Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment
Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of amyotrophic lateral sclerosis (ALS). Specifically, this guidance addresses the Food and Drug Administration’s (FDA’s) current thinking regarding the clinical development program and clinical trial designs for drugs to support an indication for the treatment of ALS. ALS is a progressive neurodegenerative disease that primarily affects motor neurons in the cerebral motor cortex, brainstem, and spinal cord, leading to loss of voluntary movement and the development of difficulty in swallowing, speaking, and breathing. This guidance addresses the clinical development of drugs intended to treat the main neuromuscular aspects of ALS (i.e., muscle weakness and its direct consequences, including shortened survival). This draft guidance is intended to serve as a focus for continued discussions among the Division of Neurology Products, pharmaceutical sponsors, the academic community, and the public. This guidance does not address in detail the development of drugs to treat other symptoms that may arise in ALS, such as muscle cramps, spasticity, sialorrhea, pseudobulbar affect, and others.

This guidance focuses on specific clinical drug development and trial design issues that are unique to the study of ALS. General issues of concern in ALS drug development, such as the quantity of efficacy evidence needed to support approval for serious and life-threatening diseases or approaches to adaptive study design, are discussed in the guidance for industry Providing

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1 This guidance has been prepared by the Division of Neurology Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

2 For the purposes of this guidance, all references to drugs include both human drugs and therapeutic biological products unless otherwise specified.

3 In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of drugs for the treatment of ALS.
Contains Nonbinding Recommendations
Draft — Not for Implementation

Clinical Evidence of Effectiveness for Human Drug and Biological Products and the draft guidance for industry Adaptive Design Clinical Trials for Drugs and Biologics, respectively. This guidance also does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry E9 Statistical Principles for Clinical Trials and E10 Choice of Control Group and Related Issues in Clinical Trials, respectively.

In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

ALS is a motor neuron disease that occurs most often as a sporadic disease with no known cause or inheritance pattern. However, in a minority of patients, the disease has a clear familial inheritance pattern that may be associated with an identified gene. ALS can present with weakness and muscle atrophy in different areas of the body, with about 75 percent of patients first experiencing weakness in the limbs, and about 25 percent of patients presenting with difficulty swallowing and/or speaking (bulbar-onset ALS). ALS is a heterogeneous disease, but all forms of the disease share the defining features of degeneration of both upper and lower motor neurons. The diagnosis of ALS is based on the identification of its characteristic clinical symptoms and signs, along with the exclusion of other diagnostic possibilities. ALS is also considered a multisystem neurodegenerative disorder that can include cognitive and behavioral changes in addition to muscle weakness.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Early Phase Clinical Development Considerations

Intrathecal drug delivery may be necessary for some drugs for ALS. Early phase studies can often be conducted using single-dose intrathecal injection, but if long-term intrathecal delivery from a device is anticipated, consideration should be given to drug-device codevelopment issues early in development.

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4 We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

5 When final, this guidance will represent the FDA’s current thinking on this topic.
2. **Drug Development Population**

Sponsors should base eligibility for enrollment in efficacy trials in ALS on current consensus diagnostic criteria, with a focus on history, physical exam, and objective tests appropriate for determining the presence of ALS and for excluding conditions that can mimic ALS.

ALS drug development can be targeted to an identified ALS patient subgroup(s) or to ALS variant(s) when scientifically justified (see the draft guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*). However, if sponsors expect an investigational drug to be generally effective in ALS, studies should include a broader ALS population.

3. **Efficacy Considerations**

Efficacy should be established by demonstration of a clinically meaningful effect on symptoms or function, or of a favorable effect on survival. Effects on mortality, either positive or negative, should be characterized in all ALS development programs, because they are important to the consideration of the overall safety and effectiveness profile.

4. **Safety Considerations**

Clinical trials in ALS generally should be conducted under the oversight of a data monitoring committee (DMC). The DMC should look at frequent intervals for emerging safety signals and, if necessary, take appropriate measures to ensure that patients are not placed at unreasonable risk of harm. It is important to recognize that a relatively high percentage of patients will have serious adverse events or will die in studies of ALS, especially in trials of relatively longer duration, and those events should be monitored to distinguish effects of the investigational drug from effects of the underlying disease.

To support marketing approval, drug safety must be supported by an adequate number and duration of patient exposures to characterize drug risks. FDA generally will consider the serious and life-threatening nature of ALS and the treatment benefit when determining the minimum number and duration of patient exposures needed.

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6 When final, this guidance will represent the FDA’s current thinking on this topic.

7 See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*.

8 21 CFR 314.125(b)(2)

9 21 CFR 314.105(c); FDA is required to exercise its scientific judgment to determine the type and quantity of data and information a sponsor is required to provide for a particular drug to meet the statutory standards.
B. Specific Efficacy Trial Considerations

1. Study Design

FDA strongly recommends that sponsors conduct randomized, placebo-controlled, double-blind, studies. Generally, these studies are the most efficient way to demonstrate efficacy of drugs for the treatment of ALS. This recommendation includes add-on designs in which a treatment previously shown to be effective is given to patients in both arms, with patients then randomized to the added drug or added placebo. Other designs, such as dose-response trials, can also be used.

Studies can be designed as time-to-event trials with attainment of a clinically meaningful worsening in disease as a primary endpoint. Patients can be transitioned to open-label treatment if there is documented disease progression.

Historically controlled trials for ALS are strongly discouraged. Among individual patients, the course of ALS progression is highly variable, and various controlled trials have demonstrated differences in rates of progression and survival among placebo cohorts. Thus, results from historically controlled trials are likely to be difficult to interpret unless the effect size on an objective endpoint is very large.

2. Efficacy Endpoints

Although existing outcome measures that have been developed for ALS may be appropriate, FDA will also consider proposals for the use of new outcome measures that are capable of measuring clinically meaningful effects in patients.

Efficacy in ALS can be supported by the demonstration of a survival benefit. An assessment of a treatment effect on survival should be combined with an evaluation of the need for full-time (or nearly full-time) respiratory support, because such support can affect survival time. Efficacy can also be supported by the demonstration of a treatment effect on function in daily activity, as measured, for example, by the ALS Functional Rating Scale-Revised, Appel ALS Rating Scale, or similar scales. In general, in addition to the primary endpoint, sponsors should include assessments of various efficacy outcomes in trials. For effective drugs, the results of these additional outcomes would be expected to be supportive.

3. Study Procedures and Timing of Assessments

Study procedures should be designed to decrease potential for biases, such as those that may arise because of partial unblinding from adverse effects. Endpoints measuring daily function generally rely on subjective patient reporting, and endpoints of strength and respiration are affected by patient motivation and effort. These types of measures are susceptible to expectation bias if there is unblinding (or if there is no internal control group).

For trials based on functional endpoints, the first in-treatment assessment should be within a few months of randomization so that at least one on-drug assessment can be recorded for all or most
patients. Second and even third measurements should be performed at appropriate reasonably-
spaced intervals, to reduce the effect of random variation and more reliably verify that
progression has occurred. Use of the mean measurement obtained on two or more occasions may
decrease the effect of random variation. Variability may also be decreased by obtaining baseline
assessments on more than one occasion.

For safety monitoring, we also recommend early assessment of efficacy endpoints, which may
identify adverse effects on disease progression earlier than mortality endpoints or analyses of
adverse events.

4. Statistical Considerations

a. Prognostic factors

Although mean survival in ALS is 3 years after symptom onset, survival time varies greatly.
Also, an increasing number of clinical prognostic predictors are being identified in ALS. FDA
recommends that sponsors use randomization methods that help ensure that treatment arms are
balanced with respect to key prognostic factors.

b. Integrated assessment of function and survival

Functional endpoints can be confounded by loss of data because of patient deaths. To address
this, FDA recommends sponsors use an analysis method that combines survival and function into
a single overall measure, such as the joint rank test.

5. Accelerated Approval Considerations

Given the typically rapid progression of disease in ALS patients (recognizing that there is
considerable heterogeneity in the course of individual patients), it is generally feasible to
establish a clinical benefit in clinical studies of practicable duration, even if the benefit is
modest. 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. In the future, greater scientific understanding of ALS may provide opportunities for
discussion of surrogate endpoints that are reasonably likely to predict clinical benefit and that
might serve as a basis for accelerated approval. Sponsors considering a development program
intended to support an accelerated approval in ALS should discuss this approach and the overall
development program with FDA early in drug development.

6. Risk-Benefit Considerations

When making regulatory decisions about drugs to treat ALS, FDA will consider patient tolerance
for risk, and the serious and life-threatening nature of the condition.
C. Other Considerations

1. Relevant Nonclinical Safety Considerations

Nonclinical studies provide important information based on which it can be determined whether clinical trials are reasonably safe to conduct, and to inform clinical dose selection and safety monitoring. For serious and life-threatening diseases for which treatments are not available or are inadequate, as a general matter, it may be appropriate to permit clinical trials to commence based on less than usual nonclinical testing if scientifically justified. In certain cases, the duration of dosing in humans may exceed that of the nonclinical studies, if justified based on the available nonclinical and clinical data. Sponsors are encouraged to discuss this approach with the Division of Neurology Products early in clinical development. Carcinogenicity studies generally can be conducted after approval for drugs intended to treat ALS, given the unmet need for effective therapies.

2. Pharmacokinetic/Pharmacodynamic Considerations

Given the serious and life-threatening nature of ALS, the full array of typically required clinical pharmacology studies may not be needed prior to approval. For example, studies of effects of renal or hepatic impairment potentially may be able to be deferred until after approval or waived if the patient population and metabolic pathways of the drug, considered together, suggest a low likelihood of clinically meaningful pharmacokinetic and pharmacodynamic effects. Sponsors are encouraged to discuss this approach with FDA early in clinical development.

During drug development, sponsors should generally explore the relationship between exposure (drug concentration in plasma or other biological fluid) and efficacy and safety endpoints. Exposure-response relationships using biomarkers from early dose-finding studies can help identify dose and dosing regimen(s) for controlled effectiveness studies and the need for dose adjustment for various extrinsic and intrinsic factors such as drug-drug interactions and age, among others. Importantly, assessment of exposure-response can also contribute to interpretation of evidence of effectiveness from controlled studies. The response variables used in the exposure-response analyses should include prespecified primary and secondary endpoint(s), as well as results involving biomarkers collected in the studies for efficacy and safety.

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10 Ibid.
11 Ibid.
12 Ibid.