Merit Cudkowicz, MD
Chair, Dept of Neurology, Mass General Hospital
Director Sean M. Healey & AMG Center for ALS, Mass General Hospital
Julianne Dorn Professor of Neurology, Harvard Medical School
Hearing Testimony
House Energy& Commerce Subcommittee on Health
July 29th, 2021

Chairwoman Eshoo and Members of the House Energy & Commerce Subcommittee on Health, thank you for inviting me to testify today. It is so good to see so many familiar faces and to meet new people from Congress who care about curing ALS. I am Dr. Merit Cudkowicz and since 1994 I have cared for thousands of families living with ALS. As a clinical trialist, I designed and led many ALS trials, including the recent trials of AMX035 and NurOWN and the first platform trial approach in ALS. I currently lead a National Institute of Health supported phase 2 clinical trial network for brain disorders and am grateful for long standing support both from the NIH and the FDA.

I spent my career building collaborative teams to accelerate finding effective treatments for ALS – teams of neurologists and other health care providers, people living with ALS patients, scientists and foundation leaders – because I believe that only by placing our patients at the center of all our efforts, and working together, will we be able to provide the BEST care and ACCELERATE the RESEARCH needed to bring us to the cures. That is why we are here today. We need Congress, FDA and NIH also on the ALS Team. It has long been a dream of mine to reach a point where we can begin to think about a world without ALS. Central to this effort is a focus on much more efficient and faster approaches for ALS therapy development. We must be global leaders on both the development of treatments and regulatory approval approaches. We are all in this together –and together can achieve great things for people with ALS and other neurodegenerative disorders. We are so very close to ways to slow and stop ALS progression. And we will not stop until we get there.

ALS – also known as Lou Gehrig's disease or Motor Neuron Disease, **attacks the nerve cells** in the brain and spinal cord, **robbing people** of the ability to **move, speak** and ultimately, **breathe**. Progression is dauntingly rapid. After diagnosis, the median survival is only 2-3 years. It often

strikes in the prime of life - it can occur as young as in 20s and also in people who are in their nineties. No race, sex or ethnicity is spared. Thought of as rare disorder, it as common as Multiple Sclerosis and the numbers are increasing at an alarming rate. The worldwide number of people with Motor Neuron Disease, or ALS -- is expected to rise > 40 % in the next decade or two. There is an urgency to act!

The huge advances in understanding brain disease allow us to imagine curing diseases once thought incurable. **ALS is one of these.** There had previously been no hope for ALS patients, but now there is : there are thousands of scientists in the field, new brilliant insights into the underlying disease biology, more than 160 companies with ALS drugs in pipeline, several treatments with positive phase 2 and 3 trial results in people already and the first platform trial approach to speed drug development is enrolling faster than any previous trial. We are at a **major therapeutic turning point** for ALS. Increased funding for science, clinical trials, expanded access and combined with new policies/processes to accelerate the regulatory approval of treatments for ALS are critical to ensure that people living today with ALS can have access to effective treatments.

You have heard from many people with ALS of the urgency for access to therapies. There is an urgent need for access to trials, access to experimental treatments through expanded access (compassionate use) programs and access to marketed treatments. People with ALS do not have time. Every month, sometimes every day, people lose function. In the United States, every 90 minutes someone is diagnosed with ALS, and someone dies from ALS. Referred to as the 'ALS Turnstile of Death' this is a very cruel illness. We must move faster and change this ALS clock.

The husband of one of my patients shared these thoughts about the chance to be part of research.

“What does your research mean to us? It gives us HOPE.
Hope begins at diagnosis. You hope they got it wrong. Then you hope you have a slow version.
Then you hope you’ll get to experience specific holidays and graduations.
But through it all, the greatest HOPE is that someone will find something to make this all go away.
And research provides that.”
Mr. Kolb, Caregiver, CENTAUR Investigator Meeting, Boston 1/30/2017

WHY NOW

ALS is a complex disease driven by multiple factors leading to neurodegeneration. Scientists have made major inroads in understanding some of the pathways that lead to motor neuron loss. However, one of the major factors that has hindered progress towards the goal of effective treatment and prevention is the lack of more informative biomarkers of disease activity and progression, therapeutic target engagement and treatment response, and diagnosis. Valid, sensitive, specific, precise and pragmatic biomarkers of all these processes are needed to facilitate clinical treatment trials. We want to work with the FDA and NIH to conquer this challenge.

A second challenge is that conventional "parallel-group" clinical trials in ALS are too large, long and expensive and too often exclude many people who want to be part of the research. These large trials are also often insensitive to clinical changes and unable to meet the urgent needs for effective treatments. Such trial designs must have very large samples and broad measures of change to accommodate the marked heterogeneity among individuals. Alternatives to this approach include "platform" trials, in which several therapies are tested at once, and "N-of-1" trials, in which a therapy is tested on just one patient, or a small number of people, to determine the specific impact. We have and will continue to find treatments that work in subsets of patients- we must find a way to accelerate approvals of these treatments. This includes working with the FDA and more funding for ALS research.

We must disrupt the current, slow approach to therapy development and partner expertise from our field and other fields with the FDA to think more creatively and become more effective in choosing the best treatments for the right person at the right time.

We have begun to do this with the AMX035 (Centaur), NurOWN and Toferson (SOD1 gene therapy) trials and the new Healey ALS Platform Trial. Partnership with the FDA is key and

desired to move all these treatments forward fast. Time is not an option for people living with ALS.

Our partnership with the two founders of Amylyx culminated in a two-drug combination that BOTH slows disease progression AND prolongs survival. This is the first in what we know will be a series of successes that will lead to the cures. The trial of AMX0035 (Centaur trial) was designed as an efficient trial. Last July, the results were published in the New England Journal of Medicine. AMX0035 combines two old (repurposed) drugs, sodium phenylbutyrate (PB) and tauroursodeoxycholic acid (TUDCA), to tackle the loss of neurons in the motor cortex and spinal cord. AMX0035 is under review in Canada for full approval. It will be submitted to EMA for provisional approval. We do not current have that regulatory option for ALS in the United States. A drug developed and tested in the United States will likely be approved elsewhere before approval in the United States.

We have heard reports from people in the NurOWN trial and expanded access program of improvements in function. This is not something we typically see or hear in ALS. There were important changes in important biomarkers in the phase 3 trial and better responses in people who started treatment in an earlier stage of the disease. The manuscript with full results is under review. Continued dialogue with the FDA on how to identify subsets of responder is critical as it is very likely that this treatment and many future treatments will work better in one group of people than another.

This year marked the launch of the exciting HEALEY ALS Platform trial – despite the challenges of COVID-19, enrollment has been 4x faster than any other ALS trial ever – over 500 people have already enrolled across the 52 clinical sites throughout United States who are partnering with us.

We adapted this new trial approach from our colleagues in oncology, who used it successfully to treat cancer. But we are refining it to make it even more flexible. It is **a revolutionary approach to accelerating drug development.**

Test several treatments at once

Increase access/minimize placebo

Accelerate speed of decision making
The Healey ALS Platform Trial reduces the time it takes to evaluate a treatment in half.
Costs of drug development are greatly reduced.

Best of all, unlike traditional clinical trials, we don't have to stop the trial when we finish testing one therapy – we can keep it running, until we find the cures.
We launched the trial with 3 therapies – we then added a fourth **– In record time- < 30 days** and hope to add 2 more in the coming months. From day one, the Neurology team at the FDA was instrumental in helping us design this innovative therapy approach.

Incredibly, we will have our first results next spring– not from one, but from all 4 drugs! Our patients say "**Platform trials may possibly be the best thing I have seen since my diagnosis**. **We feel this trial is working on the ALS clock."**

With few treatments and no cures available for ALS, we must offer patients access to experimental drugs. As science is evolving and the drug pipeline is becoming much more targeted to subpopulations of the disease, inclusion criteria for patients to enroll in trials have become more restrictive. More than 50% of people with ALS still do not qualify for clinical trials. This is where **Expanded Access Programs** (EAP) come in as essential. Through EAPs people with ALS who don't qualify for other clinical trials can receive access to experimental therapies – providing hope, some symptom relief and the knowledge they are contributing to the search for the cures. EAPs do not prevent the conduct of controlled, well -designed clinical trials. EAPs are for people who do not qualify for clinical trials. These can be and must be set up to include only people ineligible for existing clinical trials. We can and must do these in parallel with well designed clinical trials. People with ALS and prescribing physicians want drugs on the market where we have reasonable confidence on both efficacy and safety.

At the Healey Center for ALS at Mass General we currently have 130 patients receiving 9 therapies under expanded access. We want to expand this throughout the United States. The FDA has greatly simplified the process for approval of EAPs. EAPS can be designed to also learn about ALS. For example, in one of our EAPs, we learned about how to best dose the medication,

using biomarkers. In another we found that breathing function improved in several of the participants. One person noted that they could swim in pool again, where before they felt that they could not breath if water was chest high. Another person, who was supported by a ventilator to breath, found he could stay off the ventilator for longer periods of time. These participants were not eligible for any clinical trial, the EAP was their only option to try an experimental treatment for their ALS.

The primary hurdles to providing investigational therapies under expanded access include the willingness of the manufacturer to make the investigational drug available for treatment use, the costs to make additional investigational product for the EAP and the clinical center costs associated with safely providing the treatment that is rarely covered by insurance.

Thank you for supporting the ALS ACT initiative to provide funding for Expanded access.

Our goal is to make sure every individual confronting ALS has options – and that no one with ALS is told there is nothing we can do.

Our scientific community has achieved some major breakthroughs in ALS science and therapeutic development. There is more to be done to understand ALS science, but there are treatments out there today with positive results in ALS trials, and we must find a way to make these available to our patients.

I have great respect for the members of the FDA Neurology review team. They could not have been more helpful as we together paved new ground in bringing the HEALEY ALS platform trial forward. I do worry however, that we do not have a process for provisional approval of treatments for ALS. We know that this is possible for other serious life-threatening disorders in the United States and for ALS in other countries. We ask that investigational new treatments with positive phase 2 or 3 results in ALS have a faster pathway for approval (provisional or not). For these treatments, there is clear need and ability to also do post-marketing studies to confirm efficacy. Everyone wants that too. People living with ALS today though do not have time for second and third confirmatory trials prior to market approval. There is a known regulatory

pathway for provisional approval of treatments for serious life-threatening disorders. We must have this for ALS. The Promising Pathways Act is one approach to accomplish this – there may be others. We want that flexibility and dialogue with the FDA and for a solution soon! They need the funding and policies in place to make this possible.

We are seeing pharmaceutical companies go to other countries for their phase 1 and 2 studies – as they claim the regulations are fewer in Canada or Australia. Whether this is true or not is not entirely clear, but my ask is that the US FDA continue to be the world leaders in regulatory science and approaches to accelerate therapy development for ALS and other serious disorders. Working together, creatively and flexibly, we will find the cures for ALS.

I would like to end with some thoughts from **Alexandra Cavaliere who actively participates in ALS research and advocacy.**

"I was diagnosed with ALS at age 28. It was a few months before my wedding to my law school sweetheart. We learned that I have an incurable disease that steals my ability to move, speak, express myself, and eat on my own. No one who hasn't received that news can ever imagine what it feels like.

Soon I will be forced to retire from my career as an attorney, at age 30. Before long I will eventually need an in-home care aid. But the hardest thing for me is that thanks to ALS, my husband and I can't have children. I probably wouldn't live to see them reach age 3.

While ALS is rare to develop in one's 20's, I am not alone. I have interacted with dozens of young men and women, in their 20's, 30's, and 40's, in the ALS community in my situation--how many young lives, careers, families, like mine, destroyed by this cruel disease before their time.

But there are glimmers of hope. Since my diagnosis, I've learned about dozens of promising ALS treatments in testing. I've heard patients in drug trials report that their symptoms have stopped worsening during their trials, only to resume after they stop taking the study drug. In

some trials, certain sub-groups of patients have seen benefits, even if not all. But these therapies are limited to the clinical trial setting. Most of the trials are not available to patients unless they can enroll within a short window of their diagnosis and meet other criteria. If we don't meet the criteria to enroll, it is as if these potential therapies--those hopes--do not exist.

Allowing expanded access to safe, investigational ALS drugs, even if they are unproven, could change this. Treating ALS like we treated cancer could change this.

I think I speak for others in the ALS community when I say this: I know that there will not be a miracle cure for ALS in my lifetime. There may not be a new drug that shows clinical benefit in all patients. But we don't have time. We don't have options. We don't have the luxury of a full 3-stage clinical trial program for every potential ALS drug. What we do have is a will to live. We do have a willingness to take informed, science-based risks that might save our lives, or at least make our disease more bearable. What we need is the opportunity." **Alexandra Cavaliere 07/2021**