October 25, 2019

Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

RE: Docket number FDA-2013-N-0035 for “Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry”

Dear Sir or Madam,

The undersigned individuals and organizations, respectfully submit the following comments to further inform the Food and Drug Administration’s (FDA or Agency) implementation of the Final “Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment; Guidance for Industry.” We deeply appreciate the FDA’s commitment to accelerate therapies to people with ALS. Their unmet medical need is profound, and our sense of urgency must reflect this reality.

These comments are the latest in a series of strategic actions led by The ALS Association and the community to strengthen and accelerate ALS drug development. Chief among these steps have been the landmark community-led draft guidance leading to the FDA draft version of its drug development guidance, feedback comments on the Agency’s draft, and a national workshop and resulting report to inform the finalization of the guidance.

These actions have been taken in consultation with people with ALS and their caregivers, academics, clinicians, ALS advocacy organizations, industry stakeholders, and additional topic experts to ensure an informed perspective. We gratefully acknowledge the leadership of the patient and caregiver advocacy committee (PCAC) that helped develop the community-led draft guidance and support its recent comments on the Final guidance.

**General Observations**

The signatories acknowledge the Agency’s efforts to address concerns raised by the community throughout the guidance development process. These efforts are reflected in the changes made from the draft to finalized versions of the guidance, including the need to reduce the burden of clinical trials to people with ALS and their caregivers, the recognition of the value of patient reported outcomes (PROs), the encouragement of broader inclusion criteria, and support for innovative trial designs, including platform trials, in an effort to reduce the number of people exposed to placebo.

We particularly appreciate the Agency’s stance that no person with ALS should be denied an effective therapy to participate in a clinical trial. The FDA’s recognition of the value of patient input and experience data is reassuring to the community. We appreciate the FDA explicitly recognizing that people living with ALS are experts and should be central to the development of therapies.

Very importantly, the Agency’s recognition of the serious and unmet medical need in this population is reflected in the guidance language stating FDA will use available regulatory flexibility to approve effective drugs as quickly as possible. We also are encouraged to see the Agency calling on drug
sponsors to interact directly with the FDA early and often to discuss areas such as innovative trial design, novel outcome measures, and surrogate biomarkers for accelerated approval.

Finally, we thank the FDA for its recognition that the ALS pipeline includes small molecule drugs, biologics, cell and gene therapies, and for making it clear that this guidance applies to such potential therapies.

Specific Comments

I. Early Phase Clinical Development and Drug Development Population (Section A.1-2)

The Agency’s guidance confirms that people living with ALS are central to the drug development process and their views should be solicited by those developing treatments for ALS and reflected in clinical trial design. We are pleased to see the Agency’s encouragement for sponsors to work with those living with ALS to understand how they view treatment goals and risk tolerance, and to communicate the expectations with respect to a potential therapy’s effectiveness and safety.

We also are encouraged that language in the final document urges sponsors to not exclude patients from trials unnecessarily based on characteristics such as age or disease stage unless scientifically justified. We agree with the Agency’s recommendation that broader inclusion criteria will allow more rapid trial enrollment and potentially accelerate drug development. Along these lines, we urge the FDA in its discussions with sponsors to make it clear the Agency is not discouraging enrichment approaches. Increased use of enrichment approaches means the study population could include participants who might be uniquely sensitive to an intervention and could lead to more efficient trials in certain cases, when scientifically justified. This beneficial potential effect is incredibly important in communities like this one, where the eligible patient population is by definition limited.

Additionally, we are glad to see the FDA’s framework supporting broad inclusion criteria for trials while indicating that the Agency is open to primary analyses based on a subset of the sample defined by clinical characteristics and/or biomarkers, and an analysis of the full trial population being secondary/supportive. A prespecified subset analysis is also a way to realize shorter (i.e., 6 months) clinical trial durations. This framework provides a good balance between broad inclusion criteria, our desire for shorter trials and statistical concerns.

The signatories are encouraged by FDA’s recognition of the burden of clinical trials on people with ALS and their caregivers. We agree with the consideration of alternative trial designs such as decentralized studies using mobile technologies and other methods used to collect data in patients’ homes or through their local health care providers.

Approaches like these will make clinical trial participation more attractive to people with ALS and caregivers. We expect their adoption to lead to more efficient trial enrollment, improved retention, and enhanced data completeness.
II. Effectiveness and Safety Considerations, Relevant Nonclinical Safety Considerations and Pharmacokinetic/Pharmacodynamic Considerations (Section A. 3-4, and Section C. 1 -2)

We appreciate the Agency’s commitment to exercise regulatory flexibility in applying the statutory standards to drugs for serious diseases with unmet medical needs, such as ALS, while preserving appropriate assurance of safety and effectiveness. While we agree that experimental drugs must be proven both safe and effective before being approved to market, we continue to emphasize that those living with ALS are willing to accept significant risk for a potential treatment benefit. **To move therapies to patients as quickly as possible, we urge the FDA to work with sponsors to employ alternative methods to assess safety in a timelier manner, rather than the one-year requirement for people with ALS to be exposed to the experimental drug.**

We commend the FDA’s willingness to permit clinical trials to commence based on less than usual nonclinical testing, if scientifically justified. However, we are concerned by the FDA’s removal of the language from the draft to the final guidance on the Agency’s willingness to waive or defer the full array of typical clinical pharmacology studies to post-approval, given the serious and life-threatening nature of ALS. **We ask the FDA to do everything in its power ensure this stance does not slow the process of delivering potentially effective treatments to people with ALS, and to monitor when this stance might be affecting the approval of potential therapies.**

We also commend the FDA for encouraging sponsors to include prospective plans for interim effectiveness analyses to allow for the detection of early benefit in a clinical trial. This advance planning is critical to facilitating prompt assessments of efficacy, even in trial sub-populations, and to speeding therapeutic development.

III. Trial Design (Section B. 1)

The final guidance notes that people in ALS trials should receive the best standard of care and that no individual should be denied effective therapies to be randomized to a placebo-only arm. We are encouraged to see the FDA respond to the community’s urging to allow development strategies that minimize unnecessary exposure to placebo and to expedite trials, including the Agency recommendation that sponsors consider master protocols, adaptive design (including Bayesian features) and enrichment strategies. The signatories note the Agency’s final guidance is open to add-on design. **We are pleased the Agency recommends that all patients have access to a potentially effective treatment or treatment that has already been proven effective, so that no patient receives a placebo alone; we urge the Agency to continue to reduce exposure to placebo and encourage more innovative and human trial designs.**

In terms of historical controls, we recognize that they alone may not be appropriate in all circumstances, and the challenges they present because we do not fully understand the heterogeneity or progression of ALS. However, we continue to believe strongly there are a variety of ways to improve efficiency of trials with respect to limiting placebo groups. We recognize FDA uses the word “entirely” in the context of its recommendation that trials not be based entirely on historical controls and commend the FDA for allowing flexibility when scientifically justified. **We expect the FDA will consider historically-controlled trials as our understanding of ALS improves, and in trial arms where the natural history of the population (e.g. specific genetic mutations) is well understood.**
The final guidance language observes that historically-controlled trials are likely difficult to interpret unless the effect size on an objective endpoint is very large. As mentioned in previous communications to the Agency, we request the FDA provide examples of historically-controlled trials in which a large effect with an objective endpoint was accepted as the basis for approval in other disease areas so the ALS community, and others, might use these examples as shared learning.

IV. Effectiveness Endpoints, Study Procedures, Timing of Assessments and Statistical Considerations (Section B.2-4)

We are very pleased with the Agency’s support for new outcome measures (beyond survival) capable of measuring clinically meaningful effects in people with ALS, as well as the specific encouragement to sponsors to use the input of people with ALS and their experiences to develop new measures. The voice of people with ALS and their caregivers is central to determining clinical meaningfulness.

We also appreciate the final guidance reference to the inclusion of patient reported outcomes (PROs). As The ALS Association and community stakeholders embark on the ALS Focus initiative to determine what is most important to people living with ALS across the spectrum of disease, and to develop an ALS health index to measure those items, we are reassured to see the FDA’s recognition of the importance of these outcome measures and need for input by people with ALS in their development.

We also commend the Agency’s recognition that multiple endpoints, such as muscle strength and respiratory function, are acceptable beyond the endpoint of survival— as survival endpoints can potentially increase trial duration, whereas functional measures can demonstrate benefits in a shorter timeframe. **We encourage FDA to consider rigorously-developed PRO tools that measure what is most important to patients and, in turn, to recognize these outcomes, such as delay in losing what is important (slowing progression), as acceptable endpoints as well.**

For trials based on functional endpoints, we strongly support the FDA’s recommendation to perform the first on-treatment assessment at the earliest possible time, and no later than 2-3 months after randomization.

The final guidance emphasizes the burden of clinical trials to people with ALS and strategies to reduce these challenges, such as remote monitoring. We are reassured by the FDA’s continued recognition and specific encouragement to limit the need for travel to study sites (e.g., decentralized clinical trials with key endpoint measures at baseline and at intervals during the trial conducted in a standardized fashion at central testing facilities, as well as remote monitoring for some of the visits). Further, the FDA’s willingness to explore the utility of digital biomarkers as clinical endpoints is encouraging. The community looks forward to ongoing collaboration with the Agency on these issues.

V. Accelerated Approval Considerations (Section B.6)

The signatories are pleased to see new language encouraging sponsors to incorporate exploratory biomarkers in all phases of development of ALS drugs. **We urge the agency to continue to commit to policies that encourage the development of new surrogate candidates for accelerated approval.**
VI. Benefit-Risk Considerations (Section B.7)

This section includes an important acknowledgment that FDA will consider the tolerance for risk among people with ALS. Moreover, the impact of the serious and life-threatening nature of ALS is clear in the final guidance. We continue to encourage the Agency to consider rigorous patient experience data on benefit-risk preferences, including what is submitted from community stakeholders, as part of the review of new therapies.

We thank the FDA for engaging the ALS community throughout the development of the guidance. As the Agency notes, the science of ALS is not stagnant. We must make every effort to incorporate new learning into these processes moving ahead. We look forward to continuing our shared resolve to help advance treatments that defeat ALS.

Sincerely,

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