Proposed Patient Population and Outcome Measures for a First in Human Study of PR006, an AAV9-Based Gene Therapy, for Frontotemporal Dementia Patients with Pathogenic GRN Mutations

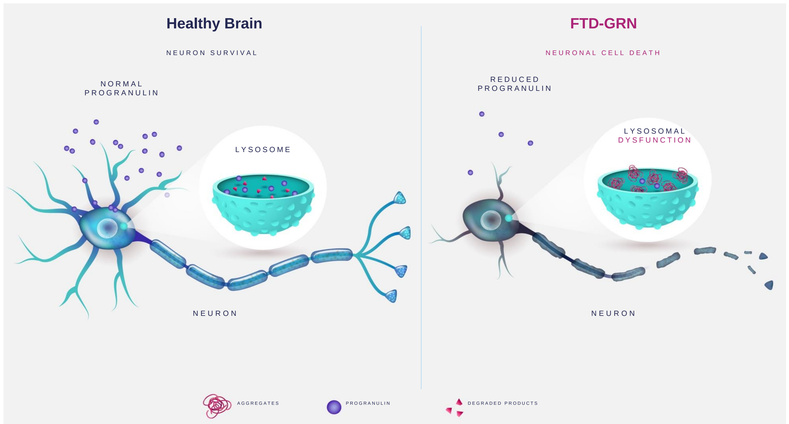
Olga Uspenskaya, Jamie Benoit, Erin Mahoney, Jenny Velaga, Patricia Sondergaard, Mark Lowrey, Jeffrey Sevigny
(Prevail Therapeutics, New York, NY, USA)

Frontotemporal Dementia with GRN Mutations (FTD-GRN)

Frontotemporal dementia (FTD) is a devastating dementia syndrome encompassing a heterogenous group of clinical syndromes characterized by neuroinflammation and neurodegeneration, leading to progressive deficits in behavior, executive function, and language. The age of onset is typically between 45 and 64 years of age.

Up to 40% of FTD cases are familial, and about 5% to 10% of all FTD cases are caused by mutations in the progranulin gene (*GRN*).

Patients suffering from FTD-GRN carry a mutation in a single copy of the *GRN* gene, resulting in an approximately 50% reduction in the levels of the encoded progranulin protein (PGRN).



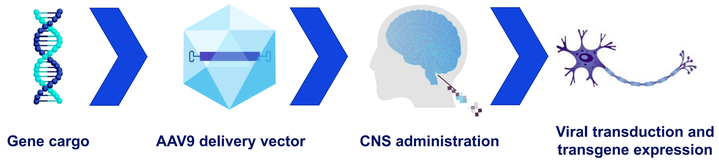
- Healthy levels of progranulin are necessary for cellular processes such as lysosomal function and neuronal survival , as well as to control neuroinflammation
- Progranulin deficiency leads to lysosomal defects
- FTD-GRN pathology is characterized by the presence of ubiquitin and TDP-43 protein aggregates, which are believed to be toxic, in brain cells
- Whereas mutations in a single GRN gene copy (allele) lead to age-associated FTD-GRN, rare individuals with mutations in both copies of GRN present with a severe neurological syndrome, termed *neuronal ceroid lipofuscinosis-11*, in early adulthood.

We hypothesize that CNS delivery of a functional copy of the *GRN* gene to FTD-GRN patients will normalize PGRN levels, restore lysosomal function, suppress neuroinflammation, and slow or stop neurodegeneration. As multiple brain regions are affected in FTD-GRN, we believe broad biodistribution of such gene therapy is needed. We believe the AAV9 vector is particularly well suited to deliver the *GRN* gene to the CNS, given its ability to transduce multiple CNS cell types, including neurons, the persistence of expression of the transgene, and its safety record.

By expressing functional PGRN in patients with FTD-GRN, we aim to slow or stop disease progression.

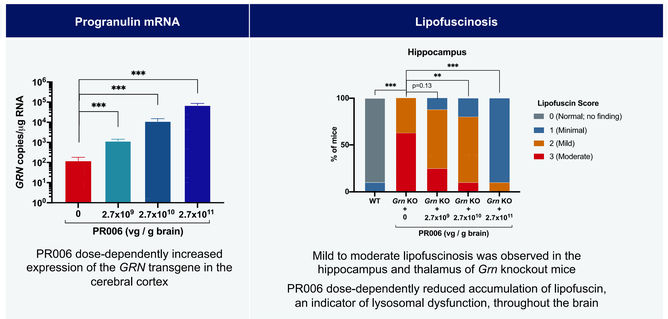
PR006 Background

- AAV9-based therapies have demonstrated safety in patients across multiple programs as well as the ability to distribute broadly across the CNS, transduce multiple cell types, and produce durable transgene expression[1,2]
- PR006 is intended to directly treat the underlying genetic cause of FTD-GRN, and to thereby modify the course of the disease
- Single injection into the cisterna magna is planned to achieve maximal brain distribution
- Intra-cisterna magna injection has been shown in non-clinical studies and in clinical practice to be a comparatively non-invasive and safe procedure[3]



Efficacy and Safety in Preclinical Models

- PR006 reversed lysosomal abnormalities and reduced TDP-43 pathology in FTD-GRN mutation carrier iPSC-derived neurons *in vitro*
- PR006 increased progranulin levels in the cerebral cortex of adult *Grn*$^{-/-}$ (or KO) mice
- PR006 reduced lysosomal deficiencies and neuroinflammation in *Grn* KO mice (subset of data shown below)



PR006 dose-dependently increased expression of the *GRN* transgene in the cerebral cortex

Mild to moderate lipofuscinosis was observed in the hippocampus and thalamus of *Grn* knockout mice

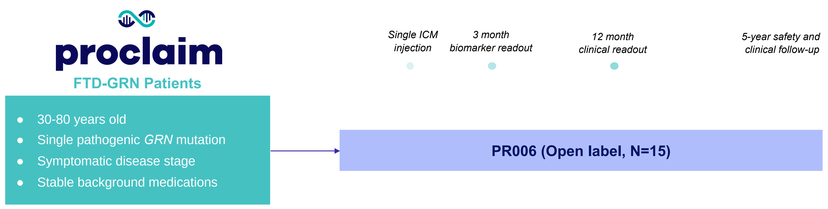
PR006 dose-dependently reduced accumulation of lipofuscin, an indicator of lysosomal dysfunction, throughout the brain

Means are presented +/- SEM (n=8-10 per group). Statistics determined by ANOVA followed by Dunnett's multiple tests correction comparing each group to excipient-treated *Grn* KO mice; *** = p<0.001 . Vector genome levels below 50 (dotted line) were considered not positive. Vg = vector genomes; LLOQ = lower limit of quantitation.

- In a 6-month GLP non-human primate (NHP) safety and biodistribution study, no adverse PR006-related findings were observed in any of the in-life assessments or histopathology
- ICM administration of PR006 in NHPs resulted in broad distribution of the transgene throughout the CNS and periphery

PROCLAIM Phase 1/2 Trial Design

A Phase 1/2 Ascending Dose Study to Evaluate the Safety and Effects on Progranulin Levels of PR006 in Patients with Fronto-Temporal Dementia with Progranulin Mutations (FTD-GRN)



PROCLAIM Phase 1/2 Trial Design

Patient Population

Key Inclusion Criteria

- Men or women aged 30 to 80 years (inclusive)
- Symptomatic FTD as per investigator assessment
- Carrier of a pathogenic *GRN* mutation including nonsense, frameshift, splice site mutations, and complete or partial (exonic) gene deletions
- Score ≥1 and ≤ 15 on CDR® plus NACC FTLD sum of boxes (SB)
- Stable use of background medications at least 8 weeks prior to investigational product dosing

Key Exclusion Criteria

- Diagnosis of a significant CNS disease other than FTD
- Contraindication to intracisternal injection and/or general anesthesia/deep sedation
- Concomitant disease or clinically significant abnormalities in laboratory test results or Brain MRI/magnetic resonance angiography (MRA) precluding study participation
- Any type of prior gene or cell therapy
- Use of blood thinners (e.g., warfarin, heparin, and novel oral anticoagulants [NOACs])
- Immunizations (live vaccines) in the 4 weeks prior to Screening

Endpoints

Primary Endpoints

- Safety and tolerability
- Quantified PGRN levels in blood and CSF

Other Endpoints

- **Secondary:** CDR® plus NACC FTLD, a measure capturing key FTD patient characteristics/symptoms
- Levels in blood and CSF of NFL (neurofilament light chain), a biomarker of neurodegeneration
- Immunogenicity of AAV9
- **Tertiary:** Measures of cognition, behavior, language, and daily living; volumetric magnetic resonance imaging to measure cortical neurodegeneration; CSF markers of neuroinflammation

Doses

- Three dose levels
- Dose cohorts will be overlapping

Interim Analysis

- Full dataset analysis when all patients complete 12 months study in low-dose, mid-dose and high-dose cohort, respectively
- Ongoing biomarker review

Duration

- Up to 5 years
- 12 months (main period) + 48 months (safety & exploratory follow-up)

Sample Size

- Up to 15 patients (up to 5/cohort)

Conclusions

- PR006 is an AAV9-based investigational gene therapy delivering a functional copy of *GRN* to CNS cells
- PR006, with a one-time injection, has the potential to be the first disease-modifying therapy that directly treats the underlying cause of FTD-GRN at the genetic level
- In NHPs and *Grn* KO mice, treatment with PR006 resulted in broad CNS distribution of the GRN transgene and a significant elevation of PGRN protein
- In *Grn* KO mice, treatment with PR006 resulted in correction of pathology caused by PRGN deficiency
- No PR006-related safety events or adverse findings observed in mouse or NHP studies
- The PROCLAIM study is a Phase 1/2 ascending dose study evaluating the safety and effects on PGRN levels of PR006 in FTD-GRN patients
- PROCLAIM study enrollment is anticipated to begin in mid-2020

430 East 29th Street, Suite 1520, New York, NY 10016

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2. Weinberg MS, Samulski JR, McCown TJ. Adeno-associated virus (AAV) gene therapy for neurological disease. Neuropharmacology. 2013;69:82-8.
3. Rosenberg JB, Kaplitt MG, De BP et al. CerebrospAAVrh.10-Mediated APOE2 Central Nervous System Gene Therapy for APOE4-Associated Alzheimer's Disease. Human Gene Ther Clin Dev. 2018; 29(1): 21-47.

Disclosure: All authors are currently employed by Prevail Therapeutics.

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