Redoubling the Urgency for Innovative ALS Clinical Trials

May 27th, 2020, Washington, DC --- "This month, the Muscular Dystrophy Association (MDA) is joining the ALS community in recognizing ALS Awareness Month, a month dedicated to pushing for progress for those living with ALS in the United States. Unfortunately, progress is sorely needed, and is not coming soon enough. ALS is still substantially underdiagnosed, often forcing those with ALS to undergo a diagnostic odyssey in search of an answer. Once diagnosed, there are few treatment options and still no FDA-approved treatments that substantially alter the course of disease progression.

ALS clinical trial design, particularly Phase III and confirmatory trial design that is intended to test the effectiveness of the investigation product, is an area where progress continues to lag, to the great detriment of the ALS community. While some advancement has been made, including the launch of the HEALEY ALS Platform Trial and the publication of an updated FDA guidance on developing drugs for ALS, the fact remains that ALS clinical trials are still far behind other neuromuscular and non-neuromuscular diseases in patient-friendly, forward-thinking designs.

For example, FDA's Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment: Guidance for Industry encourages trial sponsors to include individuals with ALS "across the disease stages". Much progress has been made in other diseases in including individuals with varying severities of disease in the same clinical trial, including with multiple experimental trial arms that do not compromise the integrity of the data collected. Yet trial designs in ALS continue to be very restrictive, often only including those patients who remain ambulatory or do not require mechanical assistance. Patients with ALS who have progressed further, or even those who otherwise have not experienced significant impact of the disease yet, are often excluded. These trial designs by their very nature exclude a substantial and often extremely vulnerable portion of the ALS community. While trial sponsors may be concerned that expanding the inclusion criteria for the trial may jeopardize findings of efficacy, the use of multiples arms that enroll ALS patients in different stages of progression should be explored.

We remain hopeful that FDA, working with sponsors, will eliminate the use of placebos in ALS clinical trials, but placebos are clearly still being employed in newly announced clinical trials. We recognize that the use of placebos will not disappear overnight, and the lack of established scientific understanding on the heterogenous progression of the disease poses challenges, but we ask that FDA and sponsors redouble their efforts to avoid placebos wherever possible. FDA and sponsors should be collaboratively investing in the science of using historical controls and Bayesian statistical approaches in ALS clinical trials. While FDA currently discourages the use of historical controls in the guidance, FDA, working with sponsors, should redouble their efforts to accelerate the viability of these innovative trial designs that avoid using placebos.

FDA also states that "Trials should include prespecified plans for a long-term, open-label extension that maintains the blind to the original treatment assignment after completion of the randomized effectiveness portion of the clinical trial". Open-label extensions (OLEs) and cross-over trial designs, programs that allow for all individuals participating in the trial no matter their previous trial cohort placement to receive the investigational therapy upon trial completion, are standard practices in other disease areas, including their employment in recent trials for Duchenne muscular dystrophy and spinal muscular atrophy. Yet we still see later-phase ALS clinical trials declining to employ open label extensions, thus taking ALS patients off of a potentially beneficial new treatment.

Furthermore, FDA also encourages the use of expanded access programs (programs that allow individuals outside of the clinical trial to still receive the investigational therapy) in ALS clinical trials. When presented with expanded access requests, FDA approves over 99 percent of requests across all diseases brought to the Agency by sponsors. Here again we see ALS clinical trial sponsors rarely employing expanded access programs to offer potentially safe and effective treatment, albeit experimental, to individuals excluded from the trial with few alternatives.

For the wellbeing of the ALS community, these practices should stop. While we are encouraged by the general direction and progress in ALS clinical research and trial design, advancement is far too slow. Today's ALS patient community deserves better. This is why this ALS Awareness Month, we are asking stakeholders including the FDA, Congress, the biopharmaceutical industry, and ALS patient organizations to join the ALS patient community in coming together to more urgently seek solutions to continuing challenges. More specifically, we are asking for:

- Innovative financing mechanisms to overcome the financial disincentives associated with including expanded access programs and open label extensions within ALS clinical trials, including ongoing late-stage or Phase III clinical trials.
- Greater effort and urgency behind ALS biomarker development that can hopefully inform surrogate endpoint development (clinical trial endpoints that likely predict effective clinical outcomes) and eventual qualification to facilitate use of FDA's accelerated approval pathway.
- FDA consideration of the utilization of innovative approaches towards expanded access, such as the Oncology Center of Excellence Project Facilitate, in progressive neurological diseases without satisfactory therapeutic alternatives, including ALS.
- Collaborative development of innovative clinical trial designs that employ historical controls, Bayesian statistical approaches, and cross-over designs with the FDA, the biopharmaceutical industry, and patient advocacy organizations leading the way.
- Sponsors of ALS therapies to commit to considering expanded access and open label extensions at the outset of their clinical studies. Sponsors should meet with patients, their loved ones, and their advocates before clinical trials commence to ensure the approach is supported by the patient community.
- Congressional consideration of legislative interventions that would lower financial and logistical barriers to employing scientifically sound, but also patient-centric, approaches in ALS clinical studies.

MDA is pleased to routinely collaborate with patient leaders, Congressional partners, FDA officials, and fellow patient advocacy organizations on how to achieve these goals as soon as possible. This ALS Awareness Month, we call on all stakeholders from across the therapeutic development spectrum to commit to think more creatively on how to address these surmountable challenges, and to heighten the urgency to find solutions."

For inquiries on this statement, please contact advocacy@mdausa.org