Poster No. 007

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

Chavez J,[1] Forman M,[1] Voss T,[1] Triglia P,[1] Ni YG,[1] Browne SE,[1] Quadrini KJ,[1] Chou W,[1] Ducharme S,[2] Irwin DJ,[3] Santana I,[4] Schulz PE,[5] Takada L,[6] Tartaglia C,[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 e 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

- PBFT02 is a non-replicating recombinant AAV1 vector, which carries a codon-optimized sequence of the human *GRN* gene under the control of the ubiquitous CB7 promoter (**Figure 1**)

Figure 1 – PBFT02 vector structure



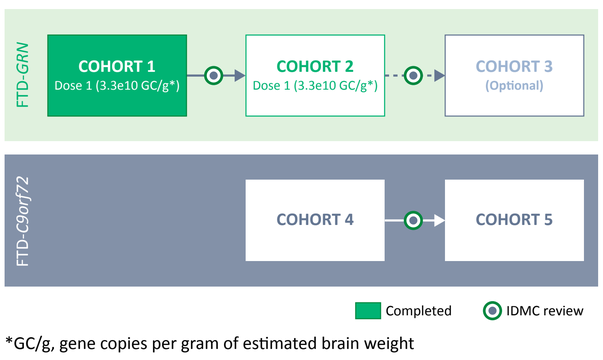
- Studies in non-human primates have demonstrated widespread distribution of PBFT02 throughout the brain when administered intrathecally in the cisterna magna[1]
- In murine models of FTD, administration of PBFT02 restores lysosomal function and reduces neurodegeneration[1]
- PBFT02 is being developed as a disease-modifying therapy for individuals with FTD-*GRN* and FTD-*C9orf72*
- Here we present interim safety and biomarker data from FTD-*GRN* participants in upliFT-D Cohort 1

Methods

Study design

- PBFT02 is being assessed in a phase 1/2 clinical trial in participants with FTD-*GRN* and FTD-*C9orf72* (upliFT-D; NCT04747431) (**Figure 2**)
- This multi-center, open-label, first-in-human study was designed to evaluate safety, tolerability, and pharmacodynamics of PBFT02
- Additional endpoints include, biomarkers of lysosomal dysfunction and neurodegeneration, immunogenicity, and clinical status
- PBFT02 is administered via ICM injection under CT guidance

Figure 2 upliFT-D study design



*GC/g, gene copies per gram of estimated brain weight

Study status

- Five participants were enrolled in Cohort 1; four participants remain in the study as of August 20, 2024 (most recent data cut)
- One participant withdrew from the study 3 months post-PBFT02 administration
- Cohort 2 is currently enrolling
- Cohort 4 is anticipated to be open for enrollment in the first half of 2025

Results

Baseline demographics and clinical characteristics

- Baseline demographics and clinical characteristics of Cohort 1 participants are shown in **Table 1**
- All participants had a confirmed pathogenic *GRN* mutation and symptomatic FTD-*GRN* (CDR, Sum of Boxes scores ranged between 7 and 17)

Table 1 Baseline demographics and clinical characteristics of Cohort 1 participants

	P1	P2	P3	P4	P5
Age (years)	51	59	60	69	71
Gender	Male	Female	Male	Male	Female
FTD-*GRN* phenotype	lvPPA	bvFTD	bvFTD	svPPA	bvFTD
Age at diagnosis (disease duration, years)	47 (4)	56 (3)	59 (1)	68 (1)	67 (4)
PGRN at screening, plasma (ng/mL)	60.9	44.8	36.0	25.5	17.4
PGRN at baseline, CSF (ng/mL)	1.9	2.8	2.9	2.2	2.3
Clinical Dementia Rating Scale, Global	1	2	2	2	1
Clinical Dementia Rating Scale, Sum of Boxes	7.5	17	12	11	7

Clinical Dementia Rating Scale, Sum of Boxes has a total score of 24; higher scores are indicative of more severe dementia phenotypes

PBFT02 was well-tolerated among Cohort 1 participants who received enhanced immunosuppression

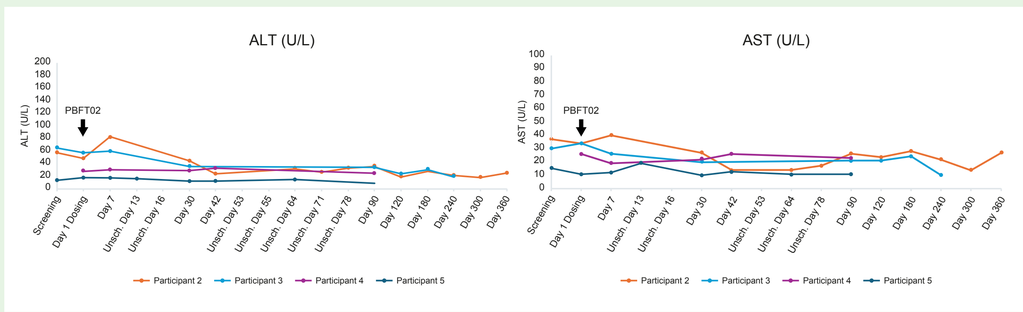
- TEAEs were reported in all participants (n=5/5 [100.0%]); most (38/40 events) were mild-to-moderate. SAEs were reported for one participant (n=1/5 [20.0%]) (**Table 2**)
- One participant, the first treated (n=1/5 [20.0%]), had two treatment-related SAEs and withdrew from the study (**Table 2**)
- The first participant treated with PBFT02 received 60 mg oral prednisone daily through 60 days. This participant had an asymptomatic cerebral venous sinus thrombosis (VST) on MRI and displayed an increase in ALT/AST 7 days and 7 weeks post-treatment, which responded to IV steroids. Bilirubin levels remained normal throughout
- For participants 2 through 5, the immunosuppression regimen was adjusted to 1 g methylprednisolone IV daily to day 3, followed by oral prednisone to day 60
- For participants receiving the adjusted immunosuppression regimen, there were no substantial increases in markers of hepatotoxicity (**Figure 3**), no evidence of VST on MRI, and no SAEs up to day 360

Table 2 Adverse events reported among Cohort 1 participants

	Cohort 1 (N=5), n (%) [events]
Any treatment-related TEAE	5 (100.0) [40]
Mild (Grade 1)	5 (100.0) [29]
Moderate (Grade 2)	4 (80.0) [9]
Severe (Grade 3)	1 (20.0) [2]
Life threatening (Grade 4)	0
Death (Grade 5)	0
Any SAE	1 (20.0) [2]
Any treatment-related SAE	1 (20.0) [2]
Any TEAE leading to early discontinuation	1 (20.0)

Most common TEAE by SOC among Cohort 1 participants was nervous system disorders (n=4; 80.0%). SAEs included hepatotoxicity and cerebral venous sinus thrombosis (asymptomatic and detected on an unscheduled MRI scan 55 days post-treatment); both were considered treatment- or procedure-related

Figure 3 Hepatotoxicity markers post-PBFT02 administration in Cohort 1 participants who received a revised immunosuppression regimen



Participant 1 received the initial immunosuppression regimen and displayed markedly increased ALT/AST levels (ALT 16x ULN; AST 4x ULN) following PBFT02 administration, which was managed with IV steroids (data not shown); participants 2-5 received the adjusted immunosuppression regimen

Immunogenicity

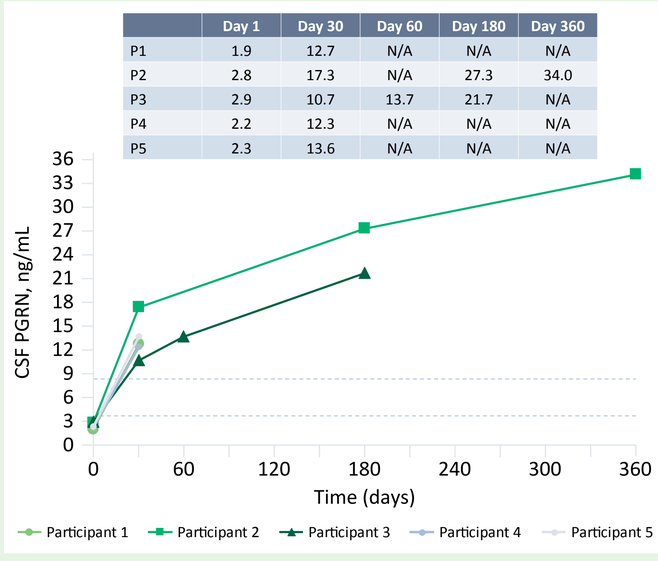
- None of the participants in Cohort 1 had anti-AAV1 neutralizing antibodies at baseline; as expected, all participants developed anti-AAV1 antibodies in CSF and serum at 30 days post-PBFT02 treatment
- Two participants developed T-cell response against AAV1 180 days post-PBFT02 treatment, with no clinical significance
- No T- or B-cell immune response against hPGRN was detected

A single dose of PBFT02 promotes a robust and durable increase in PGRN expression

- Relative to baseline, PBFT02 increased CSF PGRN expression in all participants; up to 6-fold at day 30 (n=5) and up to 10-fold at day 180 (n=2). The effect of PBFT02 was consistent across all participants (**Figure 4**)
- CSF PGRN levels remained elevated at day 360 (n=1). The rate of increase slowed between days 180 and 360 (D30-180: 58% vs. D180-D360: 26%)
- Following PBFT02 treatment, plasma PGRN expression remained below the range observed in healthy adults among all Cohort 1 participants

Figure 4 PGRN levels in CSF following PBFT02 administration

	Day 1	Day 30	Day 60	Day 180	Day 360
P1	1.9	12.7	N/A	N/A	N/A
P2	2.8	17.3	N/A	27.3	34.0
P3	2.9	10.7	13.7	21.7	N/A
P4	2.2	12.3	N/A	N/A	N/A
P5	2.3	13.6	N/A	N/A	N/A



Dashed lines represent observed range of PGRN levels in CSF from healthy adults (3.28–8.15 ng/mL, n=61)

Conclusions

- ICM administration of PBFT02 resulted in a robust and durable elevation of CSF PGRN levels, which was maintained up to 1-year post-treatment
- Plasma PGRN levels were not impacted by PBFT02 administration
- In the four participants who received the revised immunosuppression regimen, there were no SAEs and no evidence of clinically significant immune response
- Given the robust CSF PGRN response, Cohort 2 will continue to evaluate Dose 1

Abbreviations

AAV1, adeno-associated virus 1; ALT, alanine transaminase; AST, aspartate aminotransferase; bvFTD, behavioral variant frontotemporal dementia; CDR, Clinical Dementia Rating Scale; CSF, cerebrospinal fluid; CT, computer tomography; FTD, frontotemporal dementia; FTD-*GRN*, frontotemporal dementia with granulin mutation; *GRN*, granulin; ICM, intra-cisterna magna; IDMC, Independent Data Monitoring Committee; IV, intravenous; lvPPA, logopenic variant primary progressive aphasia; MRI, magnetic resonance imaging; P, participant; PGRN, progranulin; svPPA, semantic variant primary progressive aphasia; TEAEs, treatment-emergent adverse events; SAEs, serious adverse events; SOC, system organ class; ULN, upper limit of normal.

Disclosures

JC, MSF, TV, PT, YGN, SEB, KJQ, and WC are current or former employees of Passage Bio, Inc.

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https://bit.ly/3XkVb8h

Reference: 1: Data on file

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Contact: medinfo@passagebio.com

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