Preclinical development of PR006, a gene therapy for the treatment of frontotemporal dementia with progranulin mutations

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Prevail Therapeutics

**Background**

Grn encodes the glycoprotein progranulin, which is necessary for lysosomal function and central nervous system (CNS) homoeostasis. Bilobalide-function mutations in Grn lead to neuronal ceroid lipofuscinosis (NCL), whereas monallelic mutations lead to frontotemporal dementia (FTD-GRN). FTD-GRN is a rapidly progressing dementia impacting behavior and language that leads to death in 3-10 years.

**Approach**

We have developed a therapeutic strategy with the aim of increasing progranulin levels and thereby addressing the underlying lysosomal dysfunction to slow or stop FTD-GRN disease progression. PR006 is a gene therapy designed to deliver the normal human progranulin gene (GRN) using the AAV9 viral vector. The efficacy of PR006 was evaluated in both in vitro and in vivo models which were chosen since they recapitulate the underlying progranulin deficiency of patients with FTD-GRN. PR006 was evaluated in two models of FTD-GRN: (1) an in vitro induced pluripotent stem cell (iPSC)-derived neuronal model using cells from patients carrying heterozygous GRN mutations and (2) an in vivo Grn knockout (KO) genetic mouse model. Safety was evaluated in KO mice and non-human primates (NHPs).

**IPSC-derived Neuron Model Establishment**

- iPSC-derived neural progenitor cells from subjects with heterozygous FTD-GRN mutations (FTD-GRN KO1, FTD-GRN KO2) were secreted and secreted less progranulin than neural progenitor cells derived from healthy aged subjects with no GRN mutations (Control).
- All cell lines successfully differentiated into neuronal cultures that expressed classic neuronal markers.

**Figure 1. iPSC-Neuron Model Validation**

**PR006 Efficacy in the iPSC-Neuron Model**

- PR006 efficacy was examined in human iPSC-derived neuronal cultures.
- FTD-GRN neurons exhibited features of FTD-GRN pathology, including defective maturation of lysosomal enzyme cathepsin D (CTSD), and accumulation of insoluble TDP-43.
- Cells were transduced with exoplic or PR006 at an MOI of 5.3 x 10^9/gg.

**Figure 2. PR006 transduction increased secreted progranulin levels and improved FTD-GRN phenotypes**

- A two-month study was performed in aged Grm KO mice to assess PR006 efficacy in a model with a severe, progressive phenotype.
- Animals were treated with exoplic or 2.4 x 10^11 vg brain PR006 at 16 months via intracerebroventricular (ICV) injection.

**Figure 3. PR006 treatment increased CNS progranulin levels in aged Grm KO mice**

- Significant reduction in lipofuscinosis was observed at the middle and high PR006 doses.

**Evaluation of Safety**

Safety was evaluated in the mouse model by H&E staining. The brain and peripheral tissues showed no adverse histopathologic findings or evidence of toxicity due to treatment.

**Conclusion**

These studies demonstrate that PR006 effectively increased progranulin expression, reduced neuronal-related neuropathology, and improved neuroinflammation in vivo and in vitro models of FTD-GRN. In addition, PR006 treatment was well tolerated in the models evaluated. Together, these results support the clinical development of PR006 for the treatment of patients with FTD-GRN. Study summary is available as online content for PR006 patients (PROCLAIM). For more information on PROCLAIM (NCT04086265), please visit https://prevailtherapeutics.com.