Frontotemporal Dementia with GRN Mutations (FTD-GRN)

Frontotemporal dementia (FTD) is a devastating dementia syndrome encompassing a heterogeneous 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-17, 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
- 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

Efficacy and Safety in Preclinical Models

- PR006 reverses 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)

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)

- 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 complex or partial (exonic) gene deletions
- Score 21 and ≤ 16 on CDR-SB plus NACC FTD sum of boxes (SB)
- Stable use of background medications at least 8 weeks prior to investigational product dosing
- 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

- Safety and tolerability
- Quantified PGRN levels in blood and CSF
- Secondary: CDRSB plus NACC FTD, 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

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 NPHs 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 PGRN deficiency
- No PR006-related safety events or adverse findings observed in mouse or NPH 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