Genetic ALS and FTD Pre-Symptomatic Population
FDA Patient-Led Listening Session
January 12, 2023
11-12:30 PM EST

Session Objectives

- We want the FDA to understand the plight of the Genetic ALS and FTD community, especially that to date, we have been able to access clinical trials or approved interventions only after we have suffered a severe symptom burden.
- We further hope the FDA will gain a sense of the urgency regarding use of the biological learnings from the genetic ALS and FTD gene carriers who have developed ALS and FTD, often while under the eye of researchers with no interventions offered, to help evaluate potential therapies.

Summary of Topics Discussed

- Background on ALS and FTD and the situation of people impacted by genetic ALS and FTD, including the emotional and mental health impacts of being at severe risk for terminal incurable diseases.
- Information about how these diseases are active before they are diagnosed with both clinically silent biological changes and mild symptoms.
- The struggle of seeing multiple family members be impacted. The struggle of knowing a terminal disease is active with mild symptoms but you cannot get a diagnosis and access to trials or even approved disease modifying treatments until the disease spreads.

Agenda

- **FDA Opening Remarks**
- **Jean Swidler, C9orf72 Repeat Expansion Carrier, Chair Genetic ALS & FTD: End the Legacy**
    - *Introduction, Background on Genetic ALS & FTD, Current State of care provided to our community and our perspective on it, results of a 174-person Community Survey on desires for pre-symptomatic treatment and willingness to take risks.*
- ***Community Perspectives:***
    - **Tucker Olsen - Sod1 Carrier**
    - **Mindy Uhrlaub - C9orf72 Carrier**
    - **Wanda Smith - From a GRN Family**

    - **Anonymous – From a Genetic ALS/FTD Family**
    - **Bonnie - TARDBP Mutation Carrier**
    - **Nicole - Caregiver of C9orf72 Patient with ALS/FTD**
    - **Debra Kumar - C9 Carrier with an ALS Diagnosis**
- **Summary - Jean Swidler**
- **Discussion / Q & A with FDA**
- **FDA Closing Remarks**

Partner Organization

Genetic ALS & FTD: End the Legacy is a nonprofit organization dedicated to supporting and advocating for their community. Operating under the ALS Hope Foundation umbrella, these organizations together will develop educational programs about familial ALS and FTD, establish support groups for members of the familial ALS and FTD community, engage the medical community to establish guidelines for care of pre-symptomatic gene carriers, and advocate for the hundreds of thousands of people at higher risk for developing Amyotrophic Lateral Sclerosis or FTD through the inheritance of a mutated gene that runs in their family.

Listening Session Summary

Introduction

Jean Swidler | Chair of Genetic ALS & FTD, End the Legacy, gene positive for C9 ALS/FTD, currently pre-symptomatic

- Following the deaths from ALS of her mother and grandparent, Jean's mother had life-long anxiety about developing the disease herself. Despite her family history, her physicians ignored her insistence that she was developing ALS, which caused a long delay until her diagnosis in 2017.
- ALS/FTD is a progressive neurodegenerative disease; it is scientifically accepted that it begins before symptoms are evident with both a symptom-free "preclinical" period and a mild symptom "prodromal" period, ahead of symptoms that would normally warrant a full diagnosis.
- We can estimate that there are 142,000 asymptomatic C9 gene carriers in the US alone, and that is just one of the genes that causes the disease; there are hundreds of thousands of people with genes that put them at risk in the US alone.
- Our communities have stepped up: we have volunteered for research studies

that require spinal taps, MRIs, cognitive tests, full-body EMGs, etc. We do it because we do not want anyone else to go through what we've seen our family members go through. And many of us have developed ALS and FTD without ever being offered approved treatments or trials, all while having our decline documented in medical offices in repeated research visits with treatments approved to treat our decline not offered. Much has been learned of the biological changes that precede full phenoconversion.

- Despite this, those of us at high risk for Genetic ALS and FTD still have no care, no prevention and no intervention. Few attempts have been made to see what possible interventions may do earlier in the disease process, and no attempts have been made to determine the best times for intervention with the currently approved medications. We want to live and be free of disabilities. We want earlier intervention to give us the best chance at a long life and no decline in function; we shouldn't have to wait to get worse to get access to intervention. Treatments that show little effect in fully symptomatic people could function essentially as a cure if provided earlier.
- Comparison to HIV/AIDs–transformational treatments improved life expectancy for AIDS patients, but were a near cure for those who were HIV+ but not yet symptomatic–what an impact that had in saving lives.
- We developed a community survey that was shared as a poster, and a journal article is in development.
    - The survey showed an overwhelming desire for treatment well before ALS/FTD would otherwise be diagnosed.
    - And we want intervention even if it has been trialed only in symptomatic patients, especially if that treatment had measurable effects or a genetic target.
    - We are also willing to hazard risks for treatments; less severe side effects were acceptable even in a modestly efficacious scenario, and even severe lifelong side effects were rated acceptable for longer life-extending treatments.

Community Perspectives on ALS & FTD

Tucker Olson | Gene positive for SOD1 ALS

Within his immediate family, Tucker has lost his grandmother, uncle, father, and aunt to SOD1 ALS. Some of Tucker's deceased family members have participated in interventional clinical trials after an ALS diagnosis. Tucker and a sister currently participate in biomarker research. Tucker was denied admittance into the only

pre-symptomatic interventional Sod1 study due to variability in length of disease progression amongst affected family members. Despite experiencing what Tucker believes to be gradually declining neuromuscular function over the past two years, Tucker also currently has no opportunity to access treatment symptomatically until further progression.

Mindy Uhrlaub | Gene positive for C9 ALS/FTD, currently pre-symptomatic

Mindy's grandfather died of ALS before she was born. Her mother died 3 years ago of C9 ALS. She is a C9 carrier, and both her sons, now teenagers, are at risk of developing genetic ALS. Mindy has enrolled in more than a dozen longitudinal studies. She is also being screened for the first ever pre-symptomatic trial of a drug in a C9 carrier, but it is only a small phase 2 trial recruiting at most two C9 carriers. But she has not been offered any of the drugs that have been approved in symptomatic patients. Her mom was diagnosed with many different things despite her family history; it took a year and a half to get a diagnosis, and by then she was ineligible for any clinical trials. The only way Mindy's children will not have to go through this familial trauma is for the FDA to help us.

Wanda Smith | Member of family with FTD progranulin deficiency

Wanda is a member of a family with FTD progranulin deficiency and many affected family members, who have donated tissues for research purposes for many years. Her sister participated in several trials–thank you for approving those so she could benefit. Please exercise multi-platform flexibility in clinical trials, accelerate approval based on biomarkers, and follow your own example in the cancer realm, where drugs are approved much more quickly.

Anonymous | Member of a family affected by ALS/FTD

The speaker lost her mother and others in her family to ALS/FTD, and for years the family was uncertain of what gene was involved. Her mother lost the ability to speak and tell her caretakers what she needed. She died in 2008. When the speaker began connecting with the ALS community, she was astonished at how many families are facing the same challenges. She runs support groups on Facebook and elsewhere in an effort to help others. We need some hope to offer our family members; please let us try these treatments.

Bonnie | Gene positive for TARDBP ALS/FTD, currently pre-symptomatic

Bonnie has a TARDBP mutation that causes ALS and FTD. Her dad's diagnosis took over a year, even with a family history of the disease. Treatments for her family members were offered only after their diagnosis. Bonnie is a carrier with two young

daughters, and participates in research. Treatments should be given earlier, and pre-symptomatic gene carriers should be included in drug trials; prevention is better than treatment! Currently, her only options are vitamins, dietary changes and avoiding environmental toxins, and she has no way to know whether any of it is making a difference because she is a research subject, not receiving care, and not being told what her biomarker readings are.

Nicole | Member of a family affected by C9 ALS/FTD

Nicole is a caregiver advocate, and considers herself a “widow-in-waiting.” Her husband’s family carries the C9 gene. Her husband’s ALS is slow-moving, but his dementia is not. There are 11 descendants in the family with a chance of carrying the gene. Each disease, ALS and FTD, is devastating, and having both is a special kind of torture. Today, her husband acts like someone around the age of 5, and he loses the right to make his own end-of-life decisions because of it. Their children have to live their lives with the fear of getting the disease, and they will not be tested, in part because one of them has said they would end their life if they were a carrier. Nicole is interested in knowing what more can be done to help families and give them hope.

Debra Kumar | Symptomatic with bulbar onset ALS Debra has bulbar onset ALS and is unable to speak, so her husband is speaking for her. Debra lost her grandfather, father, brother and uncle to ALS. She wasn’t able to get a diagnosis until the disease advanced past the point of any intervention for her speech function, despite the documented family history and her personal participation in observational studies detailing her decline. All three of her children, of childbearing age, are at risk. Will they also have to wait until it is too late to get treatment? What would have been Debra’s outcome if she had been on the approved ALS treatments two years ago?

Summary

We are thankful that FDA stayed with us through this hard conversation. In summary, we are asking that the FDA:

- Use what has been learned about the biology of ALS and FTD in observational trials, where people like Debra have developed ALS or FTD with no intervention offered, as endpoints for evaluating therapies.
- Include the presymptomatic community in treatment indications.
- Determine the best time for people with pathogenic mutations to initiate these therapies to maximize efficiency.

Given the emotional and physical burdens of these diseases, and the availability of disease modifying agents, this is required for a just and humane society.

FDA Questions and Advocate Answers

Director, Division of Neurology 1 at FDA: Thank you for your presentation. I did have one question. You raised the drug that was approved in 1995, I believe it's called riluzole, is that not offered to you when you find out you have the mutation? The other drug, the IV one, I can see the IV being a complication, but for the earlier one I assume it's being used.

Answer: That's a reasonable assumption, but quite the opposite is true. In fact, two top genetic ALS experts recently asked each other in a public symposium whether approved treatments should be offered earlier, and admitted that they simply didn't know. How is that question not only unanswered, but not even asked, 27 years after the drug's approval? It is being trialed for depression. One of the other things to consider, I'm familiar with a C9 carrier and who was told they had mild cognitive impairment, and he asked if he should be prescribed riluzole, but the doctor was not sure. Why are drugs being prescribed for C9 ALS, but not C9 FTD? Mindy's neurologist just offered to prescribe riluzole to do a N=1 trial to see if it does something!

Director, Division of Neurology 1 at FDA: Well I just want to be clear that from the FDA's perspective, we do consider the presymptomatic stage in genetic mutation carriers as part of the ALS disease process. They would appropriately be in clinical trials for ALS.

Patient Affairs Team reading a written question: Was the survey asking about just drugs or just genetic therapy?

Answer: It included both. The wording was phrased as "theoretical intervention." All the survey data is available, if you would like it. We're happy to give it all to you.

Patient Affairs Team reading a written question: Has the pre-manifest community had had an opportunity to connect with industry about what's important to you?

Answer: The firms with clear genetic-targeted drugs have been interested–we are trying to talk with everyone in the field, but not everybody is interested.

Patient Affairs Team reading a written question: What is a clinically meaningful endpoint for presymptomatic populations?

Answer: Preventing symptoms entirely would be the most meaningful! Tucker shared that having a genetic mutation for a highly penetrant, terminal disease should be the endpoint of a qualifier for access to treatment; we should not have to sacrifice our muscular function to any extent to get access.

We are also big proponents of looking at biological changes. The currently approved treatments do not affect biological markers. One way to develop further evidence for drugs that do not modify biomarkers would be to give those treatments in a placebo-controlled trial to people in the mild motor impairment / prodromal state and see the time to a full diagnosis of ALS or FTD, and then the rate of decline for a set period after the full diagnosis, with the placebo ending at time of full diagnosis. Right now, nothing is offered, until you have two affected regions. We are not saying that the prodromal trial design is what should happen, because some very smart experts have said that people in our position could be on them prophylactically right now, absent any new evidence. We offer it to say what could be possible. But for sure we are advocating for using biological endpoints.

Another issue this raises is the lack of genetic protections and how little the Genetic Information Nondiscrimination Act (GINA) actually does for our community. Also, we know other people suffer from chronic diseases that give them difficulties in getting insurance, and that has nothing to do with GINA.

Julie raised the comment made earlier in the Q&A, (Director, Division of Neurology 1) asked if presymptomatic treatments are discussed or available to us. We are so far from being offered even presymptomatic monitoring, much less treatment, it's incredible. I found a neurologist who after testing was willing to monitor me, and that is incredibly rare.

Director, Division of Neurology 1 at FDA: What's it like when you try to get care after you test positive for the mutation - I assume you see a neurologist after that, where do you go to get evaluation/care?

Answer: No, care or monitoring from a neurologist is not standard. As an example, Mindy just picked a random neurologist at Stanford, who said she would have to pay thousands to get the test, and to make sure she had life and long-term care insurance before the test. Mindy had no idea you could get in a study and get tested for free. She would have enrolled in a study and gotten free testing, and in rare cases would get my results back. Insurance doesn't pay for it, and you don't want that anyway because you don't want it on your medical record.

Wanda's family members still have challenges with getting diagnosed, despite their extensive family history of disease, waiting six to eight months to get an appointment to get counseling, a test, then results, through a study. For a test, the cost quoted was $2500 when referred by a neurologist. At least Wanda's sister was able to enroll in a trial once she got the result, but even with a known gene, it is very expensive to get a test.

It's very rare for us to be seen by a neurologist until we are disabled enough to get an ALS or FTD diagnosis. We're working on a process to establish standards for presymptomatic care with Dr. Terry Heiman-Patterson.

Patient Affairs Team reading a written question asked whether the pre-manifest community is willing to participate in trials that are placebo-controlled?

Answer: Yes, people are equally willing to be in placebo-controlled trials as to receive treatment, that was evident in our study data.

Closing/Wrap Up Remarks

As the meeting hit the appointed end time with questions still coming in, the Patient Affairs Team noted that if anyone had additional comments or questions, they may send them via email to patient.affairs@fda.gov.

Following the meeting, there was one additional question from the FDA, relayed by email by the Patient Affairs Team, asking whether "any members of the patient community had experience using technologies with wellness features or wearables products with wellness features (e.g., smart watches) to provide clinicians with insight into their day-to-day experiences and routines? For example, iPhones have a wellness walking steadiness feature."

Answer via email: Jean uses an Apple Watch and was quite excited to discover the walking steadiness feature. She has shared this with the community. Researchers in the longitudinal study space (at least ALLFTD and DIALS) don't seem very interested, as Jean gathers, they prefer to use trackers they can get all the data from, and the assumptions that have gone into the Apple walking features are not freely available to see.

FDA Divisions Represented
Office of the Commissioner (OC) – 4 *offices*

- OC/OCPP/PA – Office of Clinical Policy and Programs/Patient Affairs (organizer)
- OC – Office of the Commissioner
- OC/OCPP/OOPD – Office of Clinical Policy and Programs/Office of Orphan Products Development
- OC/OCPP/OPT – Office of Clinical Policy and Programs/Office of Pediatric Therapeutics

Center for Biologics Evaluation and Research (CBER) – *4 offices/divisions*

- CBER/OCD – Office of the Center Director
- CBER/OCD/PS - Office of the Center Director/Policy Staff
- CBER/OTAT-- Office of Tissues and Advanced Therapies
- CBER/OTAT/DCEPT/GMBII – Office of Tissues and Advanced Therapies/Division of Clinical Evaluation and Pharm/Tox/General Medicine Branch II

Center for Devices and Radiological Health (CDRH) – *4 offices/divisions*

- CDRH/OPEQ/OHTIII/DHTIIIC - Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology III C
- CDRH/OSPTI -- Office of Strategic Partnerships and Technology Innovation
- CDRH/OSTPI/DAHRSS – Office of Strategic Partnerships and Technology Innovation/Division of All Hazards Response, Science and Strategic Partnerships
- CDRH/OSPTI/DDH – Office of Strategic Partnerships and Technology Innovation/Division of Digital Health

Center for Drug Evaluation and Research (CDER) – 6 *offices/divisions*

- CDER/OND/ODES/DCOA – Office of New Drugs/Office of Drug Evaluation Science/Division of Clinical Outcome Assessment
- CDER/OND/ON - Office of New Drugs/Office of Neuroscience
- CDER/OND/ON/DNI – Office of New Drugs/Office of Neuroscience/Division of Neurology I
- CDER/OND/ON/DP – Office of New Drugs/Office of Neuroscience/Division of Psychiatry
- CDER/OND/ORDPURM/DRDMG – Office of New Drugs/Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine/Division of Rare Diseases and Medical Genetics
- CDER/OTS/OB/DBI – Office of Translational Sciences/Office of Biostatistics/Division of Biometrics I

Patients Represented

- Four pre-symptomatic positive gene carriers for genetic mutations that cause ALS/FTD

- Three members of families affected by Genetic ALS/FTD
- One symptomatic patient with Genetic ALS/FTD

Disclaimer

Discussions in FDA Patient Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects Genetic ALS & FTD: End the Legacy's account of the perspectives of patients and caregivers who participated in the Patient Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of ALS and/or FTD, health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire ALD and FTD patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.