Adeno-Associated Viral Vector Serotype 1 (AAV1) Gene Therapy for FTD-*GRN*: A Phase 1b Dose-Escalation Study to Assess Safety, Tolerability, and Pharmacodynamic Effects of PBFT02

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Background

- In FTD-*GRN*, progranulin (PGRN) concentrations are reduced by 30%–50%, leading to adult-onset neurodegeneration.[1,2]
- PBFT02 uses an adeno-associated virus serotype 1 (AAV1) vector construct to deliver a functional copy of the *GRN* gene to the central nervous system (CNS) via an intracisternal magna (ICM) injection.[2]
- PBFT02 may provide sustained elevation of PGRN levels to overcome the PGRN deficiency in *GRN* mutation carriers with potential to modify FTD-*GRN* disease trajectory.[3-5]
- The **upliFT-D** study is a first-in-human clinical trial of PBFT02 that will assess the safety, tolerability, and pharmacodynamic effects of this treatment in patients with FTD-*GRN*.[5]

Preclinical Evidence

- **Rationale for AAV1 serotype selection:** In nonhuman primates (NHPs), administration of the AAV1 vector construct resulted in an increase of ~5× PGRN in cerebrospinal fluid (CSF) versus other vectors without further elevating peripheral levels (**Figure 1**).[6] Furthermore, human PGRN (hPGRN) levels in CSF reached levels that were many fold higher than those observed in healthy human volunteers, suggesting supraphysiologic levels of PGRN may be achieved in patients with FTD-*GRN* (data not shown).[6] Dose-related increases in CSF PGRN were seen at 14 days postdose (**Figure 2**).[7]

Figure 1 Production of hPGRN in CSF and plasma in NHPs following ICM AAV delivery[6,7,a]

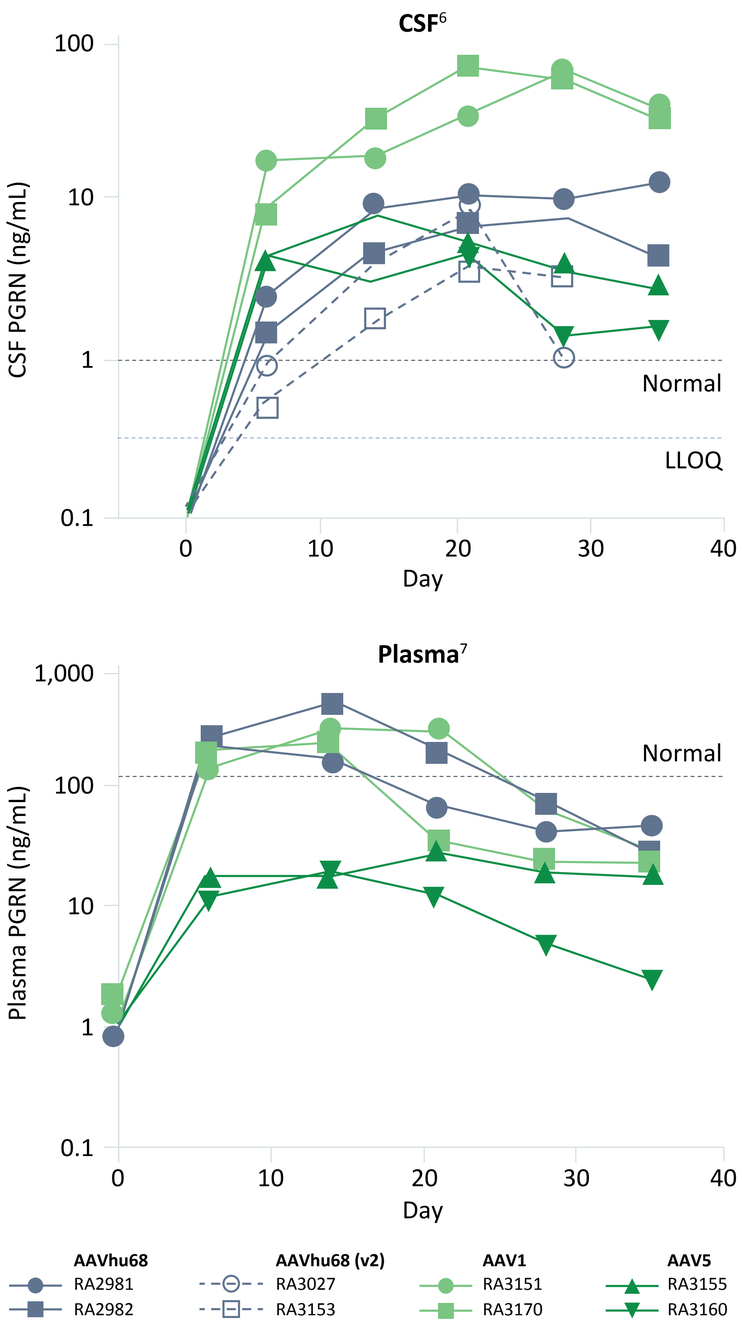
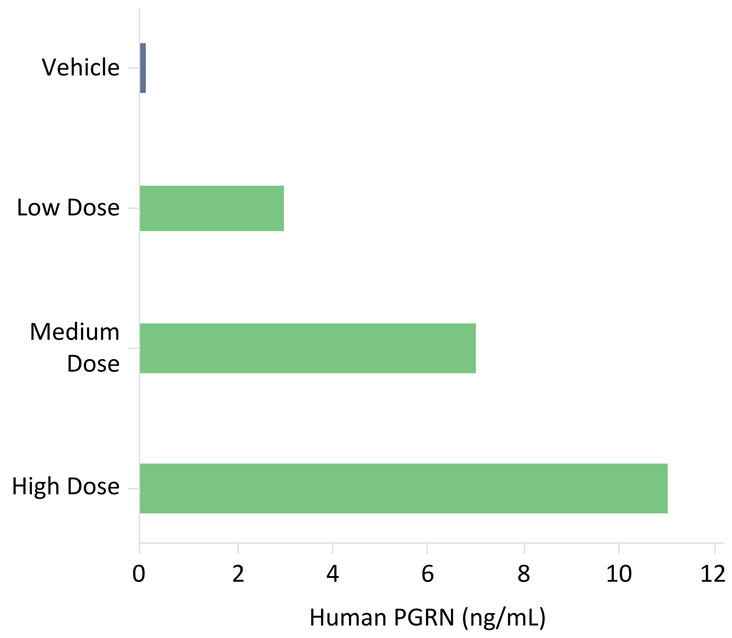


Figure 2 AAV1 Showed Dose-Related Increases in CSF PGRN at 14 days postdose[8]



The upliFT-D Study

- The upliFT-D trial is a multicenter, open-label, single-arm, dose-escalation study (**Figure 3**).[5] The treatment duration is detailed in **Figure 4**.[10] Eligibility criteria are shown in **Figure 5**.[5] The primary and secondary outcomes are shown in **Figure 6**.[5]

Figure 3 Study Design[5,10]

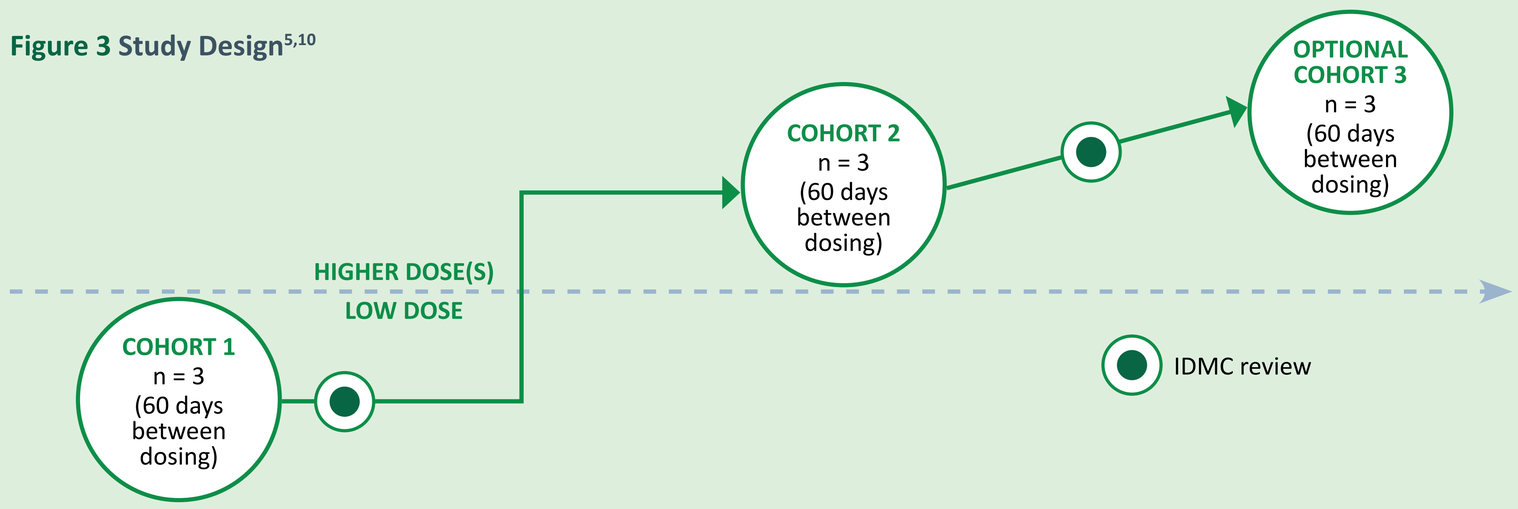


Figure 4 Treatment Duration[5,10]

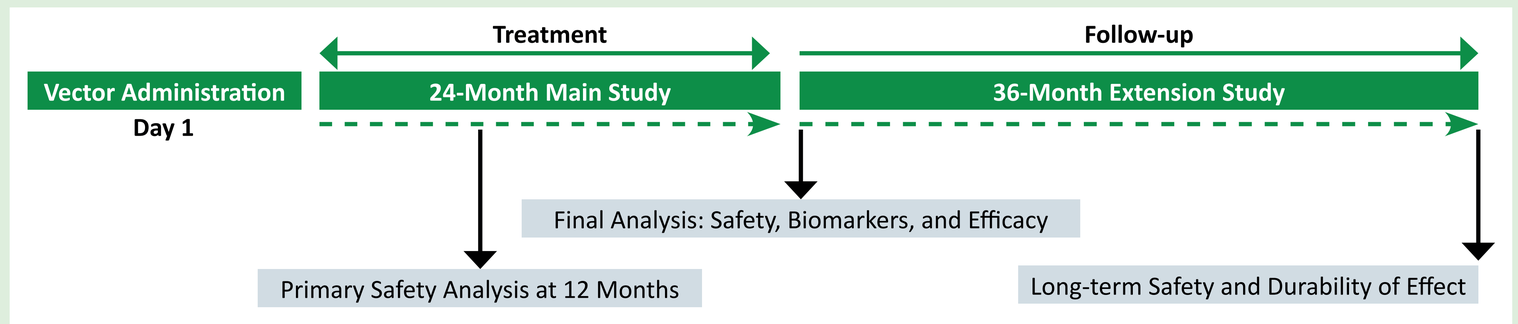


Figure 5 Eligibility Criteria[5,b]

Select Inclusion Criteria

- Aged 35 to 75 years
- Clinical diagnosis of possible behavioral variant FTD or primary progressive aphasia
- *GRN* mutation carrier
- Has a reliable informant
- Living in the community

Select Exclusion Criteria

- Liver disease
- Peripheral sensory neuropathy
- Contraindications to MRI or LP
- Taking anticoagulants

Figure 6 Primary and Secondary Outcomes[5]

Primary Outcomes

- Number of participants who experience one or more adverse events
- Change from baseline (CFB) in nerve conduction studies
- Changes in humoral and cell-mediated immune responses against the capsid and transgene product, as measured using anti-AAV1 total and neutralizing antibodies, anti-hPGRN total antibodies, and interferon-gamma ELISpot assays

Secondary Outcomes

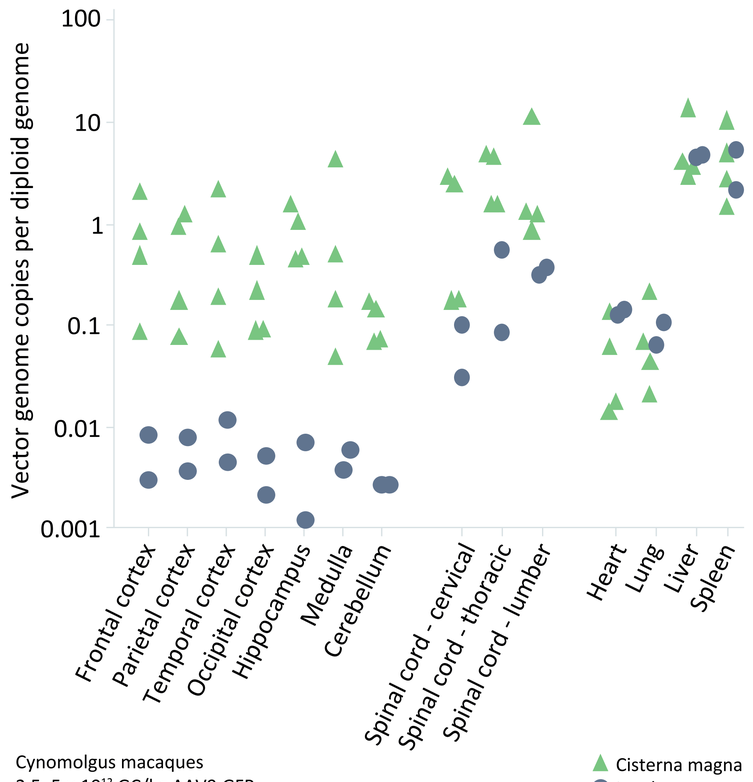
- Clinical: CDR plus NACC FTLD Sum of Boxes CFB
- Target engagement: CSF PGRN levels CFB

Other Biomarkers:

- Plasma and CSF NfL CFB
- Plasma GFAP
- Retinal nerve fiber layer thickness and lipofuscin deposition CFB
- Cortical atrophy and white matter integrity via MRI

- **Rationale for ICM delivery:** Preclinical studies demonstrated that ICM administration leads to a 10–100× increase in CNS distribution of AAV vectors, optimizes CNS biodistribution, and is not limited by the impact of neutralizing antibodies[9] (**Figure 7**).

Figure 7 ICM vs LP Intrathecal AAV Delivery of GFP[9]



Cynomolgus macaques
2.5–5 × 10^{12} GC/kg AAV9.GFP
GC/dg=vector genome copies per host diploid genome.

CDR plus NACC FTLD Sum of Boxes=Clinical Dementia Rating National Alzheimer's Coordinating Center frontotemporal lobar degeneration domains; dg=diploid genome; ELISpot=enzyme-linked immunos; GC=genome copies; GFAP=glial fibrillary acidic protein; GFP=green fluorescent protein; IDMC=independent data monitoring committee; LLOQ=lower level of quantification; LP=lumbar puncture; MRI=magnetic resonance imaging; NfL=neurofilament light;
[a]LLOQ for hPGRN in CSF at a 1:5 dilution. [b]For full list of criteria, please visit clinicaltrials.gov at https://www.clinicaltrials.gov/ct2/show/NCT04747431.

Discussion

- upliFT-D, a first-in-human clinical trial, will examine whether a single dose of PBFT02, administered via ICM injection, is safe, well tolerated, and increases CSF PGRN levels in adult participants with FTD-*GRN*.[5]
- Results from preclinical studies indicate that a single ICM administration promotes widespread biodistribution of the AAV1 vector construct to the CNS, leading to robust CNS transgene expression at lower dosages versus intravenous or intrathecal lumbar delivery routes.[6,9]
- upliFT-D initiated dosing in August 2022 and is currently enrolling globally (**NCT04747431**).[5]

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Disclosures

MG is supported by NIH (AG066597, AG052943), Department of Defense, and foundation sources (Samuel Newhouse Foundation, Peisach Family Foundation), and currently participates in trials sponsored by Prevail, Biogen, and Life Molecular Imaging. **DJI** receives research support to conduct therapeutic trials from Alector and Prevail and is supported by grants from NIH (R01-NS109260, P01-AG066597, P30-AG10124, U19-AG062418) and the Penn Institute on Aging. **PES** participates in trials with Lilly, Roche, UCB Pharma, Biogen, Passage Bio, Inc. and others and has been an advisor and speaker for Lilly, Roche, and Biogen. He is funded by a dozen NIH grants and several foundations. **LCdS** has no conflicts of interest to disclose. **TV**, **PT**, **KJQ**, **PN**, and **MSF** are full-time salaried employees of Passage Bio, Inc. and have received stock options.

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Presented at ISFTD 2022, November 2–5, 2022, Paris/Lille, France

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