FTD DISORDERS REGISTRY®

The VOICE of FTD

WINTER 2020

FEATURED STUDY

A Study of PR006 in FTD with Progranulin Mutations (FTD-GRN)

The PROCLAIM study, sponsored by Prevail Therapeutics, is evaluating the safety and effectiveness of a one-time **investigational gene therapy** (**PR006**) intended to treat people diagnosed with a form of frontotemporal degeneration caused by mutations in the **progranulin gene** (*GRN*), referred to as FTD-GRN.

This Phase 1/2 clinical trial will also examine the effects of PR006 on **progranulin** protein levels in the **plasma** (the liquid component of blood) and in the **cerebrospinal fluid** (CSF; fluid from the area surrounding the brain).

Progranulin protein is a product of the *GRN* gene and is decreased in people with FTD caused by *GRN* mutations. PROCLAIM will test whether PR006 can increase progranulin levels and result in modification of the underlying disease process to possibly slow or halt progression of the disease.

Results from PROCLAIM will inform further clinical investigation and potentially allow approval of PR006 by the U.S. Food & Drug Administration (FDA) and the health authorities of other countries.

This glossary was created to offer definitions of words used in this article. Glossary terms are listed in bold the first time they appear.

FTD and *GRN*

Frontotemporal dementia (FTD) or frontotemporal lobar degeneration (FTLD) refers to a group of disorders caused by progressive degeneration of **neurons** in the brain's **frontal lobes** (the areas behind your forehead) or its **temporal lobes** (the regions behind your ears). These regions of the brain are important for decision-making, behavioral control, emotion, and language.

FTD is often **inherited**, with genetic forms making up to 20% of all FTD cases. Mutations in the *GRN* gene are a common genetic cause of FTD.

Patients with *GRN* mutations have significantly lower levels of progranulin protein, which is found in **lysosomes** or "recycling centers" in cells that break down cellular waste and excess proteins. Without enough progranulin, the lysosomes cannot effectively degrade or recycle proteins. This can lead to **inflammation** of the brain and **neurodegeneration**.

Available data from observational clinical studies as well as experiments in animal models of FTD support the idea that restoring progranulin levels may slow, halt, or possibly reverse the disease process.

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There are no disease-modifying therapies available for patients with FTD, and current treatment consists of management of symptoms and supportive care.

The FDA designated PR006 an **orphan drug** in December 2019. Orphan Drug designation is granted to drugs or biologics intended to treat a **rare disease** or condition, which include those that affect fewer than 200,000 individuals in the United States. FTD is estimated to affect about 60,000 people. Last month the European Commission also granted orphan designation to PR006.

What is gene therapy?

Genes are stretches of DNA that contain instructions for making proteins, the essential building blocks of the cells in your body. Genetic differences, or "mutations," can result in the malfunctioning, reduction or complete loss of proteins necessary for important biological functions. In some cases, these mutations can lead to, or increase the risk of, certain diseases such as FTD-GRN.

Genetic testing enables individuals and their physicians to identify potential disease-associated mutations.

Gene therapy is a form of treatment that involves adding or modifying genetic material in a patient's cells, in most cases to introduce a healthy copy of a mutated gene. The majority of gene therapies for central nervous system (CNS) disorders are designed to be one-time and lifelong treatments.

How does PR006 work?

PR006, the therapy being evaluated in the PROCLAIM study, is composed of a carrier called a vector that is **genetically engineered** to deliver a normal copy of the *GRN* gene. The vector is called **adeno-associated virus 9 (AAV9)**. These viruses are specially modified so they cannot cause disease in people, and the body's immune system clears the virus after the gene enters the cell nucleus and the virus is no longer needed. Gene delivery with an AAV9 vector has a track record of efficacy and safety. AAV-based gene therapies have been successfully used in treatments for other serious illnesses, and the FDA has approved gene therapies for treating spinal muscular atrophy and an inherited form of blindness.

PR006 is an investigational gene therapy product, which means regulatory agencies like the FDA have not approved it for the treatment of FTD-GRN or any other indication. PR006 has not been tested previously in humans, but has been approved for use in **clinical trials** by the FDA. It has been tested in animal experiments (mice and non-human primates), where no PR006-related adverse events were observed at the doses that will be used in this clinical study.

Prevail announced on December 11, 2020, that the first person with FTD-GRN has received a dose of PR006.

"Dosing the first patient in our PROCLAIM clinical trial marks an important milestone in our efforts to advance a potentially disease-modifying treatment for patients with frontotemporal dementia with *GRN* mutations," said Asa Abeliovich, M.D., Ph.D., founder and chief executive officer of Prevail. "We are excited to progress

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clinical development of PR006 and to bring forward a much-needed therapy for this rapidly progressing neurodegenerative disease."

Eligibility and Protocols

The PROCLAIM study is seeking participants who:

- Are between 30 and 80 years of age
- Have been diagnosed with FTD with a disease-causing *GRN* mutation
- Are experiencing symptoms related to FTD (examples include personality changes or changes in language skills)
- Are using stable doses of background medications
- Are living in the community (i.e. not in a nursing home); although some levels of assisted living may be permitted
- Have a study partner – i.e., someone who is close to them, such as a family member or close friend – who can attend study visits with them
- Are able to safely undergo the procedure, in the study doctor's opinion
- Have never before received a cell or gene therapy

Study participation will last for up to five years and will involve 20 visits to the study center, including one three-day visit, two or three days of which will be inpatient.

The procedure to administer PR006 is minimally invasive and has been used by neurosurgeons and neuroradiologists for many years. The investigational drug will be injected into the back of the head near the top of the neck, into an area near the brain called the **cisterna magna**, by a neurosurgeon or an interventional radiologist. This type of administration is designed to achieve maximal brain distribution. Direct administration of PR006 into the cisterna magna reduces its exposure to the rest of the body, potentially minimizing the risk of side effects. This procedure will be done in the hospital under either general anesthesia or deep sedation. The neurosurgeon or interventional radiologist will use computed tomography scans (similar to X-rays) to safely guide the injection needle into the appropriate area.

All participants taking part in this study will also receive medications to reduce the risk of experiencing a reaction or other side effects during and after the injection.

As a part of baseline and follow-up visits, trial participants will undergo:

- blood draws
- electrocardiograms
- Magnetic Resonance Imaging (MRI; produces images of your brain) scans
- Magnetic Resonance Angiography (MRA; produces images of blood vessels in your head and neck) scans
- Dual-Energy X-ray Absorptiometry (DEXA; to assess bone density) scans
- lumbar punctures for CSF testing
- clinical scales to assess changes in cognition, behavior, language, and daily living.

READ PROCLAIM STUDY ON CLINICALTRIALS.GOV

History

Prevail Therapeutics was founded by Dr. Abeliovich, a neurologist and researcher who was deeply moved by his own patients' desire to change their destiny. Prevail's interest in FTD-GRN stems from Dr. Abeliovich's work with dementia patients earlier in his career as an attending physician in neurology at New York-Presbyterian Hospital. He witnessed firsthand the toll that dementia takes on patients and their families, along with the lack of available treatment options, and brought that experience with him to Prevail.

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"Patients lie at the heart of Prevail's mission," said Dr. Abeliovich. "We are committed to developing gene therapies with the potential to slow or stop the progression of genetically defined neurodegenerative diseases."

The excitement that brought the Prevail team together to work on PR006 arose from recent major scientific and technical advancements, including an improved understanding of how certain genetic mutations can cause neurodegenerative diseases, and the development of a leading gene therapy platform designed to deliver therapies to the brain. Prevail uses these advancements to develop treatments for a range of diseases that have not been adequately addressed by other approaches.

"We are pioneering the use of gene therapy for both rare and common neurodegenerative diseases, based on biology we understand and technology we can deliver," Asa Abeliovich, M.D., Ph.D.

Under Dr. Abeliovich's direction, the Prevail team developed PR006. Researchers conducted a series of experiments in animal models, which demonstrated increased progranulin expression and decreased neuroinflammation with no related adverse events. This preclinical work provided the rationale that led to the development of the PROCLAIM study.

Dr. Jonathan Rohrer, honorary consultant neurologist at the National Hospital for Neurology and Neurosurgery and clinician scientist at the Dementia Research Centre, University College London, is an expert in FTD and its genetic causes and consulted with the Prevail team on the development of the PROCLAIM study.

"Frontotemporal dementia due to progranulin mutations is a devastating condition, with no disease-modifying therapeutic options available," said Dr. Rohrer. "We anticipate studies like PROCLAIM will further increase our understanding of this disease and inform future clinical evaluation of promising new therapies like PR006, an experimental gene therapy in development for the treatment of patients with progranulin mutations."

LEARN MORE ABOUT PROCLAIM STUDY

VIEW THE GLOSSARY

PROCLAIM: A Study of PR006 in FTD with Progranulin Mutations (FTD-GRN)

Brief Title: Phase 1/2 Clinical Trial of PR006 in Patients With Frontotemporal Dementia With Progranulin Mutations (FTD-GRN)

Official Title: A Phase ½ Ascending Dose Study to Evaluate the Safety and Effects on Progranulin Levels of PR006A in Patients with Fronto-Temporal Dementia with Progranulin Mutations (FTD-GRN)

Summary: Study PRV-FTD101 is a Phase 1/2, multi-center, open-label ascending dose, first-in-human study that will evaluate the safety and effect of intra-cisternal PR006 administration on progranulin protein (*PGRN*) levels in patients with frontotemporal dementia with progranulin mutations (FTD-GRN). Three escalating doses (low dose, medium dose, and high dose) cohorts are planned. The duration of the study is five years. During the first year, patients will be evaluated for the effect of PR006 on safety, tolerability, immunogenicity, biomarkers, and efficacy. Patients will follow up for an additional four years to monitor safety and changes on selected biomarkers and clinical outcomes.

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Condition or Disease: Frontotemporal Dementia

Study Type: Interventional (Clinical Trial)

Study Phase: Phase 1, Phase 2

Estimated Enrollment: 15 participants

Allocation: Non-randomized

Intervention Model: Sequential Assignment

Masking: None (open-label)

Primary Purpose: Treatment

Actual Study Start Date: July 30, 2020

Estimated Primary Completion Date: December 2027

Estimated Study Completion Date: December 2027

Low Dose: Participants will receive:

- PR006, a single dose administered intra cisterna magna
- Methylprednisolone, a single IV pulse administered as concomitant medication
- Sirolimus, a loading dose, followed by a maintenance dose, followed by dose tapering; administered as concomitant medication
- Prednisone administered orally as concomitant medication, followed by dose tapering

Medium Dose: Participants will receive:

- PR006, a single dose administered intra cisterna magna
- Methylprednisolone, a single IV pulse administered as concomitant medication
- Sirolimus, a loading dose, followed by a maintenance dose, followed by dose tapering; administered as concomitant medication
- Prednisone administered orally as concomitant medication, followed by dose tapering

High Dose: Participants will receive:

- PR006, a single dose administered intra cisterna magna
- Methylprednisolone, a single IV pulse administered as concomitant medication
- Sirolimus, a loading dose, followed by a maintenance dose, followed by dose tapering; administered as concomitant medication
- Prednisone administered orally as concomitant medication, followed by dose tapering

Primary Outcome Measures:

1. Number of Adverse Events (AEs), Serious Adverse Events (SAEs), and Adverse Events Leading to discontinuation *[Time Frame: Year 5]*
2. Sum of adverse reactions (ARs) and suspected ARs *[Time Frame: 5 years]*
3. Sum of serious ARs and serious suspected ARs *[Time Frame: 5 years]*
4. Incidence of procedure or treatment-emergent AEs *[Time Frame: 5 years]* Measured by brain MRI
5. Change in *PGRN* immunogenicity in blood *[Time Frame: Baseline and 12 months] PGRN*: progranulin protein. Measured by level of antibodies and ELISPOT
6. Change in *PGRN* immunogenicity in CSF *[Time Frame: Baseline and 12 months]* CSF: cerebrospinal fluid
7. Change in AAV9 immunogenicity in blood *[Time Frame: Baseline and 12 months]* Measured by level of antibodies and ELISPOT
8. Change in AAV9 immunogenicity in CSF *[Time Frame: Baseline and 12 months]* Measured by levels of antibodies
9. Change in *PGRN* levels in blood *[Time Frame: Baseline and 12 months]*
10. Change in *PGRN* levels in CSF *[Time Frame: Baseline and 12 months]*

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Secondary Outcome Measures:

1. Change in CDR plus NACC FTLD *[Time Frame: Baseline and 12 months]* CDR: Clinical Dementia Rating staging instrument. NACC FTLD: National Alzheimer's Coordinating Center frontotemporal lobar degeneration domains
2. Change in NfL levels in blood *[Time Frame: Baseline and 12 months]* NfL: neurofilament light chain
3. Change in NfL levels in CSF *[Time Frame: Baseline and 12 months]*

Eligibility Criteria:

Ages Eligible for Study: 30 years to 80 years (adult, older adult)
Sexes Eligible for Study: All
Accepts Healthy Volunteers: No

Inclusion Criteria:

- Bodyweight range of ≥40 kg (88 lbs) to ≤110 kg (242 lb) and a BMI of 18 to 34 kg/m2.
- Has symptomatic frontotemporal dementia (FTD) per investigator assessment.
- Stable use of background medications at least 8 weeks prior to investigational product dosing.
- Carrier of a pathogenic GRN (progranulin gene) mutation.
- Negative screening test for Mycobacterium tuberculosis (MTB) or documented negative MTB test within 1 year prior to screening.
- Age- and gender-appropriate cancer screenings are up-to-date.
- Patient and/or patient's legally authorized representative has the ability to understand the purpose and risks of the study, and provide written informed consent and authorization to use protected health information.
- Patient has a reliable study partner/informant (e.g. family member, friend) willing and able to participate in the study as a source of information on the patient's health status and cognitive and functional abilities.
- Patient is not dependent on a walker or wheelchair.
- Patient is living in the community (i.e. not in a nursing home); some levels of assisted living may be permitted at the discretion of the investigator.
- Pneumococcal pneumonia and shingles vaccines are required within 10 years of screening (allowed to be performed during screening, but must be given at least four weeks prior to administration of immunosuppressant at the start of the study).

Exclusion Criteria:

- Diagnosis of a significant CNS (central nervous system) disease other than frontotemporal dementia (FTD) that may cause FTD symptoms or confound study objectives.
- Brain magnetic resonance image (MRI) / magnetic resonance angiography (MRA) showing clinically significant abnormality considered to prevent intracisternal injection.
- Hypersensitivity or contraindications to corticosteroid and/or sirolimus use.
- Clinical evidence of peripheral symmetric sensory polyneuropathy (stable sensory mononeuropathies and radiculopathies are not exclusionary).
- Concomitant disease or condition within six months of screening that could interfere with, or treatment of which might interfere with, the conduct of the study or that would, in the opinion of the investigator, pose an unacceptable

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safety risk to the patient or interfere with the patient's ability to comply with study procedures.
- Clinically significant laboratory test result abnormalities assessed at screening.
- Participation within three months prior to screening in another therapeutic investigational drug or device study with purported disease-modifying effects on FTD, unless it can be documented that the patient received placebo only.
- Any type of prior gene or cell therapy.
- Immunizations (live vaccines) in the four weeks prior to screening. Pneumococcal vaccine and shingles vaccine administration is allowed during screening.
- Use of blood thinners in the two weeks prior to screening, or anticipated use of blood thinners during the study. Antiplatelet therapies may be acceptable.
- Contraindications or intolerance to imaging methods (MRI, CT) and intolerance to contrast agents.
- Contraindications to general anesthesia or deep sedation.

Other protocol-defined inclusion/exclusion criteria may apply

Locations:

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Responsible Party: Prevail Therapeutics
ClinicalTrials.gov Identifier: NCT04408625
Other Study ID Numbers: OPRV-FTD101
Studies a U.S. FDA-regulated Drug Product: Yes
Studies a U.S. FDA-regulated Device Product: No

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