General Information about ALS TDI's Phase IIA Clinical Trial of TDI-132 (Gilenya™)

In 2009, the ALS Therapy Development Institute discovered the costimulatory pathway as a novel disease target as the result of a large, unbiased gene expression experiment. The Institute then showed in 2010 that an antibody (antiCD40L) targeting the costimulatory pathway slowed disease progression and extended survival in the SOD1 mouse model (*Nature Genetics*, 2010). Building on that novel discovery, the Institute sought out additional potential treatments, such as fingolimod (TDI-132/Gilenya), with properties that target different aspects of the costimulatory pathway. In this case, Gilenya was chosen by ALS TDI for its known ability (in multiple sclerosis based research) to alter the trafficking and circulation patterns of certain immune cells known to be associated with damage to motor neurons, contributing to the progression of the disease. Preclinical testing of Gilenya in SOD1 mice at ALS TDI showed a trend toward an overall positive effect on progression and survival rates (presented during a webinar in 2011 at the 23rd ALS/MND Research Symposium in Chicago in 2012 and during a Keystone meeting in Santa Fe in 2013).

Since Gilenya is an FDA-approved drug used to treat multiple sclerosis, we have been able to go directly to Phase IIA in ALS rather than starting from scratch at Phase I. This clinical trial is specifically designed to help us understand whether or not Gilenya is safe and tolerated in ALS patients. This will be done by looking for any discernible adverse effects of the drug in people with ALS. It will NOT measure efficacy of the drug as a treatment for ALS.

There are very few large, late-stage, therapeutic-aimed clinical trials enrolling ALS patients today. This trial will provide a clinical opportunity for patients to participate in a study evaluating an experimental therapy for this disease in which treatment options are currently limited.

Frequently Asked Questions

What is the name of the study?
Phase IIA Double-Blind, Placebo-Controlled Study to Evaluate the Safety of Oral Fingolimod in Patients with ALS

What is the purpose of this Phase IIA clinical trial?
The primary purpose of this Phase IIA clinical trial will be to determine the safety and tolerability of TDI-132/Gilenya in ALS patients.

What is ALS TDI's involvement in the Phase IIA clinical trial?
ALS TDI is the sole funding sponsor of this clinical trial. ALS TDI made the original preclinical discovery that TDI-132/Gilenya may have potential to be a treatment for ALS. ALS TDI is funding the trial and taking ownership over its rapid completion and outcomes. ALS TDI has contracted the Northeast ALS Consortium (NEALS) to manage the trial and is working closely with them to execute it as rapidly as possible. NEALS is responsible for conducting all enrollment and data/sample collection. A Data and Safety Monitoring Board (DSMB) and Institutional Review Board (IRB) have been put together to monitor the trial and to provide guidelines for initial data analysis. ALS TDI will review and analyze the data further upon the trial's completion.

What is the drug that is being tested in the study? What disease indications does it treat today?
The drug is fingolimod (Gilenya™), which ALS TDI preclinically tested under the name TDI-132. Gilenya is currently being marketed by Novartis AG as a treatment for multiple sclerosis.

Why did ALS TDI choose to look at a drug that is used as a treatment for multiple sclerosis?
In 2010, the Institute discovered the costimulatory pathway as a novel disease target. It also showed that an antibody (antiCD40L) targeting the costimulatory pathway slowed disease progression and extended survival in the SOD1 mouse model. Building on that novel discovery, the Institute sought out additional potential treatments, such as fingolimod (TDI-132/Gilenya), with properties that target different aspects of the costimulatory pathway. In this case, Gilenya was chosen by ALS TDI for its known ability (in multiple sclerosis based research) to alter the trafficking and circulation patterns of certain immune cells known to be associated with damage to motor neurons, contributing to the progression of the disease. Preclinical testing of Gilenya in SOD1 mice at ALS TDI showed a trend toward an overall positive effect on progression and survival rates. It is important to note that simply because this drug is an approved treatment for MS, doesn't mean that other or any or all MS drugs hold the same promise as potential treatments for ALS.

Is there any published data on the drug for ALS?
No; however, ALS TDI has presented data on Gilenya in the SOD1 mouse model online via webinar as well as at scientific conferences, including the 23rd annual Research Symposia on ALS/MND held in Chicago in December 2012 and a Keystone meeting in Santa Fe in February 2013. ALS TDI hopes to publish data in peer reviewed journals as well.

Is the drug safe for people with ALS to take even if they do not participate in this Phase IIA clinical trial?
It is crucial that anyone living with ALS consult with their medical team before taking any medication off label – including Gilenya. There is no evidence that shows that the use of Gilenya by ALS patients is either safe or beneficial as a treatment for their disease. In addition, we do not know what dosages of Gilenya might be helpful for ALS patients, as this might differ from that currently being prescribed for MS patients. These are the types of questions that this Phase IIA clinical trial is designed to begin to answer. Until the study is complete, we do not know whether Gilenya is safe for people with ALS or how the drug will affect people with ALS.

Where can more information about the drug be found?
Information about Gilenya (fingolimod, TDI-132) can be found here: http://www.als.net/TDI-132. Additional information about Gilenya from Novartis can be found here: http://www.gilenya.com/index.jsp.

Who can participate in this Phase IIA clinical trial?
Please see the inclusion/exclusion criteria to determine if you are eligible to participate in the trial. The document is posted at http://www.als.net/TDI-132.

Where can people enroll to participate in the study?
Enrollment can only be done at an approved study site. ALS TDI will provide more information about this clinical trial and enrollment sites as soon as possible. In the meantime, you can learn more online about Gilenya/TDI-132 at http://www.als.net/TDI-132 or email trials@als.net to be added to a mailing list when more information is available.

Who selects the participants for the trial?
Study selection is done at one of the locations enrolling patients – not by ALS TDI. Each person with ALS will be screened against the inclusion/exclusion criteria for the trial. The attending physician, neurologist or other medical professional at the enrollment site will discuss these criteria with each individual patient. **ALS TDI does not have a say in any person's individual assessment for enrollment in this or any other trial currently enrolling patients, nor does ALS TDI have any influence over enrollment.**

How large is the study? How many people will be able to participate?
Approximately 30 people living with ALS will be able to participate in the Phase IIA study. ALS TDI intends to execute a larger Phase IIB trial if the Phase IIA trial indicates that oral fingolimod appears to be safe and tolerated in ALS patients.

Who is "leading" the study?
ALS TDI made all discoveries leading up to this trial. It funded all of that work and is the sole funder of the current Phase IIA clinical trial. James Berry, M.D., M.P.H., is the principal investigator of the clinical trial and is listed on the filing as the "sponsor" from Massachusetts General Hospital (MGH). Dr. Berry is the Unit Chief of MGH's ALS Multidisciplinary Clinic in Boston and helps to organize trials through NEALS. All data produced through this clinical trial owned outright by ALS TDI.

How long will the study take? What is the duration of the Phase II trial?
ALS TDI is committed to the discovery and development of effective treatments for ALS as soon as possible. As such, we have designed this trial, in consultation with NEALS, to be a rapid as possible. The Phase II study has two parts. The first (Phase IIA) takes each patient about one month to complete once enrolled. Based on those results, a second stage (Phase IIB) of this study will be initiated and take approximately 12 months for each enrolled patient to complete.

Why are there only a few clinics enrolling patients?
The recommendation from our clinical contractor, NEALS, was to have only a few clinics enroll due to its small size and short duration. We anticipate having many more sites added for future trials of Gilenya in ALS patients.

Who can be contacted for information about the study?
ALS TDI will provide more information about this clinical trial and enrollment sites as soon as possible. In the meantime, please email trials@als.net to be added to a mailing list when more information is available.

Where can people learn more about clinical trials?
ALS TDI has created an online resource on clinical trials in general, available here: http://www.als.net/ALS-Research/ALS-Clinical-Trials/

What will happen for Phase IIB and III?
ALS TDI is committed to its mission of discovering and developing effective treatments for ALS patients today. This Phase IIA clinical trial is an important step toward knowing if TDI-132/Gilenya is a potential treatment for ALS. If the Phase IIA clinical trial is successful in meeting its endpoints, we anticipate that this compound will move into a Phase IIB clinical trial. If that is successful, it is highly likely that a Phase III clinical trial will occur. It is likely that a new coalition of sponsors would be involved in these later stage clinical trials. A Phase III clinical trial would be the pivotal stage at which the effects of Gilenya in potentially treating ALS will be understood.

How is this trial different than other ALS trials currently happening and trials in the past?
Every clinical trial is different. This trial is different from others happening in ALS in that it targets an aspect of disease that hasn't been targeted before. In addition, since this is an FDA approved compound, we believe that Gilenya is a better candidate for rapid advancement than some others currently in clinical trial. However, we do not know if Gilenya is an effective treatment until these trials are complete and the data analyzed.

Once selected for the trial, does the participant have the right to quit?
Yes, participation in a trial is completely voluntary, and patients involved may at any time choose to discontinue their participation for whatever reason.

How will people taking the drug "off-label" or outside the trial impact the trial?
It is crucial that we enroll this trial as quickly as possible so that we can get an answer to the questions: "What does this drug do in ALS patients?" and "Does it have a positive effect?" It is only in a controlled clinical trial that we can get that answer and move this project forward. ALS TDI is focused on completing this clinical trial as quickly as possible in order to get an answer that may have impact for ALS patients.

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