****This is an updated community priorities document noting the recommendations that were in part (yellow) or in full (green) included in the finalized FDA ALS Guidance Document: Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment.**

ALS GUIDANCE: COMMUNITY PRIORITIES

I. Introduction

The purpose of the updates to the ALS Clinical Trial Guidance are to adjust the baseline by which clinical trials in ALS are developed and conducted. To make them humane and tailored to the realities faced by those living with ALS.

The purpose of this document is to ensure that in resetting this baseline, the FDA has actually heard and addressed critical changes requested by the patient community which the community believes will help facilitate both more efficacious trials and better enrollment/retention.[1] There is no group that will benefit more from innovative, bold changes that make trials more efficient, humane, and efficacious, nor one which will suffer more from ineffectual or cosmetic changes than patients.

We have outlined herein the key priorities from the patient community necessary to truly accelerate the search for effective treatments and cures. As set forth below, those priorities are perhaps most achievable within the context of an adaptive platform trial, and we encourage the FDA to recognize that observation in its Guidance Document. Stepping back, we have mapped these priorities to the sections from the Draft ALS Clinical Trial Guidance released by the FDA in 2018 so that those sections can be changed to achieve the goal of unleashing scientific innovation and progress while ensuring rigorous scientific and health standards.

The priorities reflected in this document are guided by four principles set forth below, but can be distilled down even further. A 2019 Ipsos poll of 551 patients found that:

- 78% of ALS patients are "more willing to take risks during a clinical trial than a non-terminal patient;" and
- 78% were "more willing to participate in trials to help find a cure for ALS, even though [they] may not benefit from them."[2]

These numbers are staggering, but also sobering as the reality is that the vast majority of ALS patients are excluded from trials either by reflexive, untailored exclusion criteria or the burden/cost of travel. Moreover, most of those that do enroll are thrust into randomized, double-blind placebo controlled trials that can last for

[1] According to a 2019 Ipsos Poll of 551 patients sponsored by I AM ALS and ALS TDI, 41% of ALS patients have participated in a clinical trial. 28% of patients have participated in a trial involving a drug or treatment. (Q. 9). And 86% said they wish there were more trials they could participate in. (Q21b). With such a small patient population these numbers represent a significant problem as it makes clear that the current trial designs, in particular, the exclusionary criteria and use of placebos bar many patients from participating and scare off many others. The topline data from this poll is attached to this submission. The full underlying data set is available if helpful.

[2] Ipsos Poll Q.21.

nearly a year, an eternity for an ALS patient. In an era where adaptive, innovative, and/or platform trial designs are the norm for much of medicine it is time to create a Guidance document that finally brings patient-focused drug development to the fight to end ALS.

II. Guiding Principles

It is essential that the FDA suggest and encourage trial design that addresses the following four issues:

1. Maximum reduction in the biostatistical noise caused by disease progression heterogeneity;
2. Examination of patient success as deeply and urgently as patient safety is addressed through the creation of an independent expert panel and incorporation of their learnings into adapting the trial (or by taking other appropriate action).
3. Collection of robust patient biological data (by way of example, but not limited to, genetic sequencing, cerebrospinal fluid (CSF) collection, blood collection) at entry into the trial and post participation so that significant learnings about biomarkers and patient phenotype relative to the primary trial endpoint can be gleaned and then incorporated into trial design(s) going forward.
4. Encouragement of the use of innovative, humane trial design features that promote trial recruitment, retention and statistically/scientifically meaningful outcomes.

III. Specific Textual Changes

Specifically, we request that the Guidance document include either the text below or the direct, core principle embodied in this text. To facilitate the easy inclusion of these changes we have organized them so that they correspond to existing sections of the FDA Draft Guidance. We ask that the FDA provide us as expeditiously as possible with feedback on these changes--specifically, which ones have or are being included in the final Guidance and which are not.

1. **<u>Drug Development Population</u>:**
    a. Given the severity of ALS, the limited patient population, and heterogeneity of ALS, the FDA strongly discourages the imposition of exclusionary criteria for broad subsets of patients unless the sponsor can demonstrate that the criteria is needed to protect the health or safety of the study participants. Any other exclusion criteria should only be imposed if it is validated by a plausible biological basis.

2. **Specific Efficacy Trial Considerations: Study Design**:
    a. The FDA supports the use of an adaptive platform trial design for ALS trials that include, but are not limited to, a shared control group and the constant evaluation of the adequacy of any control by evaluating its composition against well-designed historical and/or algorithmic controls.
    b. The FDA encourages sponsors to use non-survival endpoints to ascertain efficacy as well as to shift away from multi-month study observational periods or the reliance on observation data in determining a treatments efficacy.

3. **Specific Efficacy Trial Considerations: Study Design**:
    a. The FDA recommends that sponsors, wherever possible and practical, include in their study design a cross-over aspect as well as rerandomization of trial participants who progress at a statistically significant rate above the mean progression for the first three months of the trial so that they are evenly distributed between the treatment and control arms.
    b. The FDA also recommends that as biomarkers for disease progression are validated, sponsors make every effort to replace ALSFRS-R with biomarker level changes as a primary trial endpoint.
    c. Given that ALS is currently terminal, the FDA also recommends that sponsors seek as expeditiously as possible to eliminate the use of any placebos in favor of shared control groups or clinically meaningful biomarkers as those biomarkers are validated.[3]
    d. The FDA recommends that sponsors develop trials in such a way that they can both carry the trial forward to conclusion and support meaningful Expanded Access Programs and open-label extensions for trial participants.[4]

4. **Efficacy Considerations**:
    a. Given the heterogeneous nature of ALS, the FDA recommends that sponsors create an unblinded Independent Review Board (IRB) that can examine subsets of patients in the treatment arm of a trial who

[3] The Ipsos poll found that 83% of ALS patients would be more likely to participate in a phase 3 trial if placebos were not used and that 74% would be more likely to participate if there was a lower likelihood of receiving a placebo. (Q. 19(a) and (b)).
[4] The Ipsos poll found that 91% of ALS patients were more likely to participate in a phase 3 trial if they were guaranteed access to the drug after the trial (if they wanted to keep taking it). (Q. 19 (d)).

are meeting the trial's clinical endpoint or exceeding it. This examination should look at, among other items, whether there is a plausible biological explanation for why that subset is doing better, and then in consultation between the IRB and the FDA determine whether (a) the trial should be adapted to recruit more participants who meet the subset definition into the trial, (b) whether an accelerated approval or full approval with a labeling restriction is appropriate, or (c) whether expanded access or open-label continuation for patients who meet the subset definition is warranted.

5. **Study Procedures and Timing of Assessments**:
    a. In order to decrease the potential for bias and to increase robust data collection, the FDA encourages trial sponsors to design data collection and assessment procedures that utilize remote collection technologies, such as, but not limited to, wearables, monitoring applications, and voice recordings.[5]
    b. In order to increase study participation and to facilitate the retention of study participants, sponsors are encouraged to limit the need for patient travel and to reimburse in full patients and a caregiver for their costs of travel.[6]

6. **Pharmacokinetic/Pharmacodynamic Considerations**:
    a. Sponsors are encouraged to consider trial designs that collect genetic and CSF data from all participants to facilitate subgroup analyses.[7]

[5] The Ipsos poll found that 95% of ALS patients were "definitely" or "maybe" willing to use a "wearable" device during a clinical trial and 93% were "definitely" or "maybe" willing to submit voice recordings. (Q. 20 (a) and (b)).
[6] The Ipsos poll found that 83% of ALS patients were more likely to participate in a phase 3 trial if the sponsor reimbursed them for their and their caregiver's travel costs (Q. 19(i)). Similarly, large majorities said that they would be willing to engage in numerous local activities (i.e., blood draws, televisits, etc.) in order to limit their need for travel (Q. 20).
[7] The Ipsos poll found that 94% of ALS patients were willing to submit blood, saliva, skin or other samples for genetic testing. (Q.21(c).