Poster No. 103638

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

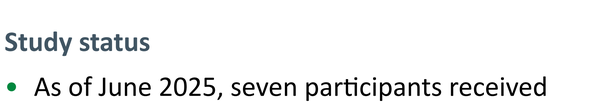
Voss T,[1] Triglia P,[1] Ni YG,[1] Browne SE,[1] Chou W,[1] Ducharme S,[2] Irwin DJ,[3] Santana I,[4] Schulz PE,[5] Takada LT,[6] Tartaglia MC,[7] de Souza LC[8]

[1]Passage Bio, Inc., Philadelphia, PA, USA; [2]Douglas Mental Health University Institute and Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada; [3]Perelman School of Medicine at the University of Pennsylvania; University of Pennsylvania Health System, Philadelphia, PA, USA; [4]Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal; [5]McGovern Medical School, UTHealth Houston, Houston, TX, USA; [6]Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; [7]University Health Network and Tanz Centre for Research in Neurodegenerative Diseases, Toronto, Ontario, Canada; [8]Hospital das Clínicas Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

Background

- Frontotemporal dementia (FTD) is a neurodegenerative clinical syndrome with no disease-modifying treatments
- PBFT02, a non-replicating recombinant AAV1 vector carrying a codon-optimized human *GRN* gene under the control of the ubiquitous CB7 promoter (**Figure 1**), is being assessed in a phase 1/2 clinical trial in FTD-*GRN* participants and FTD-*C9orf72* participants (upliFT-D; NCT04747431)

Figure 1 PBFT02 vector structure



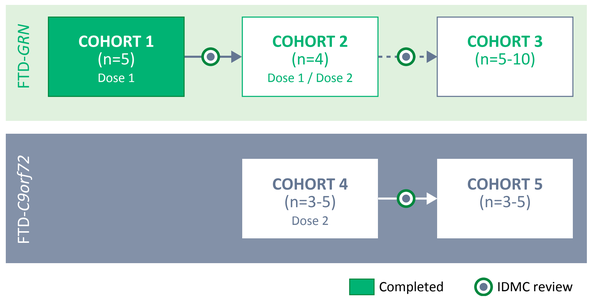
- Here we present interim safety and biomarker for the first eight participants

Methods

Study design

- upliFT-D is a phase 1/2 global, multi-center, open-label clinical trial of PBFT02 administered by single injection into the cisterna magna in participants aged 35 to 75 years, documented to be pathogenic carriers of *GRN* or *C9orf72* mutation
- The clinical trial will sequentially enroll three FTD-*GRN* cohorts and two FTD-*C9orf72* cohorts (**Figure 2**)
- The primary objective is safety and tolerability; secondary objectives include biomarkers of target engagement (eg, progranulin; PGRN), biological activity, and disease progression (neurofilament light chain; NfL)

Figure 2 upliFT-D study design



Dose 1: 4.5E13 GC; Dose 2: 2.2E13 GC.

Study status

- As of June 2025, seven participants received PBFT02 Dose 1 (4.5E13 GC) and one participant received PBFT02 Dose 2 (2.2E13 GC)
- One additional participant will complete Cohort 2, and subsequent participants will be treated as part of Cohort 3, which is now expected to consist of five to ten participants

Results

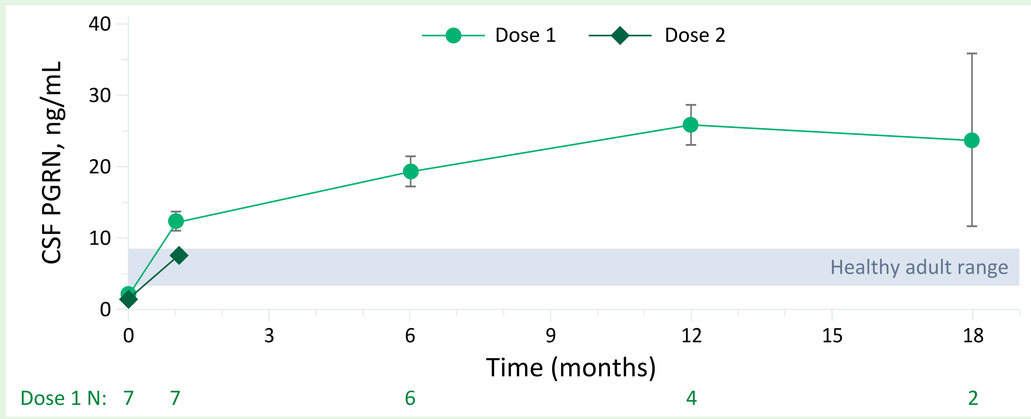
Baseline demographics and clinical characteristics

- Baseline demographics and clinical characteristics for FTD-*GRN* participants are shown in **Table 1**
- All participants had a confirmed pathogenic *GRN* mutation and symptomatic FTD-*GRN*
- Clinical Dementia Rating plus National Alzheimer's Coordinating Center Behavior and Language Domains (CDR plus NACC FTLD) Sum of Boxes scores ranged from 5 to 17

PBFT02 generated robust, durable increases in CSF PGRN in participants with FTD-*GRN*

- Dose 1 PBFT02 administration resulted in increased levels of CSF PGRN expression with sustained elevation through 18 months post-treatment
  - At baseline, mean levels of CSF PGRN were below 3 ng/mL
  - Mean levels increased to 12.4 ng/mL at one month (n=7), 19.4 ng/mL at six months (n=6), 25.9 ng/mL at 12 months (n=4), and 23.8 ng/mL at 18 months (n=2) (**Figure 3**)
- CSF PGRN levels for the first participant treated with Dose 2 PBFT02 (50% of Dose 1) increased substantially from 1.5 ng/mL at baseline to 7.6 ng/mL at one month, approaching the upper limit of a healthy adult reference range

Figure 3 Mean (±SEM) CSF PGRN expression following PBFT02 administration

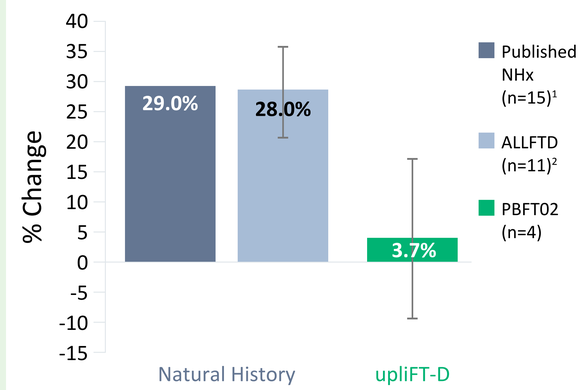


Shading: Healthy adult sample range for CSF PGRN (range: 3.28–8.15 ng/mL, mean: 4.76 ng/mL, n=61) (Passage Bio data).

Plasma NfL showed early evidence of improvement in a disease progression biomarker vs. natural history

- Based on published natural history data (n=15)[1] and sponsor analysis of ALLFTD data (n=11)[2], in untreated symptomatic FTD-*GRN* participants, expected increases in plasma NfL are ~28%–29% per year
- Participants treated with Dose 1 PBFT02 experienced a lower annual rate of change in plasma NfL compared with natural history data, with levels increasing by only 4% on average (n=4) at 12 months post-treatment (Dose 1) (**Figure 4**)

Figure 4 Mean (±SEM) annual rate of change of plasma NfL following PBFT02 administration



1. Published natural history: 15 symptomatic FTD-*GRN* patients; mean years since diagnosis: 2.9 (Saracino D, 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.

PBFT02 (n=4): Baseline plasma NfL range: 39.6 to 45.6 pg/mL. Average time since diagnosis 2.3 years.

Table 1 Baseline demographics and clinical characteristics

		PBFT02 (N=8)
Age, years (range)		64.4 (51–72)
Sex, n (%)	Male	4 (50)
	Female	4 (50)
FTD-*GRN* phenotype, n	bvFTD	5
	PPA	3
Disease duration at baseline, years (range)		2.9 (1–5)
PGRN, CSF, ng/mL (range)		2.1 (1.5–2.9)
PGRN, plasma, ng/mL (range)		36.6 (22.4–89.0)
NfL, plasma, pg/mL (range)		51.9 (12.4–111.0)
Clinical Dementia Rating Scale plus NACC FTLD, Global, %	0.5	0
	1	50
	2	50
Clinical Dementia Rating Scale, Sum of Boxes (range)		10.3 (5–17)

Values reported are means unless otherwise specified.

PBFT02 interim safety highlights (as of June 15, 2025)

- In five of eight participants, all TEAEs were mild to moderate in severity
- Three of eight participants experienced a total of four SAEs
- Two participants who were treated with Dose 1 experienced a total of three asymptomatic SAEs: venous sinus thrombosis (n=2) and hepatotoxicity (n=1)
- The participant who was treated with Dose 2 experienced the SAE of pulmonary embolism in the setting of a concurrent systemic infection and responded to treatment with anticoagulants
- No evidence of DRG toxicity in any participant
- No complications during ICM administration

Conclusions

- ICM administration of PBFT02 resulted in a robust, consistent and durable elevation of CSF PGRN levels, which was maintained up to 1.5-years post-treatment
- Early data in treated participants showed a reduction in plasma NfL rate of change when compared to natural history
- Overall, there was no evidence of DRG toxicity or complications during ICM administration
- Cohort 3 participants will receive low-dose prophylactic anticoagulation

Abbreviations

AAV1, adeno-associated virus 1; bvFTD, behavioral variant frontotemporal dementia; CDR plus NACC FTLD, Clinical Dementia Rating plus National Alzheimer's Coordinating Center Behavior and Language Domains; CSF, cerebrospinal fluid; DRG, dorsal root ganglion; FTD, frontotemporal dementia; FTD-*GRN*, frontotemporal dementia with granulin mutation; *GRN*, granulin; ICM, intra-cisterna magna; IDMC, Independent Data Monitoring Committee; ITR, inverted terminal repeat; NfL, neurofilament light chain; PGRN, progranulin; PPA, primary progressive aphasia; TEAE, treatment-emergent adverse event; SAE, serious adverse event; SEM, standard error of the mean.

References

1. Saracino D, 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.

Disclosures

TV, PT, YGN, SEB, and WC are employees of Passage Bio, Inc.

Presented at Alzheimer's Association International Conference (AAIC); July 27–31, 2025; Toronto, Canada

medinfo@passagebio.com

Medical writing support was provided by Parexel International and funded by Passage Bio, Inc.