April 17, 2018

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2013-N-0035 for “Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment; Draft Guidance for Industry”

Dear Sir/Madam,

On behalf of the undersigned, The ALS Association (The Association) respectfully submits the comments described in detail below to inform the Food and Drug Administration’s “Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment; Draft Guidance for Industry.” We appreciate the Agency’s commitment to this first ALS-specific guidance, and are pleased to work closely with the Food & Drug Administration and the ALS community to expedite the drug development process. With that in mind, The ALS Association has worked together with the ALS community to highlight areas that could be enhanced in the finalized guidance document to take full advantage of advanced regulatory tools along with science-driven progress and consensus in the ALS research and development field.

With support made possible by the ALS Ice Bucket Challenge and in coordination with the Food & Drug Administration, The Association convened a landmark patient-focused drug development (PFDD) effort across the ALS community to prepare and submit a draft guidance, in part, to advance the Agency’s work and considerations. The extensive, community-wide work product is posted in the Food & Drug Administration (FDA or Agency) docket (Docket ID: FDA-2017-D-6503) where it continues to serve as a resource to all stakeholders. Together with an imminent update to the complementary ALS Clinical Trial Guidelines, also supported by The ALS Association and authored by leading clinical experts, the community-led draft guidance represents an unprecedented initiative to improve the efficiency, reliability, and speed of the therapy development process for this devastating disease.

We also recognize that a number of key recommendations in the community-led effort are reflected in the more concise FDA draft guidance as well. At the same time, we view this as a critical opportunity to put ALS therapy development into a PFDD-leading position. The following comments were developed in consultation with the community-led draft guidance Steering Committee, patient and caregiver advisors, and other partners to build a broadly informed perspective on the elements of the FDA draft guidance. We offer them in the interest of forging a final guidance with the FDA that propels the field forward in every way possible.
Specific Efficacy Trial Considerations

I. Study Design (Section B.1.)

We are pleased the FDA is open to add-on designs and encourage the Agency to be even more forward-leaning on trial design, including endorsement of the use of platform trials in which one or more therapies may be evaluated in a single or multiple subpopulations.\(^1\) We also urge the FDA to specifically reference the use of adaptive designs as an example of other designs that increase the efficiency of studies, similar to its reference in the Guidance for Industry on Developing Drugs for Duchenne Muscular Dystrophy and Related Dystrophinopathies.\(^2\) Inclusion of this type of language would send a positive signal to therapy developers that the Agency is willing to consider such alternative trial designs.

We recognize and appreciate the Agency’s concern around the use of historically-controlled trials and the complex challenges they present. There are a variety of ways to improve efficiency of trials with respect to limiting placebo groups such as crossover design, disproportionate randomization approaches, and platform trials, and there are likely to be new methods in the future. We encourage the FDA to provide flexibility and include guidance language that supports scientifically valid approaches to reduce the size of placebo groups. Efforts are underway to develop predictive algorithms\(^3\) and stratification approaches to reduce the variability of progression, both of which would reduce the size of placebo groups and may in the future further limit placebo groups. Additionally, in reference to the FDA’s draft guidance language stating that historically-controlled trials are likely difficult to interpret unless the effect size on an objective endpoint is very large, 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 any disease area so that the ALS community, and others, might use these examples as shared learning.

Furthermore, we believe that additional language encouraging sponsors to consider the burden of trials on patients and to adopt strategies that reduce this burden would strengthen the FDA document. Recruitment and retention in ALS trials is a known challenge and approaches such as remote monitoring, wearables, and other technologies, if validated, should be encouraged. Recruitment and retention in studies also could be positively affected if sponsors provide appropriate access to participants after the trial has concluded. Exclusion criteria is another issue of great importance to the ALS community and sponsors should

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be urged by FDA to consider approaches to, among other things, include patients in later stages of the disease.

The issue of how clinical trials for ALS are designed is complicated and characterized by considerable disagreement within our community. The differences are too extensive to take a position categorically in favor of any particular type of trial design at this time. We again encourage the FDA to adopt language in the final guidance to reflect flexibility on this subject.

II. Efficacy Considerations and Efficacy Endpoints (Sections A.3 and B.2)

We welcome the FDA’s willingness to consider proposals for the use of new outcome measures capable of measuring clinically-meaningful effects in patients. We also urge the FDA to include additional language encouraging developers to explore the use of alternative outcome measures, including patient-reported outcome measures and those developed using patient experience data.

While we appreciate the Agency’s recognition that treatment effect on survival should be combined with an evaluation of the need for full-time respiratory support, as such support can affect survival time, we recommend the FDA include language that encourages the use of endpoints other than survival. Functional clinical endpoints that would suggest clear evidence of slowing progression or protection of motor abilities of importance to the patient should be considered as acceptable endpoints and the basis for accelerated approval in ALS, a disease with tremendous unmet medical need. This approach would be consistent with the advice which FDA provides in the Guidance on Expedited Programs.

III. Accelerated Approval Considerations (Section B.5)

Considering the devastating nature of ALS, we request more clarity around the Agency’s thinking on Accelerated Approval, as the current language appears to discourage trials based on new surrogate outcome candidates for accelerated approval and perhaps unintentionally paints a discouraging picture for the community. While the community appreciates the Agency’s willingness to accept credible surrogates endpoints once identified, we strongly urge the FDA to revise the language in this section to language similar to that which is included in the Duchenne Muscular Dystrophy Guidance stating “biomarkers that reliably reflect health and amount of skeletal muscle at a biochemical, cellular, or tissue

4 Excerpt from FDA Draft Guidance (pg.5): This feasibility, in addition to the current state of scientific understanding of ALS, which has not identified credible surrogate endpoints, leads FDA to advise sponsors to study clinical endpoints capable of supporting full approval in studies intended to establish clinical benefit.
level may be useful across the drug development process, including use as prognostic, predictive, or pharmacodynamic markers, or, in some instances if supported by sufficient scientific evidence and acceptable analytical methods, as surrogate endpoints to support accelerated approval.”

IV. Risk-Benefit Considerations (Section B.6)

As indicated in the community-led draft guidance, people with ALS repeatedly state their desire to accept greater risk in the search for potential therapies. The willingness of many patients to accept greater risk, the nature of this disease, and the shortfall of current treatment options have direct implications for the drug development process with regard to: the use of alternative endpoints; the significance levels for hypothesis testing; the role of placebo observations in the control arm; the method of delivery; and the use of expanded access and accelerated approval mechanisms. We appreciate inclusion of language in the FDA draft guidance considering patient tolerance for risk, and the serious and life-threatening nature of the condition. We also encourage the Agency to include language on its willingness to consider rigorous patient experience data on benefit-risk preferences submitted from community stakeholders to inform the FDA’s current thinking and support new drug applications.

Other Considerations

V. Relevant Nonclinical Safety and Pharmacokinetic/Pharmacodynamic Considerations (Section C.1 and C.2)

The ALS Association is encouraged by the FDA’s stance on pre-clinical requirements and, when appropriate, permitting clinical trials to commence based on less than usual nonclinical testing if scientifically justified.

The Association also supports the FDA’s openness to waiving or deferring the full array of typically required clinical pharmacology studies to post-approval, if at all possible and when appropriate, given the serious and life-threatening nature of ALS. Such language reflects the Agency’s recognition of urgency in the community to identify and expedite treatments for ALS.

As drafters of the community-led ALS guidance, we understand the fine line between providing clarity and direction to sponsors without being prescriptive. We appreciate the agency’s willingness to engage with sponsors and discuss

5 FDA Duchenne Guidance, pg. 11
specifics around trial design, endpoints, and outcome measures. As more treatments enter the pipeline and more information accumulates across multiple sponsors and trials, we request the FDA provide advice to all stakeholders regarding new endpoints the Agency could embrace.

Finally, as members of the ALS community, we urge the FDA to employ every aspect of regulatory flexibility provided in current law, regulation, and policy to speed the development and approval of potential therapies for this devastating disease. For example, the Agency’s recent actions regarding the edaravone application appear to be consistent with this strategic direction.

We appreciate your careful consideration of these points and look forward to the upcoming ALS guidance workshop to support a forward-leaning, finalized document. This outcome is critical to the people we serve. We must make every effort to ensure the ALS guidance helps confront their serious unmet medical need and are pleased to work closely with the FDA to achieve this.

Sincerely,

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