Interim Safety and Biomarker Data from upliFT-D Trial of PBFT02 in FTD with *GRN* Mutation

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Life-transforming therapies

Disclosures

- upliFT-D trial is also known as PBFT02-001, NCT04747431

- Sue Browne, PhD:

Company / Name	Honoraria / Expense	Consulting / Advisory Board	Funded Research	Royalties / Patent	Stock Options	Ownership / Equity Position	Employee	Other (Please specify)
Passage Bio, Inc					X		X	

Frontotemporal Dementia: A Devastating Disease Syndrome

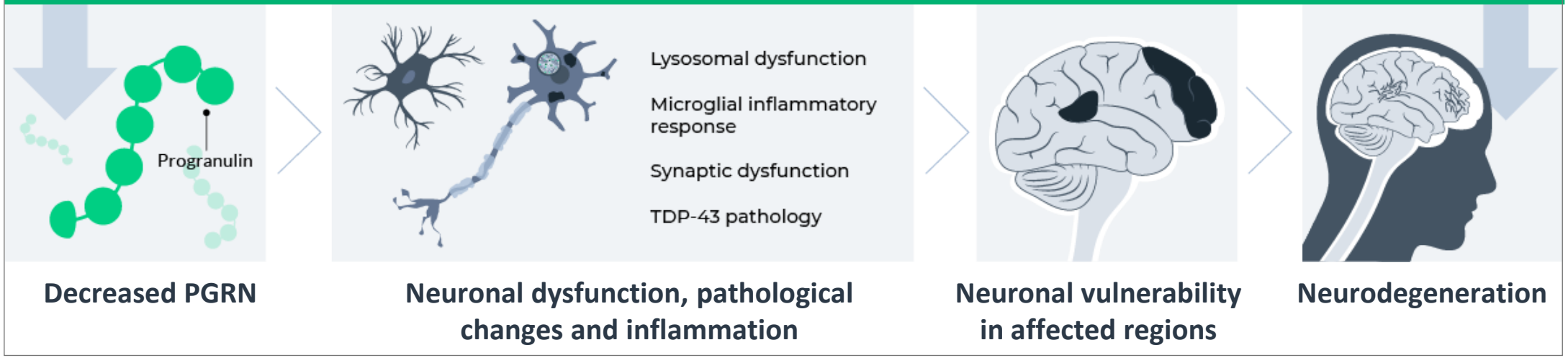
- FTD is a common cause of early-onset dementia accounting for 20% of cases, second only to AD
- Signs and symptoms typically manifest in adulthood, and are often misdiagnosed initially:
  - Impaired social cognition and altered personality
  - Apathy, depression, irritability
  - Impaired expressive and receptive language
- Pathologically, FTD is characterized by a rapidly progressive neurodegeneration, in particular affecting frontal and temporal cerebral cortex

FTD-*GRN*

- 5 to 10% of FTD is caused by mutations in ***granulin, GRN,*** gene
  - Haploinsufficiency reduces brain **progranulin, PGRN,** by 50-70%
- Prevalence in EU + US is ~18,000
- No approved disease-modifying therapy

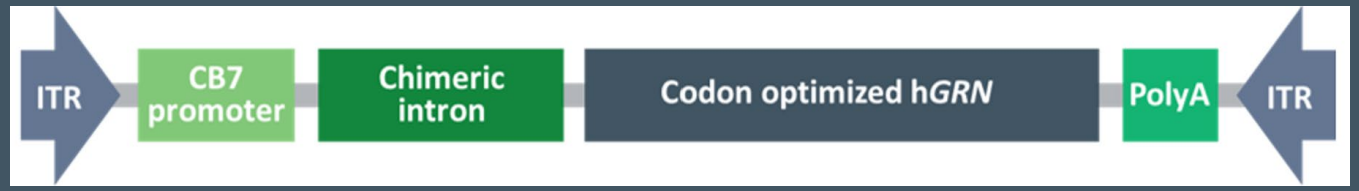
Progranulin (PGRN) Deficiency is the Defining Characteristic of FTD-*GRN*, Leading to Neurodegeneration

Progranulin is critical to maintaining CNS cell homeostasis



Our approach: **AAV gene therapy to deliver functional PGRN to the brain**

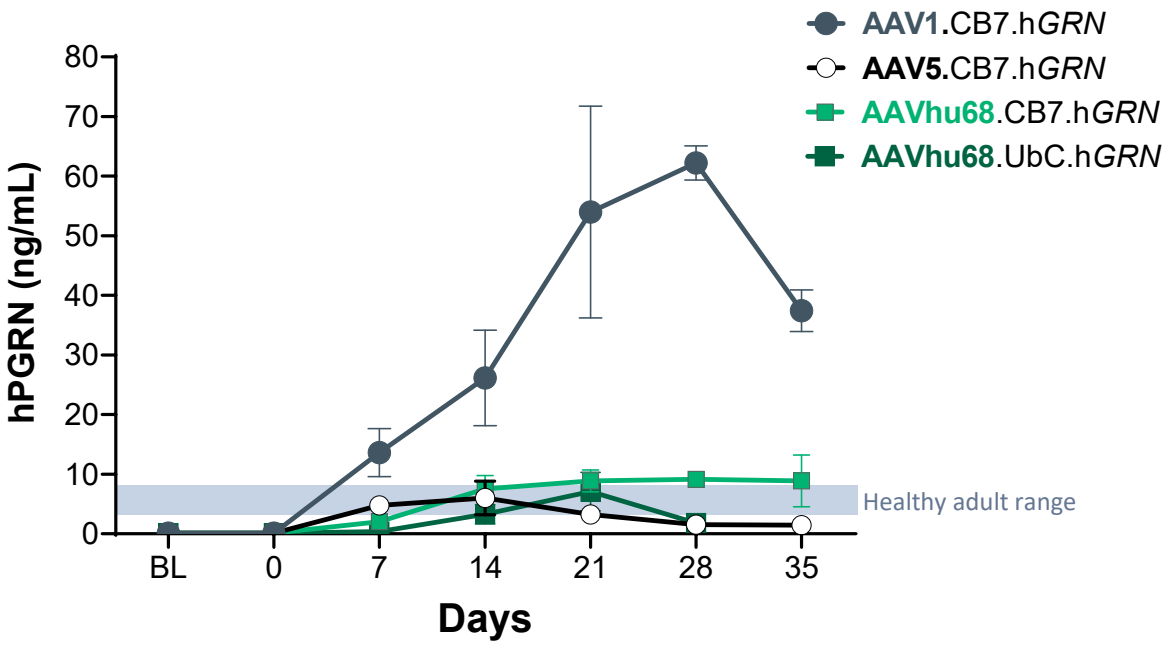
PBFT02



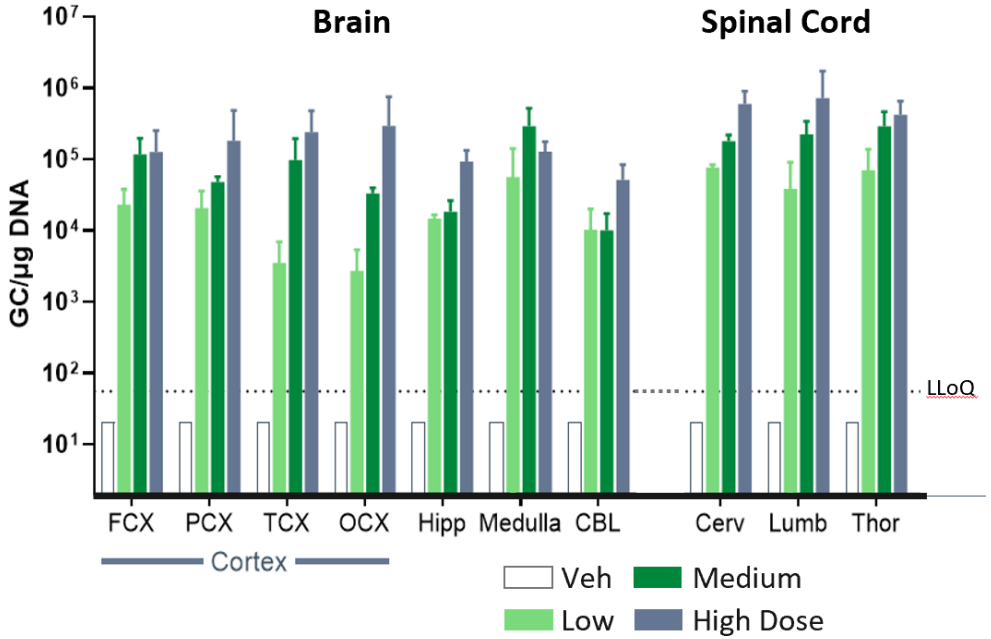
- Delivers functional *GRN* genes encoding PGRN to brain and spinal cord
- Transduces multiple CNS cell types

AAV1 Selected as Vector after Capsid Comparison in NHPs. Robust Vector Delivery to Brain Regions affected in FTD

Superior hPGRN levels in NHP CSF after ICM AAV1 compared to AAV5 and AAVhu68 (AAV9 variant)



ICM PBFT02 administration to NHPs resulted in high gene distribution throughout the CNS

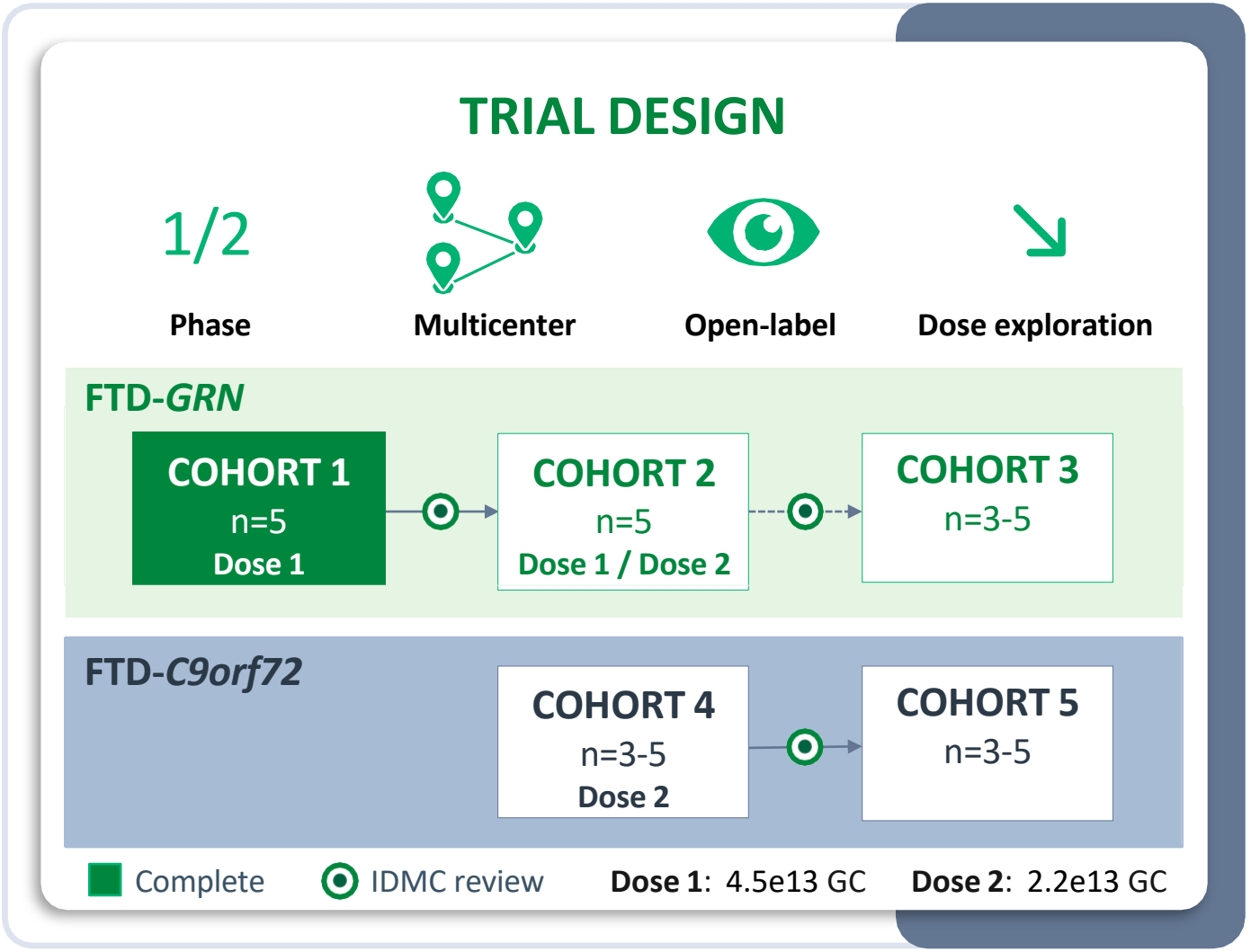


- Proof of concept demonstrated in *Grn*$^{-/-}$ mice: PBFT02 improved lysosomal function and neuroinflammation

NHPs (n=2/group) ICM-delivered AAV.h*GRN* (3.3 x 10^{11} GC/g brain), day 0. Elevation curtailed by immune response to human PGRN.

CBL, cerebellum; CSF, cerebrospinal fluid; CX, cortex (F-frontal, O-occipital, P-parietal, T, temporal); Hipp, hippocampus; ICM, intra-cisterna magna; h*GRN*, human granulin gene; NHP, non-human primate; PGRN, progranulin.

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



DURATION

2 years. Additional 3 years follow-up for safety and durability of effect

PRIMARY ENDPOINTS

Safety and tolerability

SECONDARY ENDPOINTS

Biomarkers

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

Clinical

- CDR + NACC FTLD sum of boxes

EXPLORATORY BIOMARKERS

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

GC, genome copies. *Fluid biomarkers*: GFAP, glial fibrillary acidic protein; LAMP-1, lysosomal-associated membrane protein 1; Lyso-GL1, glucosylsphingosine; NfL, neurofilament light chain.

Key Eligibility and Baseline Demographics for UpliFT-D FTD-*GRN* Dose 1 Participants

upliFT-D

Eligibility

- Ages 35 to 75, inclusive
- Pathogenic *GRN* mutation carrier
- Symptomatic FTD-*GRN*
- Able to live in the community

Learn more about upliFT-D here:

DOSE 1 (n=7)	Mean / % / n	Range
Age (yrs)	63.3	51-71
Sex	M: 57% F: 43%	
FTD-*GRN* phenotype (n)	bvFTD: 5 lvPPA: 1 svPPA: 1	
Disease duration at baseline (yrs)	2.9	1 - 5
PGRN, CSF (ng/mL)	2.3	1.5 - 2.9
PGRN, plasma (ng/mL)	38.5	22.4 - 89.0
NfL, plasma (pg/mL)	43.4	12.4 - 105
Clinical Dementia Rating Scale, Global (%)	1: 57% 2: 43%	
Clinical Dementia Rating Scale, Sum of Boxes[1]	9.6	5 - 17

[1]CDR +NACC FTLD sum of boxes.
bvFTD, behavioral variant; lvPPA, Logopenic variant primary progressive aphasia , svPPA, semantic variant PPA.

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upliFT-D: Interim Safety Profile

Interim Safety Highlights* - Dose 1 PBFT02 in FTD-GRN Patients (n=7)

- In 5 of 7 participants, all treatment emergent AEs were mild to moderate
- 2 of 7 participants experienced a total of 3 SAEs
  - Participant 1: asymptomatic venous sinus thrombosis (VST) and hepatotoxicity, leading to a revised immunosuppression regimen in all subsequent patients**
  - Participant 7: asymptomatic VST, on treatment with anticoagulants. No evidence of hepatotoxicity, atypical 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 participants in Cohort 2 to receive Dose 2: 50% of Dose 1

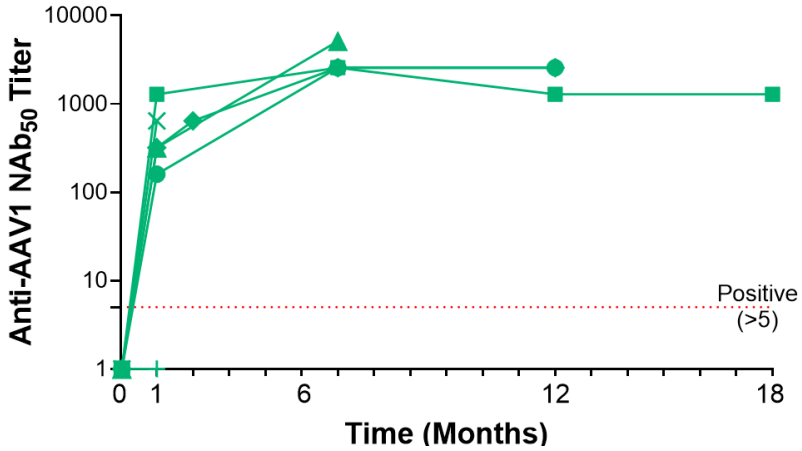
*Participant safety follow-up ranged from 1 to 18 months post-dosing as of data cutoff of January 24, 2025.
**Participant 1 received oral prednisone 60 mg daily through day 60; subsequent patients received a revised immunosuppressive regimen of 1g methylprednisolone IV daily to day 3, followed by oral 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 Dose 1 Associated with Expected Immune Responses to Capsid. No Response to hPGRN Detected

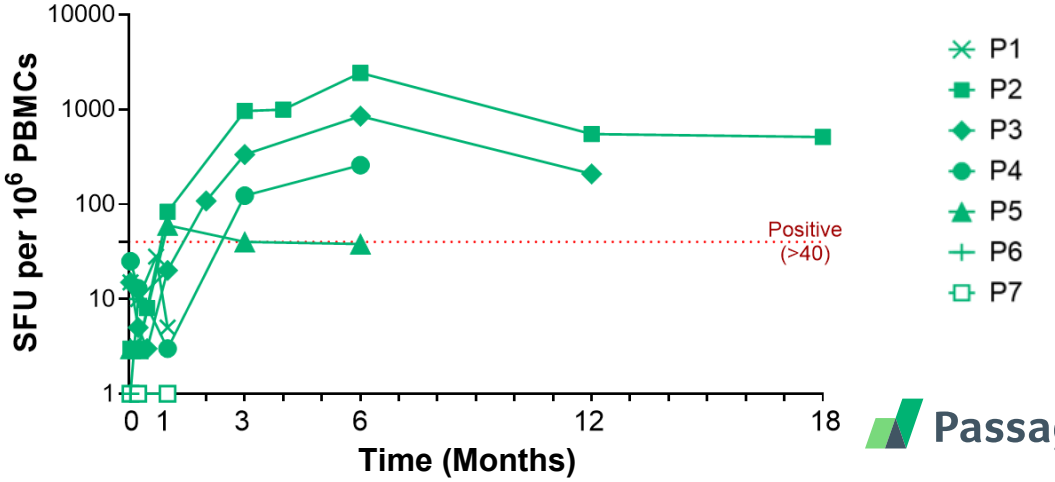
upliFT-D

- No Dose 1 participant had anti-AAV1 neutralizing antibodies at baseline
- As expected, most participants developed anti-AAV1 antibodies in CSF and serum at 30 days post-PBFT02 treatment
- Four participants developed T-cell response against AAV1 post-PBFT02 treatment, with no clinical significance
- No T- or B-cell immune response against hPGRN was detected

Anti-AAV1 Neutralizing Antibody Responses in CSF



T-cell responses against AAV1 in 4 participants



P7: CSF Nab data pending

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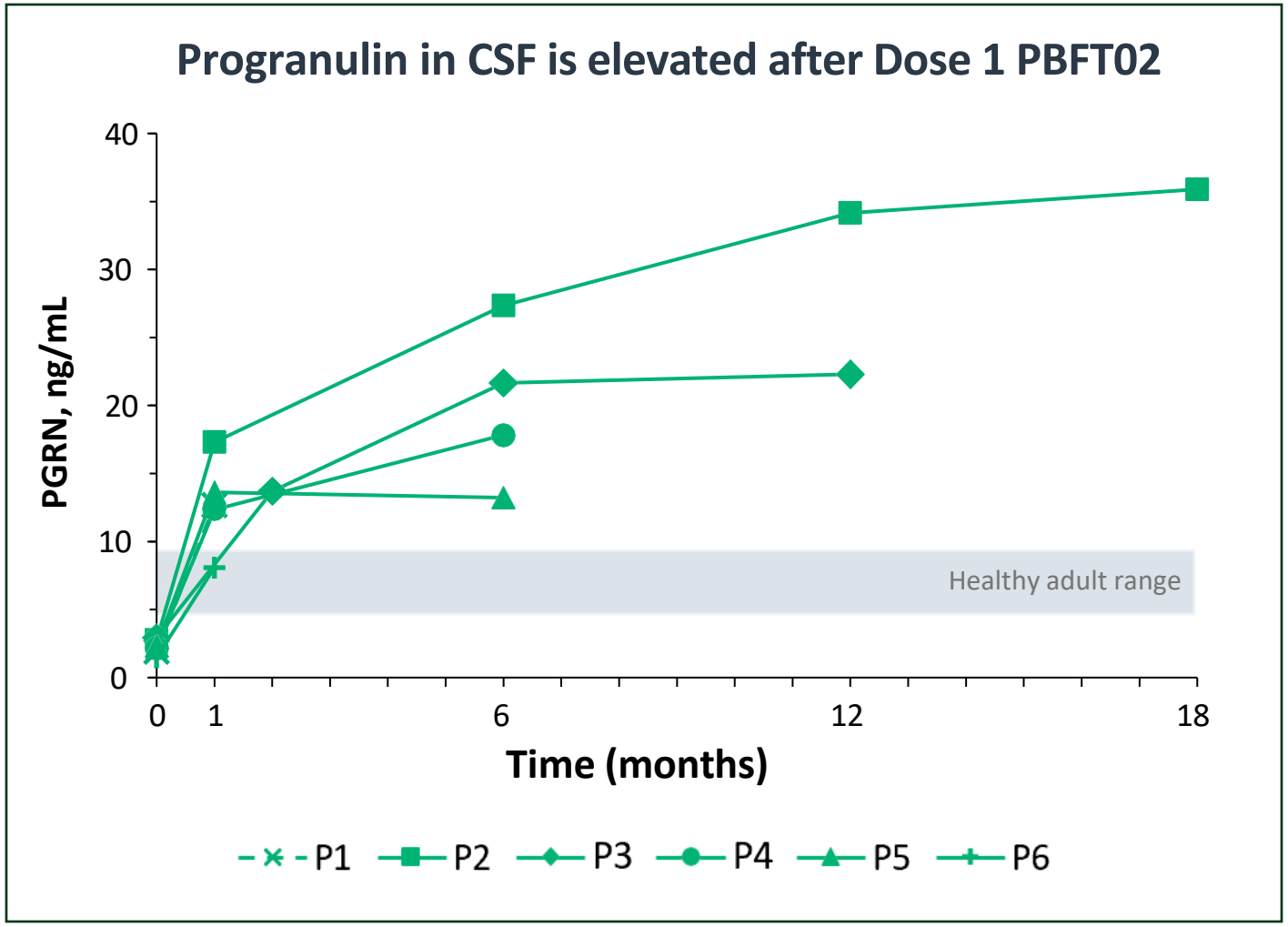
PBFT02 Generated Robust, Durable Increases in CSF PGRN



Promising PGRN profile:

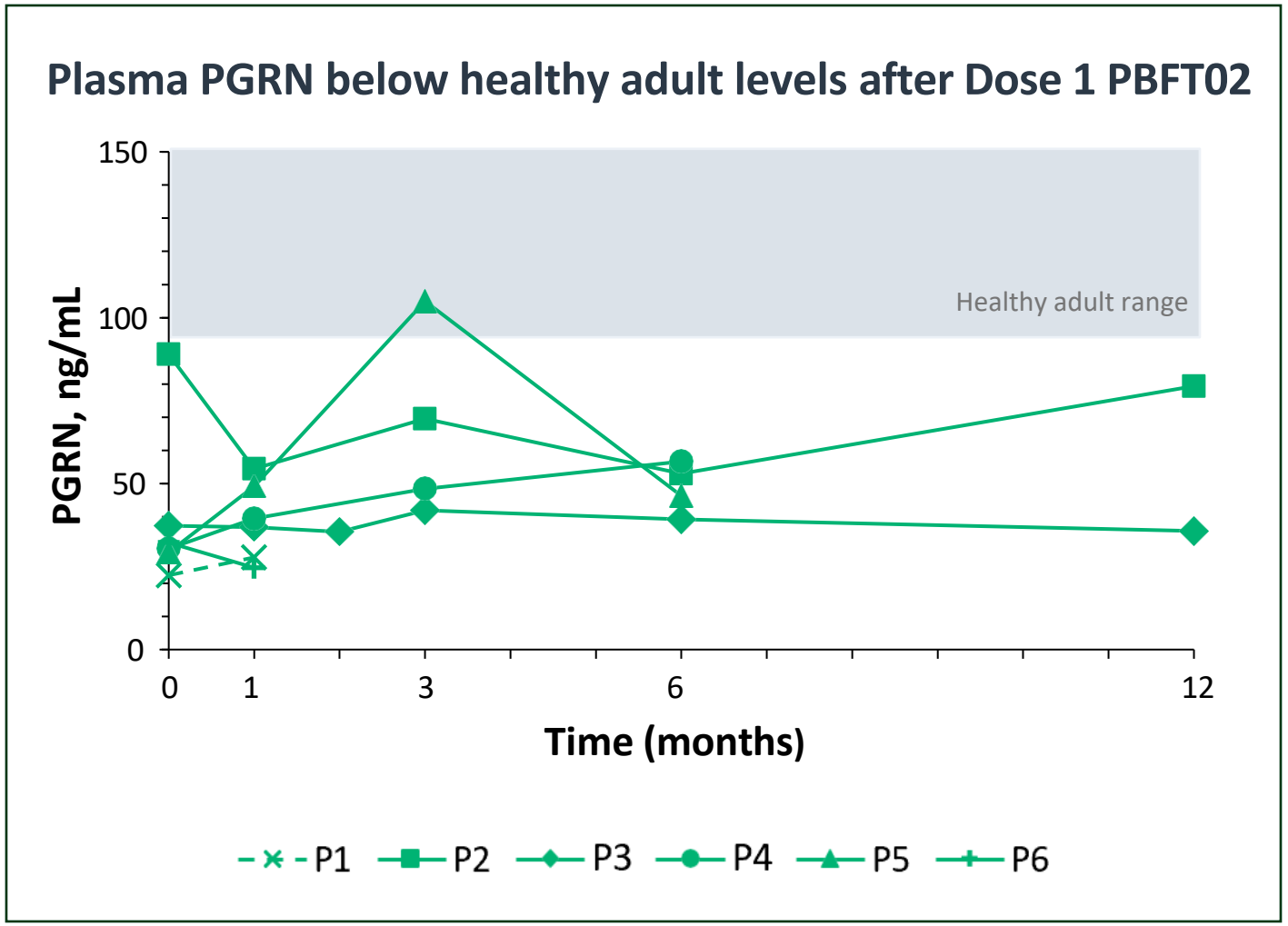
- Consistent elevation from baseline
- Durable to 18 months
- Levels overall plateauing by 6-12 months

CSF Progranulin (ng/mL) in FTD-*GRN* Participants

	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	-

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).
P7: Data pending. CSF, cerebrospinal fluid.

PGRN Elevation Localized to CNS Following ICM PBFT02 Administration



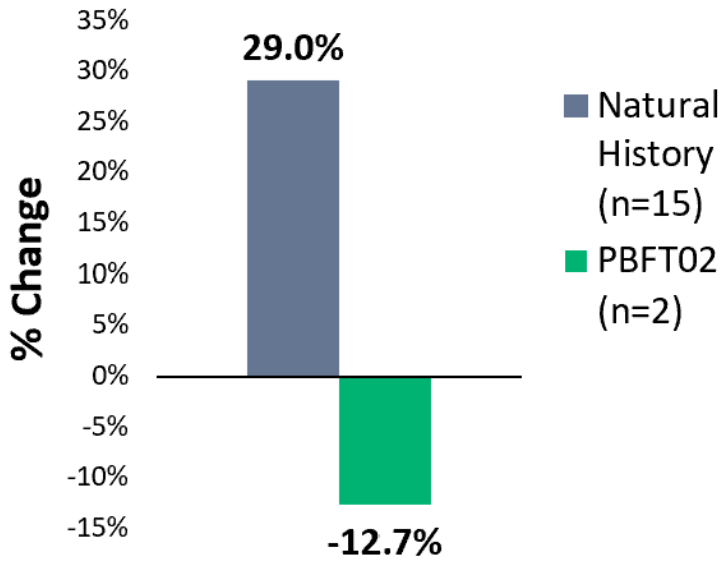
- Plasma PGRN levels remained below normal levels up to 12 months post-dose in FTD-*GRN* patients
- PGRN increased only in the CNS, where it has potential to reduce neurodegeneration

11 Shading: Lower limit of healthy adult sample range for plasma PGRN (91.6 – 372.4 ng/mL, n = 56) (Passage Bio data).
P7: Data pending

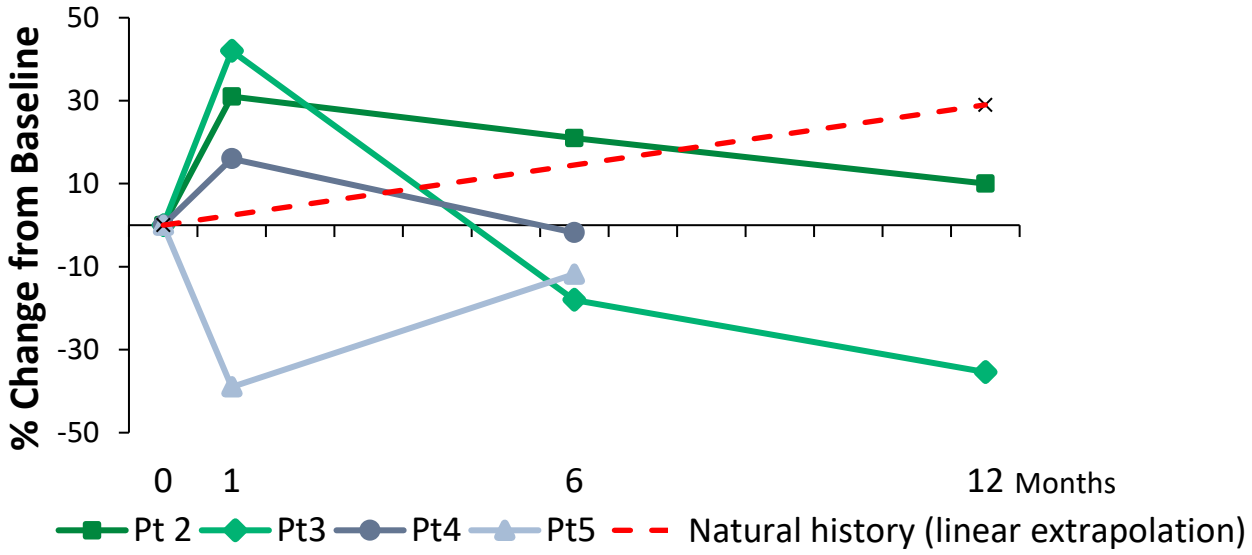
Plasma NfL Showed Early Evidence of Improvement in a Disease Progression Biomarker vs Natural History

- Plasma NfL is the only FTD-*GRN* disease progression biomarker with published natural history data[1,2]
- Both participants 12 M post-PBFT02 had a reduced annual rate of change in plasma NfL compared to published natural history data[1]

Plasma NfL Annual Rate of Change



Plasma NfL % Change from Baseline (> 6 M 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); [2] van der Ende et al, *Lancet Neurol* 2019; 18:1103-11.

Conclusions: PBFT02 Dose 1 in FTD-*GRN*

- Dose 1 PBFT02 demonstrated robust, consistent elevation of CSF PGRN and was durable up to 18 months post-treatment
- Early evidence of improvement in disease progression vs. natural history as measured by plasma NfL
- PBFT02 was well tolerated in 5 of 7 Dose 1 recipients with modified immunosuppression regimen[1]
- 2 of 7 Dose 1 participants had SAEs, which were asymptomatic
- Currently enrolling FTD-*GRN* and FTD-*C9orf72* participants to receive Dose 2 PBFT02 (50% of Dose 1)

[1]Patient safety follow-up ranged from 1 to 18 months post-dosing as of data cutoff of January 24, 2025.
CSF, cerebrospinal fluid; NfL, neurofilament light chain; SAE, serious adverse event.

We would like to thank the patients, families, caregivers, investigators, and our collaborators