FTD DISORDERS REGISTRY®

The VOICE of FTD

SUMMER 2020

An Overview of the Clinical Trial Process

Learn about research and the steps taken to evaluate interventions

Research occurs in many formats and can involve anyone. It is especially important for **rare diseases** like frontotemporal degeneration (FTD), which scientists have estimated affects about 60,000 people in the United States.

Clinical studies offer hope for many people as they are an opportunity for researchers to find and develop better treatments. When people volunteer to take part in research, they help doctors and scientists learn more about a specific disease and improve health care.

"Participating in research has many advantages to persons diagnosed with FTD and their families," said FTD Registry Director Dianna Wheaton, Ph.D. "These include providing special access to medical expertise and current information on **emerging** treatments. It also means directly contributing to the growing knowledge base for understanding FTD disorders."

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

The term **clinical study** refers to all scientific methods to evaluate preventions, diagnostic techniques, and treatments of a disease. In these studies, researchers work with human volunteers to advance medical knowledge. According to the National Institutes of Health (NIH), the goal is to try to understand whether a medicine, technique, or treatment is safe and effective. With no known treatment or cure for FTD, these studies are critical for advancing the science.

Studies can take place in doctor's offices, at research centers or hospitals, through home visits, or online. The length of a study varies; they can be as short as a couple of weeks, or longer, involving years. Participating is a personal choice, and volunteers can withdraw at any time.

There are different types of clinical studies. Each is used in different circumstances. The two main types are **observational studies** and **clinical trials** (also called **interventional studies**).

OBSERVATIONAL STUDIES

In observational studies, researchers monitor volunteers and measure outcomes without affecting results. Over a period of time, investigators watch and document the naturally occurring changes in a participant's health, behavior, cognitive, and functional abilities in a group of people with the same condition.

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Collected observations from **natural history studies** have shown that FTD-diagnosed persons can have various symptoms, including changes in personality, speech, executive function, or movement. This makes obtaining an accurate diagnosis challenging. Observations by Katrina M. Moore et al (2019) have shown **autosomal dominant** genetic inheritance in 10% to 25% of patients, although a large proportion of familial and sporadic forms of FTD still have an unknown genetic origin.

Most of the inherited types of FTD are caused by mutations in one of three genes: **PROGRANULIN (*GRN*)**, **microtubule-associated protein tau (*MAPT*)**, and chromosome 9 open reading frame 72 (***C9orf72***). Individually, each of these three genetic mutation groups causes between 5% and 10% of all FTD, according to Caroline V. Greaves and Jonathan D. Rohrer (2019).

Mutations in a single copy of *GRN* decrease the level of progranulin and invariably leads to the development of FTD, called FTD-*GRN*. The *MAPT* gene carries the instructions for making the tau protein, a protein that occurs in all neurons and is essential for normal neuronal shape, functioning, and metabolism. Mutations in *C9orf72* are associated with abnormal accumulation of the protein TDP-43, which is also seen in FTD-*GRN*.

Patient **registries** are another example of observational studies. As a **Research Registry**, FTDDR collects information from participants who live in the United States and Canada and also sends them targeted study notices via email based on their research profile. (FTDDR is also a **Contact Registry** for persons around the world who want to receive Registry newsletters and FTD research updates.)

Observational data collection through the Research Registry begins by completing three intake surveys: the Demographics Survey, the Disease Impact Survey, and the Research Ready Survey. FTD Registry members act as **citizen scientists** working to drive new research,

change the way clinical trials are run, and help answer key questions about FTD, Dr. Wheaton said. *(Read a recent summary of the Registry's Research Survey Results.)*

"As a **patient-centric** registry, the FTD Disorders Registry seeks to empower people with knowledge and understanding while also creating the means to participate in research," explained Dr. Wheaton. "While the Registry is an example of observational research, registries also play a central role in promoting and recruiting for external clinical studies."

Currently, most FTD research is done through observational studies. Questions raised in observational studies often become clinical trials.

CLINICAL TRIALS

In a **clinical trial** (or interventional study), investigators evaluate the safety and effectiveness of different medical **interventions**: drugs, treatments, medical devices, etc.

All studies follow a protocol, or plan, that explains why the study is being conducted, what the volunteers will have to do, and how the volunteers will be monitored. The protocol also includes:

- Clear criteria for eligibility
- Detailed information about the purpose of the study
- Who is conducting it
- The exact procedures
- Risks and potential benefits

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Researchers present the essential information about a trial to potential participants and provide time for these volunteers to ask questions and hear the answers. This information is also given in writing so participants can review it and sign as part of an **informed consent** process for joining the study.

When conducting clinical research involving human beings, obtaining informed consent is required. Informed consent is a procedure through which competent people, after having received and understood all the research-related information, voluntarily decide to participate in a clinical trial. A valid informed consent for research must include three elements:

1. Disclosure of information
2. Competency of the participant to make a decision
3. Willingly agree to participate

In order to protect the safety and rights of research volunteers, an independent team of at least five people reviews and monitor the study. These people serve on an Institutional Review Board (IRB) and include at least one person who focuses on the scientific aspect, one person who focuses on the non-scientific aspect, and one person who focuses on the viewpoint of the volunteers.

CLINICAL TRIAL PROCESS

Most often found in people younger than 65 years old, FTD progresses rapidly and currently has no approved treatments. However, the number of clinical trials studying potential interventions to treat symptoms, slow progression, and reverse damage, are increasing as more is learned about these disorders. Today on ClinicalTrials.gov there are more than 150 studies addressing questions, symptoms, **gene mutations**, and more about FTD.

The U.S. **Food and Drug Administration (FDA)** has a drug development and approval process that ensures a drug works and the benefits outweigh the known risks. A pharmaceutical company seeking FDA approval to sell a new prescription drug must complete a five-step process:

1. Discovery/concept
2. Preclinical research
3. Clinical research (trials)
4. FDA review
5. FDA post-market safety monitoring

Clinical trials occur in **phases** — Early Phase 1 (formerly listed as Phase 0), Phase 1, Phase 2, Phase 3, Phase 4 — each with its own purpose and goal that ultimately, when taken together, forms the basis for FDA approval. Sometimes the phases are combined or seamless, while other times they may only include Phase 1, Phase 2, and Phase 3. Not all interventions will meet the **outcome measures** necessary to advance from one phase to the next.

Until recently, clinical trials related to FTD have been observational natural history studies to understand the disease, including symptoms and its progression, and small interventional studies that address symptoms. Two interventional drug studies that have completed Phase 3 include LMTM, a protein aggregation inhibitor for persons with behavioral variant frontotemporal degeneration (bvFTD), and pimavanserin, which has been approved by the FDA to treat hallucinations and delusions associated with dementia-related psychosis.

An example of an FTD drug currently working its way through the clinical trial process is AL001, Alector's INFRONT (***I***mmuno-***N***eurology ***Front***otemporal Dementia) drug. AL001 targets the **sortilin** receptor to increase the extracellular levels of the progranulin gene. On July 24, 2020, Alector dosed its first patient in Phase 3 for the INFRONT-3 study.

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ALo01 is a human monoclonal antibody designed to modulate progranulin, a regulator of immune activity in the brain with genetic links to multiple neurodegenerative disorders, including FTD, Alzheimer's disease, and Parkinson's disease. ALo01 aims to increase the level of progranulin in humans by inhibiting a progranulin degradation mechanism.

"Since our founding, Alector has been focused on advancing research that could one day lead to the development of new treatment options that slow down or stop the progression of disease in individuals at risk for or with frontotemporal dementia due to a mutation in the progranulin gene," said Robert Paul, M.D., Ph.D., Chief Medical Officer at Alector, a biopharmaceutical company pioneering immuno-neurology. "We are dedicated to a unified goal of creating disruptive change in the way the world treats neurodegenerative disorders."

ALo01 was discovered and engineered in a collaborative effort between Alector, Inc. and Adimab, LLC. It was designated an **Orphan Drug** by the FDA for the treatment of FTD in June 2018.

The INFRONT studies of ALo01 will be used to illustrate the phased, clinical trial process.

EARLY PHASE 1

Early Phase 1 is used to describe the step taken to investigate how the body affects the drug and how the drug affects the body. Formerly called Phase 0, this step is sometimes skipped, and a study will proceed to Phase 1.

Preclinical work was conducted with ALo01 in animals, however, the studies with human volunteers began with Phase 1.

PHASE 1

While ensuring safety is important throughout the clinical trial process, the primary purpose of a Phase I trial is to evaluate the safety and dosage of the proposed treatment. This includes dose tolerance, dose frequency, and duration of exposure to a medicine.

These trials are usually conducted in both healthy individuals and in patients with the target disease who are stable and generally healthy. This is one of the best ways for researchers to understand how the new potential treatment works in the human body.

Alector's INFRONT Phase 1 trial was conducted in 2018 to evaluate the safety, tolerability, **pharmacokinetics**, and **pharmacodynamics** of ALo01 in **healthy volunteers** and in both participants with and without FTD who carry the progranulin gene mutation.

Fifty healthy volunteer study participants without FTD were given a single dose of ALo01 or **placebo** intravenously (IV). In addition, six participants who carried the FTD-*GRN* gene mutations but did not show any FTD symptoms were given a single dose of ALo01, and eight participants with the FTD-*GRN* gene mutations received three doses over one month. The trial was administered at clinical sites in the United States, Canada, and England.

The results showed that ALo01 tripled the level of progranulin in the plasma and doubled it in the cerebral spinal fluid of the healthy volunteers without the FTD-*GRN* gene mutation. For the FTD-*GRN* participants, the drug restored the level of progranulin back to the normal range.

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"We were encouraged by the data from our Phase 1b trial of ALoo1, in which ALoo1 was well-tolerated and restored progranulin back to normal physiological levels in the central nervous system of FTD-*GRN* patients," said Dr. Paul.

PHASE 2

In Phase 2 trials, data is collected to understand how a drug works. It also continues to evaluate the drug's safety and effect in the study volunteers. Sometimes individuals who participate in a clinical trial may have access to the study medication following the completion of the trial prior to its approval.

The INFRONT trial, Phase 2 was designed to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and the effect of ALoo1 on participants as well as its effects on biomarkers of neurodegeneration and on cognition. In addition to enrolling individuals with FTD-*GRN*, this trial includes persons with a *C9orf72* gene mutation.

The ALoo1 Phase 2 began in September 2019 and will end in 2021. ALoo1 is given to study participants through an IV infusion every four weeks. This clinical trial is open to individuals between the ages of 18 and 85 who qualify following the inclusion and exclusion criteria. There are sites in the United States, Canada, England, Germany, Italy, and the Netherlands administering the trial. An open-label extension study is planned to be offered to study participants following completion of Phase 2.

Alector officials will be presenting results from Phase 2 of the INFRONT study at the upcoming annual Alzheimer's Association International Conference, which because of the coronavirus pandemic will be held virtually July 27-31, 2020.

PHASE 3

The effect of a new medicine and long-term monitoring of safety is determined in a Phase 3 clinical trial in the patient population. In Phase 3, researchers study whether the treatment works better than the current standard therapy or placebo. They also compare the safety of the new treatment with that of current treatments, if available. Phase 3 trials include large numbers of people to make sure that the result is valid.

INFRONT-3 is a Phase 3 double-blind, placebo-controlled study evaluating the **efficacy** and safety of ALoo1. The drug is administered intravenously in participants at risk for or with FTD due to mutations in a single copy of the progranulin gene. Up to 180 participants will be randomized to receive ALoo1 or a placebo every four weeks.

Outcome measures will include clinical assessments to determine the efficacy, safety, and tolerability, and magnetic resonance imaging (MRI) and blood-based biomarkers. *(Learn more about enrolling.)*

PHASE 4

Phase 4 clinical trials are designed to generate additional insights into medicines after they are approved by the FDA. These studies are designed to evaluate the long-term effects of the drug. Under these circumstances, less common adverse events may be detected.

Also known as Post-Marketing Surveillance Trials, Phase 4 studies are designed to provide broader efficacy and safety information in larger numbers of patients and subpopulations, and to compare and/or combine it with other available treatments.

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All phases of all clinical trials need people to willingly volunteer to participate, but especially those studies related to rare diseases such as FTD. As the FDA publication "Rare Disease and Clinical Trials" notes, rare diseases by definition comprise small populations. This means there is a smaller available pool of potentially available candidates from which to draw for each phase of a clinical trial.

Fewer people limits the opportunity for studies and replication clinical trials. Each volunteer is needed and valuable since research leads to understanding, detecting, preventing, and treating diseases. This is why clinical trials are the means to finding a cure for FTD.

ABOUT ALECTOR

Alector is a clinical-stage, biopharmaceutical company pioneering immuno-neurology, a novel therapeutic approach for the treatment of neurodegeneration. The company was founded seven years ago, initially working from a garage with a small team whose goal was to change the way the world treats neurodegenerative disorders, such as FTD and Alzheimer's disease. As the company has grown, it has remained steadfast in its vision of a world where each individual retains his or her full brain function and cognitive faculties throughout life — a world where dementia and neurodegeneration are illnesses of the past just as smallpox, diphtheria, rubella, and polio have become.

Alector has more than 140 professionals devoted to developing novel therapeutics that harness the brain's immune system to treat neurodegeneration. In this short time, the company has moved several drug candidates into human clinical trials, including two programs for FTD.

For more information about observational studies, read this article about survey data collected by the FTD Registry about research readiness.

The Registry supports and facilitates the recruitment of participants for clinical trials that cover all of the forms of FTD. Some studies, including Alector's INFRONT trial of AL001, that are currently seeking volunteers are listed on our website on the Find A Study page.

To learn more about existing FTD clinical trials, you can search the National Institutes of Health (NIH) database, a resource provided by the U.S. National Library of Medicine. ClinicalTrials.gov lists privately and publicly funded clinical studies conducted around the world. You can search broadly by FTD or specifically by type of FTD or even gene mutation.

Join the Registry.
Tell Your Story.
Advance the Science.

"Together, we can make a difference!"

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