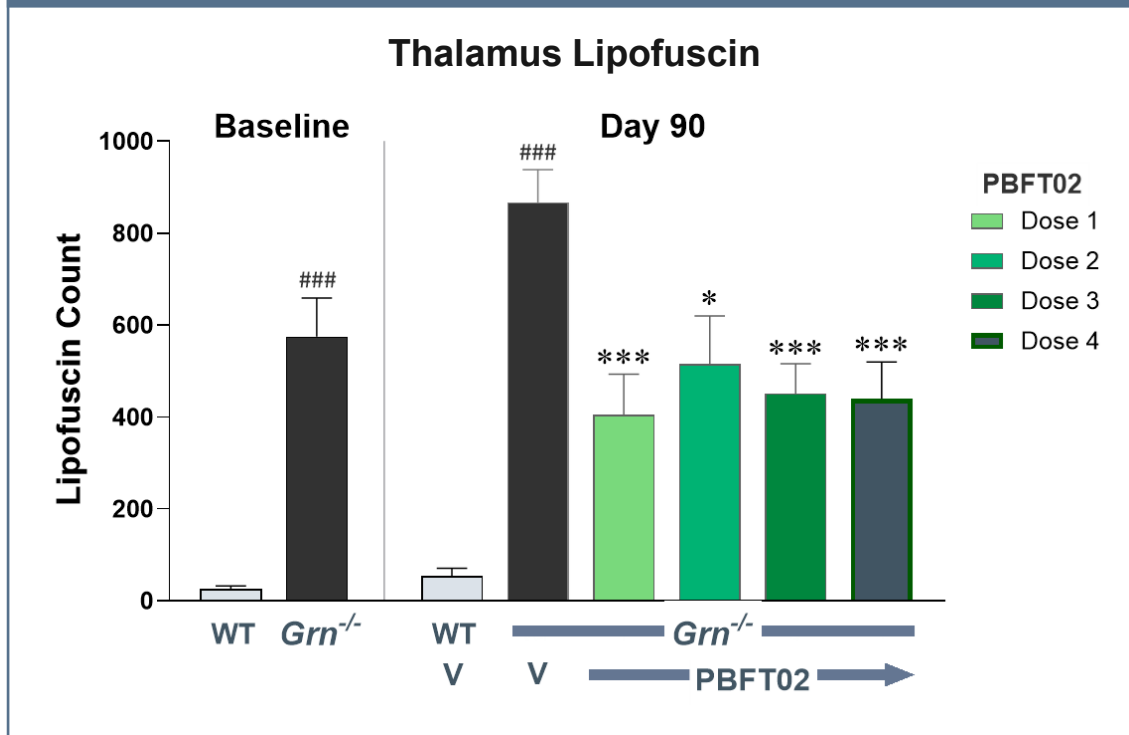
- Robust, dose-dependent vector delivery to cortical and sub-cortical brain regions affected in FTD
- NHP low dose, equivalent to clinical Dose 1 of PBFT02 in upliFT-D study, resulted in $\sim 10^4$ GC/ μ g DNA in all sampled areas throughout the brain

n=3/gp. Data are mean $\pm$ SEM.

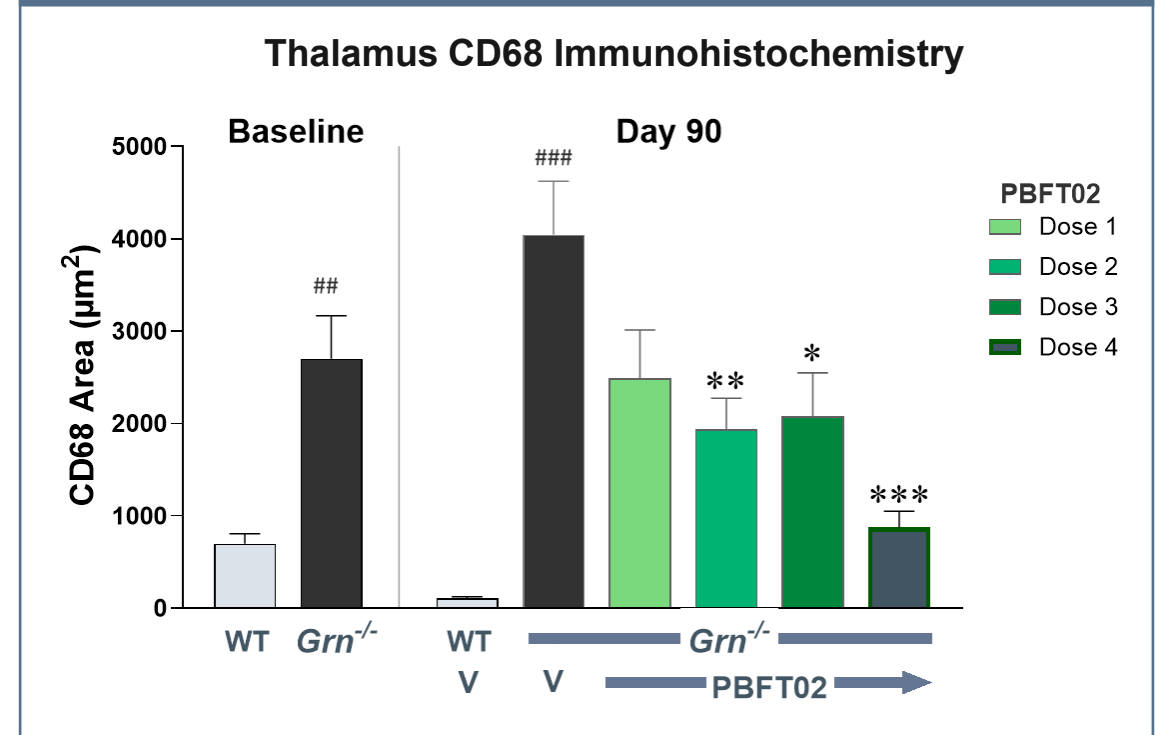
12 CBL, cerebellum; Cerv, cervical; DRG, dorsal root ganglion; FCX, frontal cortex; GC, genome copies; Hipp, hippocampus; ICM, intra-cisterna magna; LLoQ, lower limit of quantitation; Lumb, lumbar; OCX, occipital cortex; PCX, parietal cortex; TCX, temporal cortex; Thor, thoracic; Veh, vehicle

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

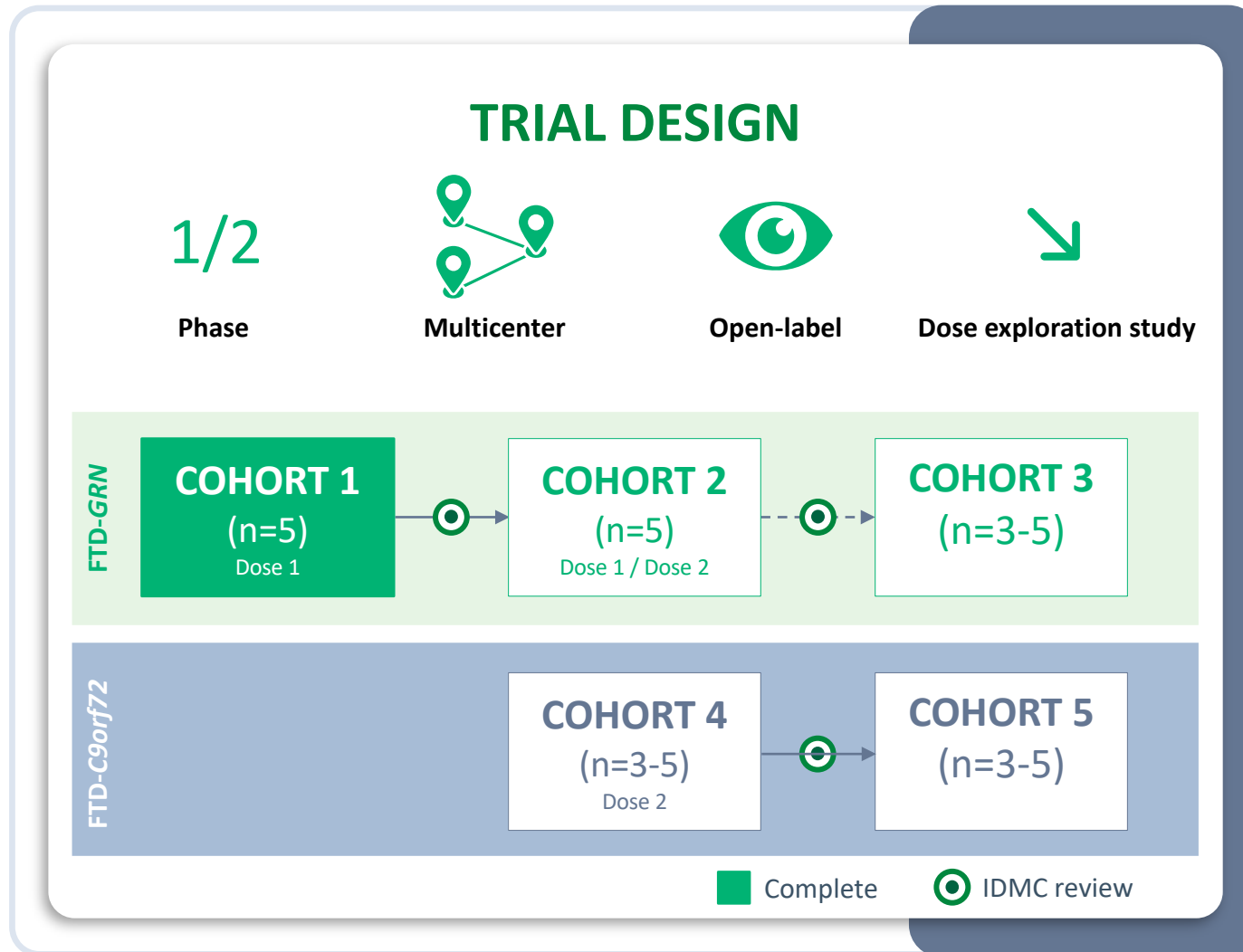
Lipofuscin deposition and microglial activation are hallmark pathologies seen in FTD; Improvements in both measures were seen in cerebral cortex, thalamus, and hippocampus after PBFT02 administration

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 < 0.01 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



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

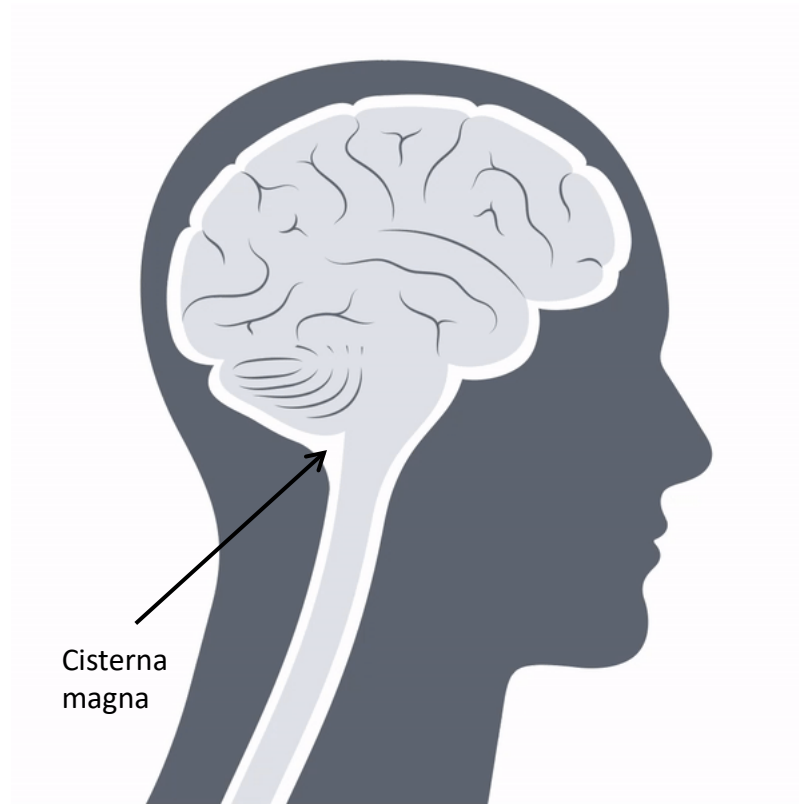
Clinical

- CDR + NACC FTLD sum of boxes

EXPLORATORY BIOMARKERS

- Cathepsin D (CSF)
- 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

upliFT-D: Interim Safety Profile

Interim Safety Highlights*

Dose 1 PBFT02 in FTD-GRN Patients (n=7)

- In 5 of 7 patients, all treatment emergent AEs were mild to moderate in severity
- 2 of 7 patients experienced a total of 3 SAEs
 - Patient 1: asymptomatic venous sinus thrombosis (VST) and hepatotoxicity, leading to a revised immunosuppression regimen in all subsequent patients**
 - Patient 7: asymptomatic VST, completely resolved prior to day 30 following treatment with anticoagulants. No evidence of hepatotoxicity, immune response or other laboratory abnormalities
- No evidence of a clinically significant immune response following introduction of new immunosuppression regimen
- No evidence of DRG toxicity
- No complications during ICM administration

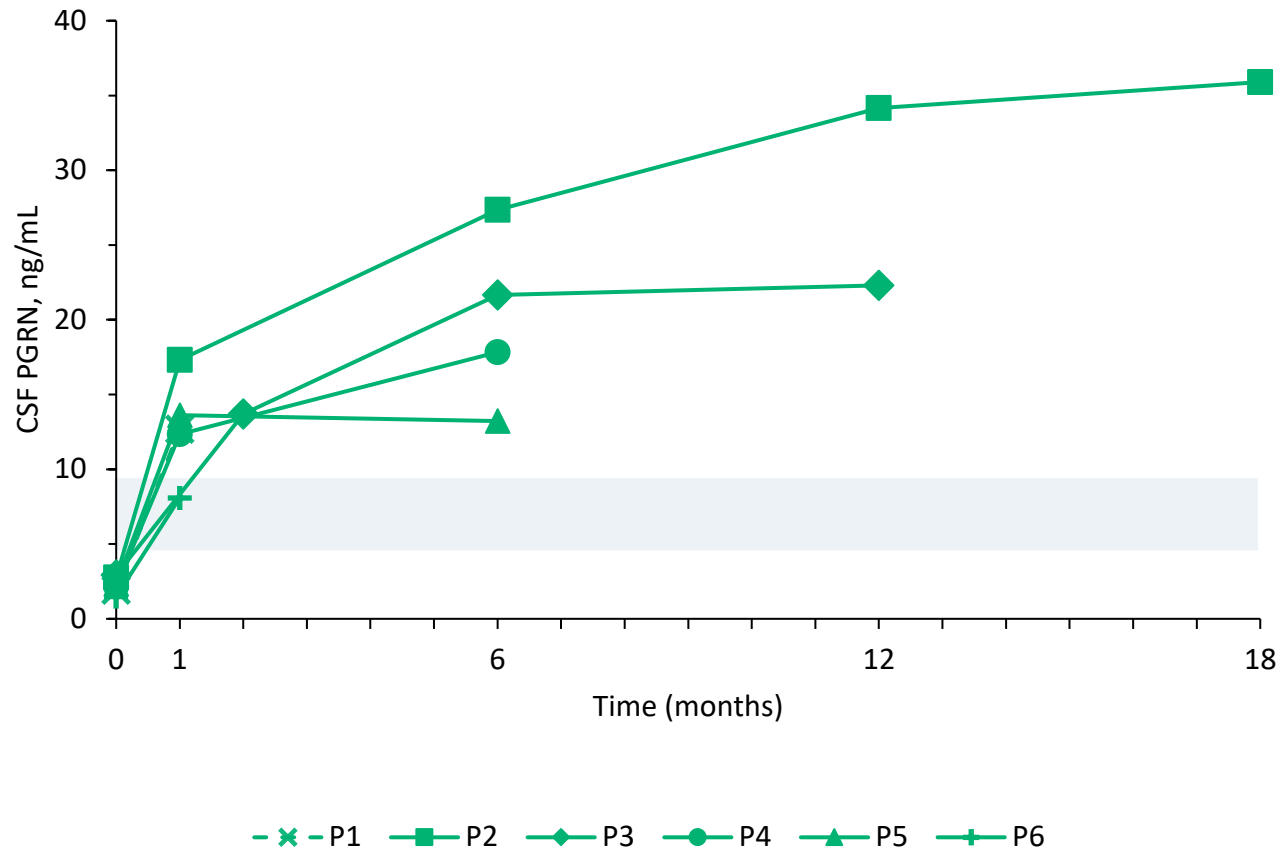
Remaining patients in Cohort 2 to receive Dose 2 (50% Dose 1)

*Patient safety follow-up up to 23 months post-dosing as of data cutoff of April 11, 2025

**Patient 1 received oral prednisone 60 mg daily through day 60; subsequent patients received a revised immunosuppressive regimen of 1g methylprednisolone IV daily to day 3, followed by oral prednisone 60 mg to day 60, then taper
AE, adverse event; DRG, dorsal root ganglion; ICM, intra-cisterna magna; SAE, serious adverse event; VST, venous sinus thrombosis.

PBFT02 Generated Robust, Durable Increases in CSF PGRN

Dose 1 Progranulin, CSF



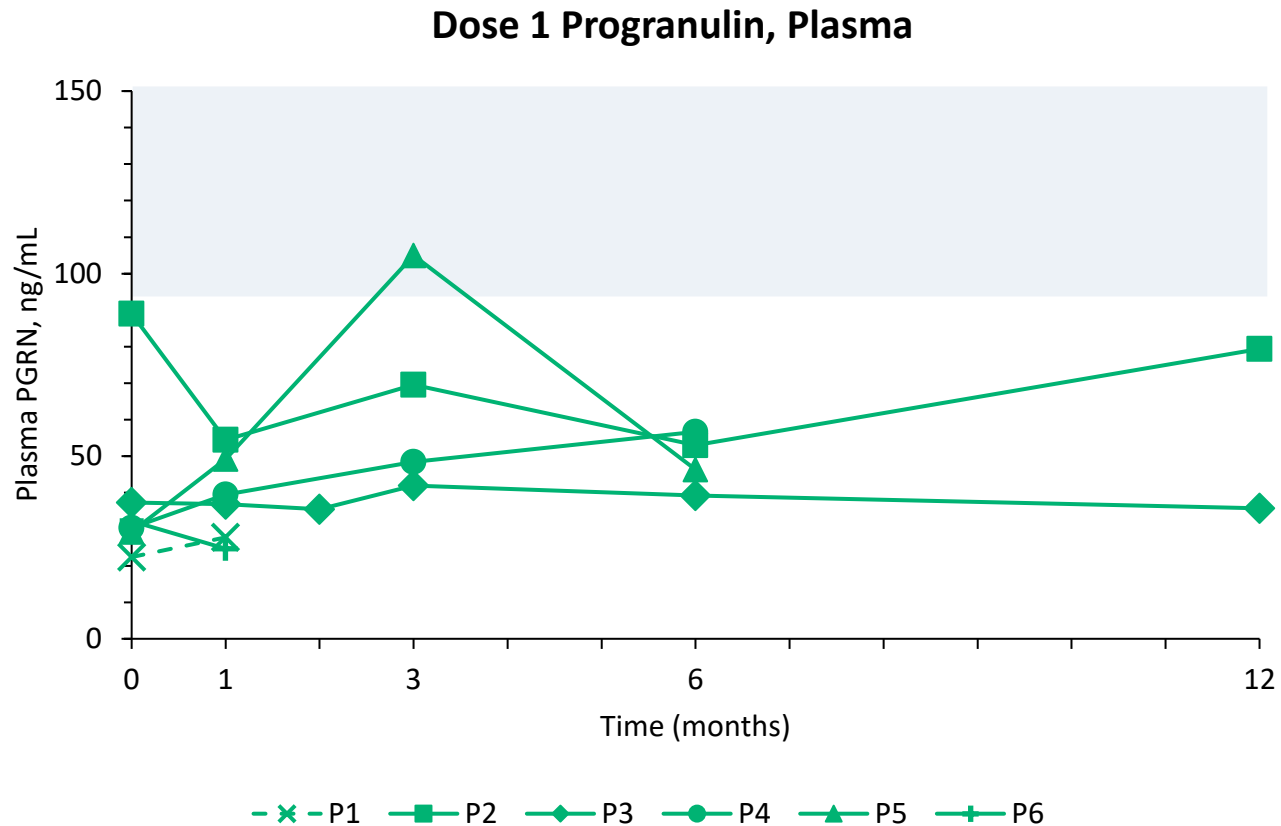
CSF Progranulin (ng/mL) in FTD-GRN Patients

	Baseline	M1	M6	M12	M18
N	6	6	4	2	1
Min	1.5	8.0	13.2	22.3	35.9
Max	2.9	17.3	27.3	34.0	35.9
Mean	2.3	12.4	20.0	28.2	-

Potential best-in-class PGRN profile

- Consistent elevation from baseline
- Durable to 18 months
- Levels overall plateauing by 6 months

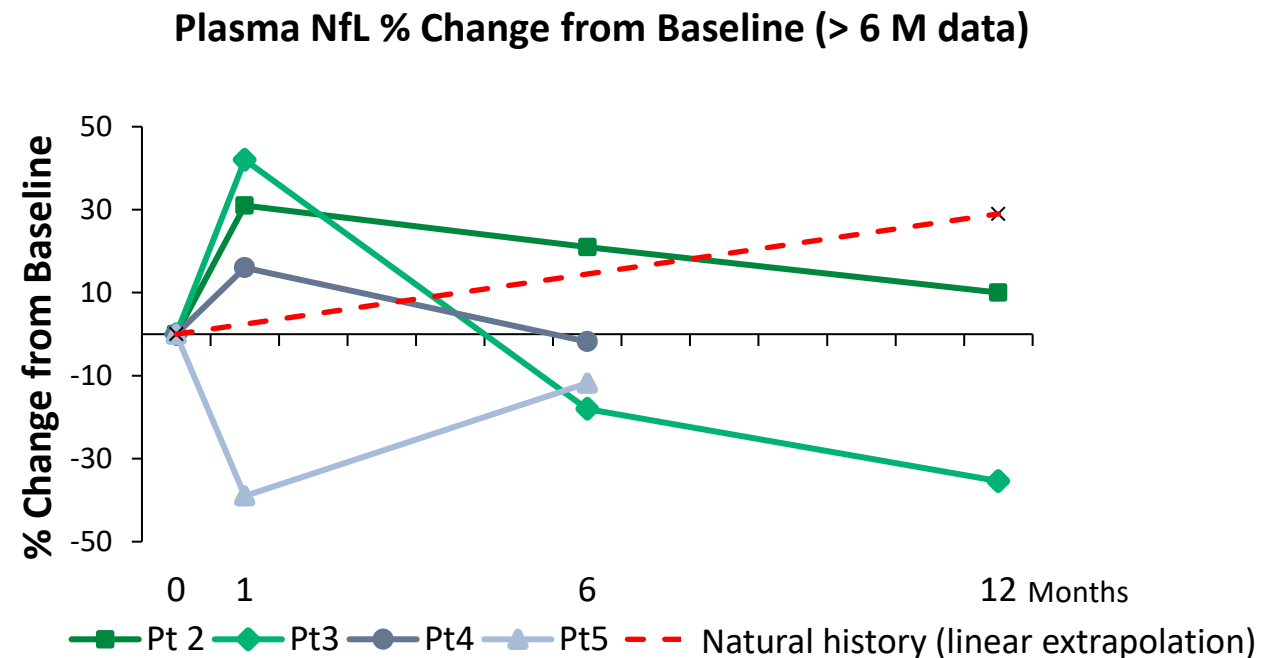
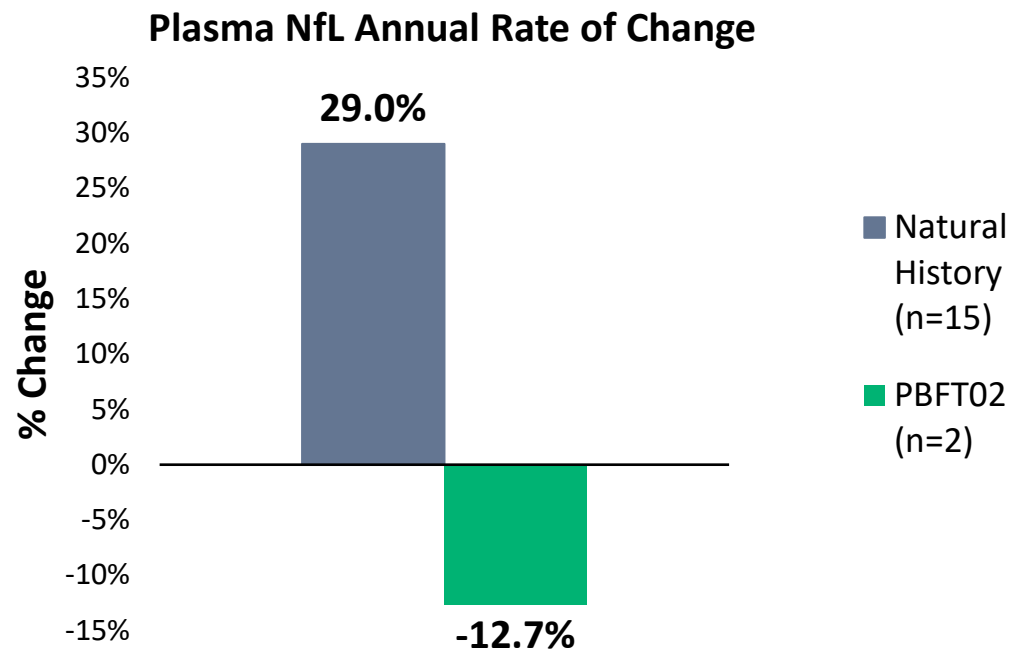
Plasma PGRN Levels Remained Below Normal Levels Post-Dose



- Plasma PGRN levels remained below normal levels up to 12 months post-dose in FTD-*GRN* patients
- PGRN increased only in the CSF, where it has potential to reduce neurodegeneration

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 published longitudinal natural history data available^{1,2}
- Both PBFT02-treated patients with 12 months follow-up had a reduced annual rate of change in plasma NfL compared to published natural history data



Baseline plasma NfL (neurofilament light chain) range: 39.6 to 45.6 pg/mL, n=4.

¹ Natural history: 15 symptomatic FTD-*GRN* patients; mean years since diagnosis: 2.9 (Saracino et al, *J Neurol Neurosurg Psych* 2021; 92:1278-1288).

Average time since diagnosis in PBFT02 patients 2 years (n=2).

² van der Ende et al, *Lancet Neurol* 2019; 18:1103-11.

PBFT02 Offers Best-in-Class Therapeutic Potential

	PBFT02		
Product Candidate	AAV1 gene therapy delivering <i>GRN</i>	Anti-sortilin antibody	AAV9 gene therapy delivering <i>GRN</i>
Stage of Development	Phase 1/2	Phase 3	Phase 1/2
Route of Administration	ICM	IV	ICM
Expected Frequency of Administration	<i>One Time</i>	Monthly	One Time
CSF PGRN Level ¹	<i>13-27 ng/mL at 6m (n=4)</i>	~4-5 ng/mL (n=9) ²	~4-8 ng/mL at 12m (n=7 higher dose) ³
Durability of CSF PGRN Expression ¹	<i>Durable at 18m (n=1)</i>	n/a (monthly admin)	Declining from 2 to 12m (n=7 higher dose) ³

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 Alector 2021 AAIC presentation. ³ Lilly/Prevail AD/PD Mar 2024 presentation and abstract.

Summary: FTD-GRN

SAFETY¹

PBFT02 Dose 1

- In 5 of 7 patients, all treatment emergent AEs were mild to moderate
- 2 of 7 patients experienced a total of 3 SAEs
- No evidence of clinically significant immune response following introduction of new immunosuppression regimen
- No evidence of DRG toxicity
- No complications during ICM administration

BIOMARKERS

- Potential best-in-class PGRN profile at Dose 1
- Robust, consistent elevation of CSF PGRN
- Durable response to 18 months
- No increase in plasma PGRN levels up to 12-months
- Plasma NfL in treated patients showed early evidence of improvement vs. natural history

ANTICIPATED NEXT STEPS

- Evaluating Dose 2 in subsequent Cohort 2 patients
- Report 12-month Dose 1 and interim Dose 2 data in 2H 2025
- Seek regulatory feedback on registrational trial design in 1H 2026

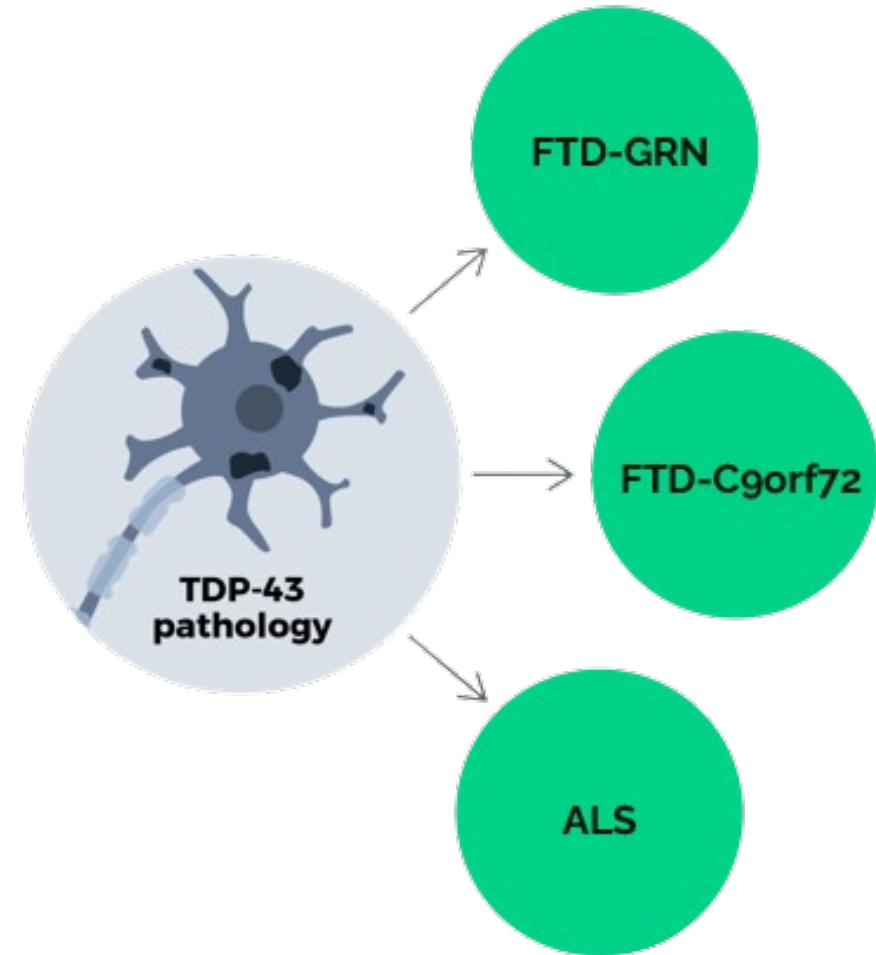


Looking Ahead

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

TDP-43 pathology is a hallmark of multiple neurodegenerative diseases¹

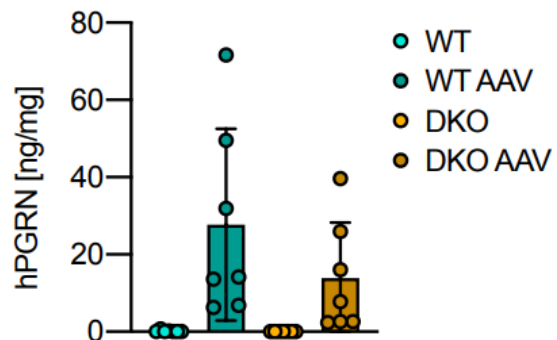
- TDP-43 mislocalizes from nucleus to cytoplasm
- Forms inclusion bodies associated with neurodegeneration



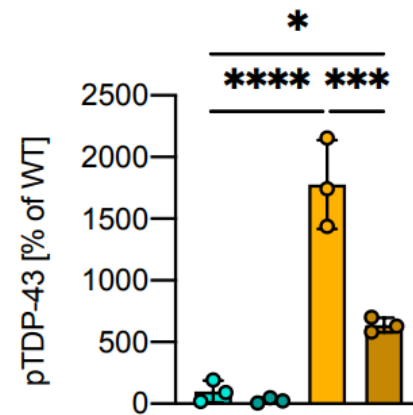
Elevated PGRN Ameliorates TDP-43 Pathology in Preclinical Models

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

AAV delivered hPGRN to mouse brain

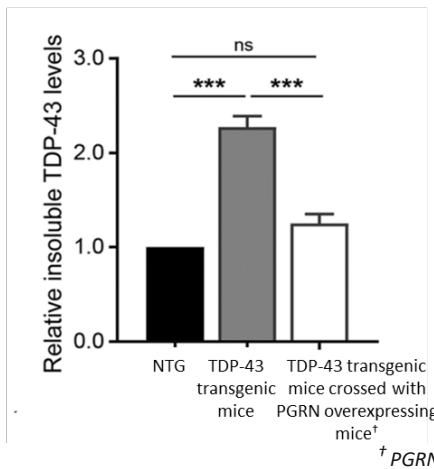


TDP-43 pathology in DKO mice reduced by AAV.hPGRN



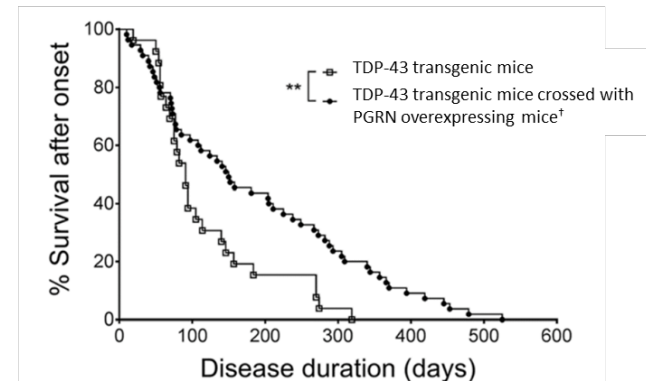
Elevated PGRN ameliorated TDP-43 pathology and disease course in a preclinical model²

Elevated PGRN reduced insoluble TDP-43 in mouse spinal cord



[†] PGRN increased to >2x endogenous levels

Elevated PGRN extended survival of TDP-43 mutant mice



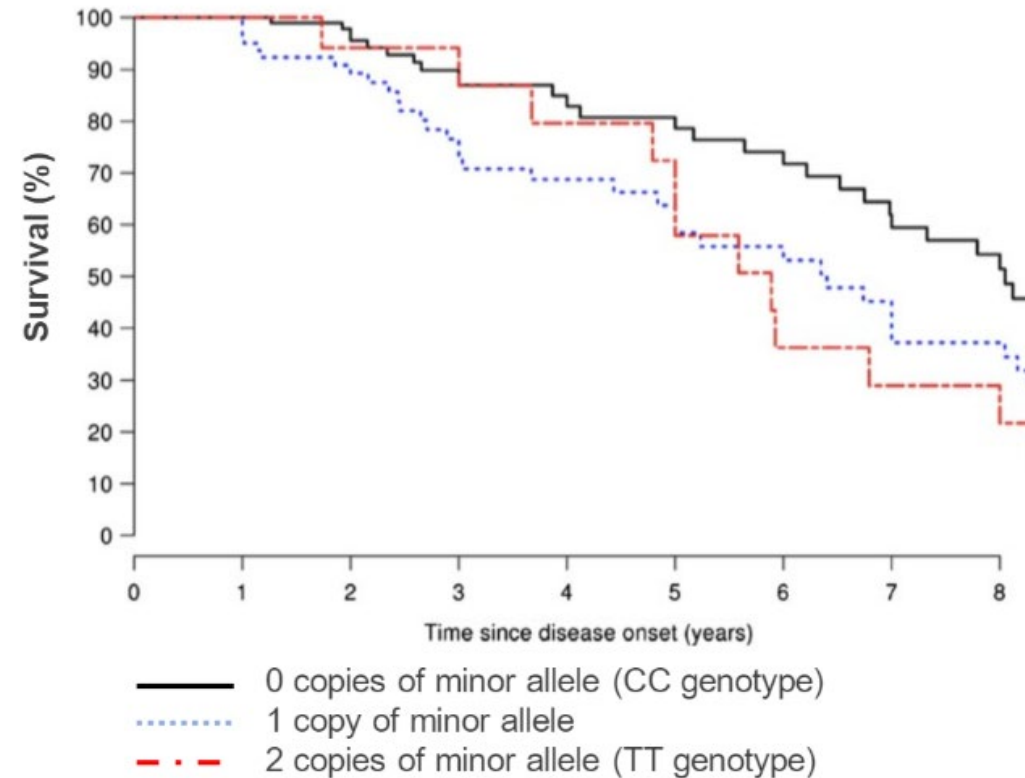
- Elevated PGRN also prevented degeneration of large axon fibers in TDP-43 mice
- PGRN neuroprotection from pleiotropic effect, not single pathway

Decreased PGRN Associated with Greater Disease Severity in Multiple CNS Conditions

PGRN SNPs are genetic risk factors for CNS diseases

- *GRN* rs5848 SNP results in ~15% reduction in PGRN levels
- PGRN SNPs increase risk for, and worsen severity of, FTD/ALS-*C9orf72* and AD¹

GRN rs5848 SNP associated with accelerated disease in FTD-*C9orf72* patients



Critical Manufacturing Milestones Achieved to Enable Late-Stage Development



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

Registrational Study Approach

- Seek feedback on registrational strategy in 1H 2026
- Leverage recent GTx precedents for utilizing natural history (NHS) data as external control
- Analyze existing FTD-GRN NHS databases with >300 patients

Upcoming Milestones and Corporate Updates

	TIMING	MILESTONE
FTD-GRN	2H 2025	Report 12-month Dose 1 and interim Dose 2 data
	1H 2026	Seek regulatory feedback on registrational trial design
FTD-C9orf72	1H 2025	Initiate dosing of FTD-C9orf72 patients

PIPELINE

- Advancing Huntington's disease preclinical program

BALANCE SHEET

- Cash balance of ~\$63 million as of 3/31/25*
- Cash runway into 1Q 2027

* Based on cash, cash equivalents and marketable securities



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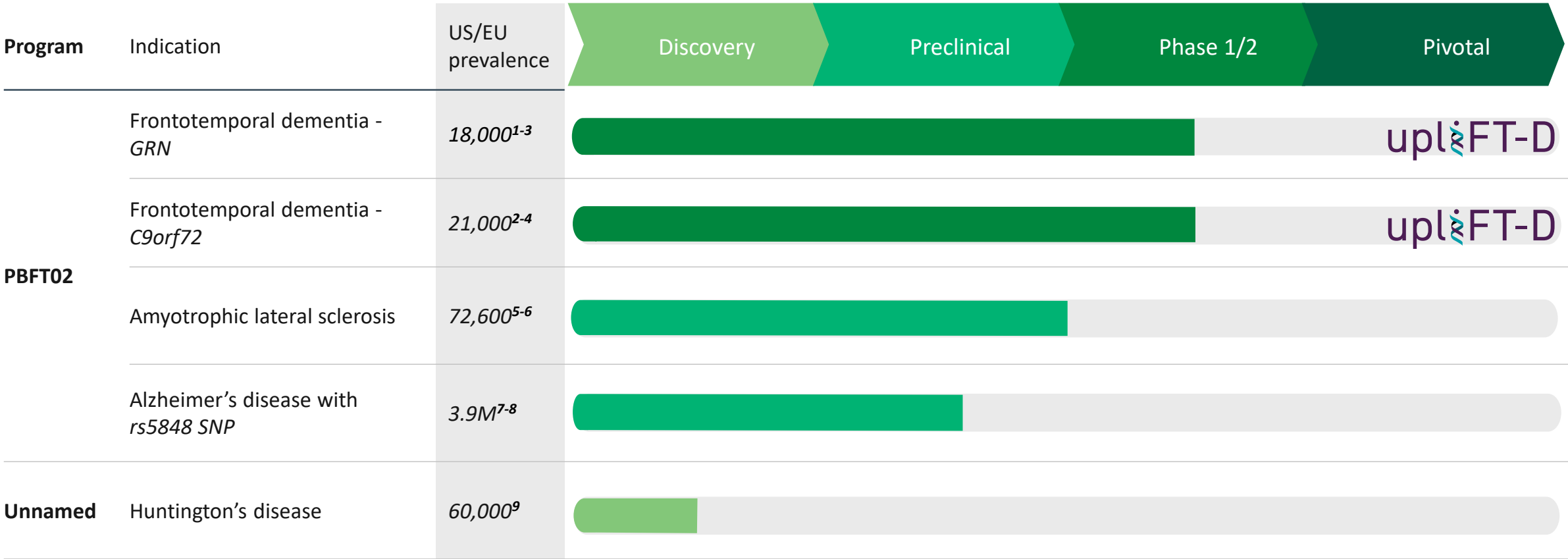


Thank You

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Focused Pipeline Addressing Rare and Prevalent Neurodegenerative Indications



Demonstrated Leadership

Deep experience in rare disease, CNS disorders and genetic medicines

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