# p-002

# Thursday

## 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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**State of the art**
FTD has no disease-modifying therapies. In FTD-*GRN,* progranulin (PGRN) concentrations are reduced by 30-50%, leading to adult-onset neurodegeneration through unknown pathologic mechanisms. Gene therapy may address causal genetic deficits by providing a functional *GRN* copy to resolve the haploinsufficiency caused by *GRN* mutation.

**Methodology**
upliFT-D (NCT04747431) is a first-in-human clinical trial of PBFT02, an AAV1 carrying the human *GRN* gene encoding PGRN*;* ICM (intra-cisterna magna) administration maximizes CNS concentrations while minimizing peripheral exposure. Participants ≥35 to ≤75 years of age with early symptomatic FTD-*GRN* will be enrolled. Two dose cohorts will enroll sequentially, with an optional third dose cohort. Primary outcomes (OCs) include adverse events, nerve conduction study changes, and immune responses to PBFT02. Secondary OCs include changes in clinical assessments (including CDR Plus NACC FTLD Sum of Boxes), change in NfL, GFAP, and volumetric MRI. The 5-year trial will involve a primary efficacy readout at 2-years and a 3-year safety extension.

**Results**
Preclinical studies demonstrated AAV1 highly transduces ependymal cells, providing the potential for high CSF levels of PGRN with broad cross-correction throughout the brain. Pre-existing NAbs and adaptive T cell responses to the AAV1 capsid did not impact CNS distribution nor produced abnormal clinical findings. hPGRN levels in NHP CSF reached levels up to 50x higher than healthy human volunteers, suggesting physiologic levels of PGRN can be achieved.

**Conclusion**
upliFT-D will examine whether a single ICM dose of PBFT02 is safe, well tolerated and increases CSF PGRN levels in adult participants with FTD-*GRN*.

## Conflicts of interest

TV is a full-time employee of Passage Bio.
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, Life Molecular Imaging.
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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.
PT is an employee of Passage Bio, Inc. and has received stock options.
KJQ is an employee of Passage Bio, Inc. and has received stock options.
PN is a full-time salaried employee of Passage Bio, Inc. and has received stock options as part of his employment agreement.
MSF is an employee of Passage Bio, Inc. and has received stock options.