
Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry

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

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*Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002*

*Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
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*Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002*

*Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
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This guidance represents 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 office 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 and biological products for the treatment of amyotrophic lateral sclerosis (ALS).² 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 and shortened life expectancy. This guidance addresses the clinical development of drugs intended to treat the main motor aspects of ALS (i.e., muscle weakness and its direct consequences, including shortened survival). 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 drug development, such as the quantity of effectiveness 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 Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998)³ and

¹ This guidance has been prepared by the Division of Neurology Products in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics 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 biological products unless otherwise specified.

³ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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the draft guidance for industry *Adaptive Designs for Clinical Trials for Drugs and Biologics* (September 2018),⁴ 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* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), 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 small minority of patients, the disease has a clear familial inheritance pattern that may be associated with an identified gene. In addition, gene mutations have been identified in some sporadic ALS patients.

ALS patients 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

Communication between sponsors and those affected by ALS to discuss expectations with respect to both effectiveness and safety is important early in drug development. Sponsors should understand how affected patients view treatment goals and risk tolerance.

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

⁴ When final, this guidance will represent the FDA's current thinking on this topic.

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2. Drug Development Population

Sponsors should base eligibility for patient enrollment in effectiveness 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.

There is a need to understand the safety and effectiveness of investigational drugs for ALS across disease stages. Although sponsors may have good reasons to use prognostic enrichment to increase the likelihood of demonstrating a drug effect (e.g., to enroll patients who are more likely to experience rapid progression) or to use predictive enrichment to direct therapy to patients with a particular disease characteristic (e.g., a specific genotype or phenotype), sponsors should not unnecessarily exclude patients from trial enrollment based on characteristics such as age or disease stage unless scientifically justified.⁵ Broader inclusion criteria allow more rapid trial enrollment, potentially accelerating drug development. An acceptable approach could include enrollment of a broad population with the conduct of the primary analysis in a study subset defined based on clinical characteristics and/or biomarkers, and analyses of the broader population being secondary and supportive. In later stages of development, sponsors can consider alternative trial designs, such as decentralized studies, in which mobile technologies or other methods are used to collect data in patients' homes or by their local providers, to facilitate broader and potentially faster enrollment.

3. Effectiveness Considerations

The statutory standards for effectiveness apply to drugs for ALS just as the standards apply for all other drugs. However, FDA has long stressed the appropriateness of exercising regulatory flexibility in applying the statutory standards to drugs for serious diseases with unmet medical needs, while preserving appropriate assurance of safety and effectiveness.⁶

Sponsors should consider including prospective plans for interim effectiveness analyses to allow for the detection of early benefit in a clinical trial.

4. Safety Considerations

Phase 1 studies can be conducted in healthy volunteers or in ALS patients, depending on the method of administration, safety profile, and potential for detecting pharmacodynamic responses in healthy volunteers relative to ALS patients. For cellular and gene therapy products, sponsors should discuss the appropriate population for Phase 1 studies with the Center for Biologics Evaluation and Research's (CBER's) Office of Tissues and Advanced Therapies.

In general, Phase 2 and Phase 3 clinical trials in ALS should be conducted under the oversight of a data monitoring committee (DMC). The DMC should look at frequent intervals for emerging

⁵ See the guidance for industry *Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products* (March 2019).

⁶ 21 CFR 312.80, subpart E, Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses.

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safety signals and, if necessary, take appropriate measures to ensure that patients are not placed at unreasonable risk of harm.⁷ It is important to recognize that a relatively high percentage of ALS patients may have serious adverse events or die, especially in trials of relatively long duration, and comparison of the rates of those events in treatment and control groups is critical to distinguishing 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.⁸ In general, FDA 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.⁹ During development, sponsors should collect safety data, including data from open-label studies or expanded access programs, from patients across the spectrum of disease stages and severities, and whenever possible, data from patients who may not have been included in effectiveness studies but in whom, based on other data, the use of the drug following approval is likely. In general, safety data from a reasonable number of patients exposed to the drug for at least 1 year is appropriate to support approval of drugs intended for chronic use in treating ALS. The administration of cellular and gene therapy products may raise different issues regarding patient exposures; thus, we recommend that sponsors of such products discuss patient exposures with CBER's Office of Tissues and Advanced Therapies.

B. Specific Effectiveness Trial Considerations

1. Trial Design

All patients in ALS trials should receive the best standard of care, and no patient should be denied effective therapies in order to be randomized to a placebo-only arm. Various strategies can be applied to expedite ALS trials and minimize unnecessary exposure to placebo. For example, master protocols (which use a single infrastructure, trial design, and protocol) allow for the simultaneous evaluation of multiple drugs, with a common or shared placebo group, and have the potential to greatly expedite the development of new drugs. Sponsors should also consider adaptive designs¹⁰ (including the use of Bayesian features) and enrichment strategies.¹¹

FDA recommends the consideration of add-on designs, in which a treatment previously shown to be effective for the treatment of ALS is given to *all* patients participating in the trial (i.e., no patient receives placebo alone), with patients randomized to the added investigational drug or

⁷ See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees* (March 2006).

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.

¹⁰ See the draft guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics*. When final, this guidance will represent the FDA's current thinking on this topic.

¹¹ See the guidance for industry *Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products*.

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added placebo. In addition, placebo-controlled trials can be designed as time-to-event trials, with attainment of a clinically meaningful worsening in disease as a primary endpoint; patients then can be transitioned to open-label investigational treatment.

At present, FDA discourages trials entirely based on a historical control in ALS because the course of ALS progression is highly variable among individual patients, 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. Thus far in ALS development, those effects that have been seen, both early and late in development, suggest that such an approach is unlikely to succeed. It is possible that historical controls will be of value in future trial designs as we develop a more comprehensive and reliable characterization of the disease course.

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. This extension should allow for additional prespecified effectiveness assessments. Patients entering the extension will all receive the active investigational drug, but the patient, investigator, site personnel, and site monitors should remain blinded to treatment group assignment from the randomized treatment period. Only sponsor staff involved in analysis of the blinded period results should have access to unblinded data and patient group assignments

2. Effectiveness Endpoints

Although existing outcome measures that have been developed for ALS may be appropriate, FDA supports the development and use of new outcome measures capable of measuring clinically meaningful effects in patients. FDA encourages the use of patient input and experience in the development of these new measures. Sponsors can also consider novel technologies (e.g., wearable biosensors), as appropriate.

In general, effectiveness should be established by the demonstration of a treatment effect (e.g., less decline, stabilization, improvement) on function in daily activities as measured, for example, by the ALS Functional Rating Scale-Revised or similar scales. In general, in addition to the primary endpoint, sponsors should include assessments of various effectiveness outcomes in trials, including patient-reported outcomes (PROs). For effective drugs, the results of these additional outcomes would be expected to be supportive.

PRO assessments, including those measuring activities of daily living, can be designed to assess the abilities and experiences of patients across a spectrum of disease stages and severities. PRO assessments can be useful to assess the clinical meaningfulness of an objective finding (e.g., muscle strength) even if of relatively small magnitude, and they therefore contribute to assessments of benefits and risk. In general, PRO instruments for ALS trials should include a limited number of items that assess the most important aspects of the outcome of interest (e.g., specific aspects that contribute to health-related quality of life, such as physical functioning). PRO instruments that are overly lengthy may increase responder burden and fatigue, increasing the potential for missing data. PRO instruments that are overly broad can be difficult to interpret and may be insensitive to meaningful change in the outcomes of major interest.

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Because loss of strength is a hallmark of disease progression in ALS, a valid measurement of muscle strength may be an appropriate endpoint for treatments intended to increase or preserve muscle strength. Because changes in muscle strength alone may not necessarily be indicative of meaningful effect on function in activities of daily living, the clinical meaningfulness of differences in muscle strength should be supported by the magnitude of the effect observed (based on the mean change or on a responder analysis of patients who exceed a clinically meaningful threshold of change) or by the demonstration of a drug effect on an appropriate measure of function in activities of daily living. Sponsors considering a measure of muscle strength as a primary endpoint should discuss with FDA their plans to establish the clinical meaningfulness of the treatment effect.

Because decline in respiratory function is a direct result of the known pathophysiology of the disease, the demonstration of a treatment benefit on respiratory endpoints may also provide evidence of effectiveness. Specific clinical respiratory outcomes can include nocturnal desaturation, aspiration pneumonia, and progression to mechanically assisted ventilation. Measures of respiratory function, such as forced vital capacity, may also be acceptable as effectiveness endpoints. As with measures of muscle strength, the clinical meaningfulness of differences in respiratory function should be supported by the magnitude of the effect observed (based on the mean change or on a responder analysis of patients who exceed a clinically meaningful threshold of change) or by the demonstration of a drug effect on an appropriate measure of function in activities of daily living. Sponsors considering a measure of respiratory function as a primary endpoint should discuss with FDA their plans to establish the clinical meaningfulness of the treatment effect. In general, unless the enrolled patient population is only capable of manifesting a benefit on respiratory function or the drug is expected to have an effect unique to respiratory function, drug effects on pulmonary endpoints would be expected to be supported by a treatment benefit on broader measures of function in activities of daily living.

Sponsors should characterize an effect on mortality in all ALS development programs because it is important to the consideration of the overall safety and effectiveness profiles. If patient function is intended to be assessed by the primary outcome, mortality should be integrated into the primary outcome by an analysis method that combines survival and function into a single overall measure, such as the joint rank test (see section III.B.4.b., Integrated assessment of function and survival). In that situation, the independent assessment of a drug effect on survival should be a secondary endpoint. The independent assessment of 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. Survival is also acceptable as a primary outcome measure.

3. Study Procedures and Timing of Assessments

For trials based on functional endpoints, the first on-treatment assessment should be performed at the earliest time when a treatment effect is expected and no later than 2–3 months after 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 the character of any disease progression that has occurred. Use of the mean measurement obtained on two or more

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occasions may decrease the effect of random variation. Variability may also be decreased by obtaining baseline assessments on more than one occasion. Sponsors should consider the burden to patients in setting the frequency and type of assessments (e.g., in clinic versus remote).

FDA encourages the use of approaches and technologies to minimize the burden of trials on ALS patients and 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, remote monitoring for some of the visits). FDA is open to exploring the utility of digital biomarkers as clinical endpoints.

4. Statistical Considerations

a. Prognostic factors

Survival time in ALS varies greatly. Also, an increasing number of clinical prognostic predictors are being identified in ALS. If applicable, FDA recommends that sponsors use randomization methods that help ensure that treatment arms are balanced with respect to key prognostic factors. Some of these factors may also be prespecified as covariates in the study analysis plan.

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

FDA encourages sponsors to incorporate exploratory biomarkers in all phases of development of ALS drugs. 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.

Given the typically rapid progression of disease in ALS patients (recognizing considerable heterogeneity in the course of individual patients), it is feasible and most efficient to establish a clinical benefit based on clinical endpoints capable of supporting full approval, even if the benefit is modest. In general, that benefit can be established in trials of practicable size and duration (i.e., 6 to 12 months).

6. Benefit-Risk 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 in the context of statutory requirements for safety and efficacy.

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C. Other Considerations

1. Relevant Nonclinical Safety Considerations

Nonclinical studies provide important information to help determine whether clinical trials are reasonably safe to conduct, and to inform clinical dose selection and safety monitoring. As a general matter, for serious and life-threatening diseases for which treatments are not available or are inadequate, FDA may 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. FDA encourages sponsors to discuss this approach with the Agency early in clinical development. In general, carcinogenicity studies can be conducted after approval for drugs intended to treat ALS, given the unmet medical need for effective therapies.

2. Pharmacokinetic/Pharmacodynamic Considerations

During drug development, in general, sponsors should explore the relationship between exposure (drug concentration in plasma or other biological fluid) and effectiveness 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. 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 endpoints, as well as results involving biomarkers collected in the studies for effectiveness and safety. The exposure-response relationship can help determine the need for dose adjustment for various extrinsic and intrinsic factors, such as drug-drug interactions and organ impairment, among others.

Because pharmacokinetic/pharmacodynamic considerations are different for cellular and gene therapy products, sponsors of these products should discuss their development plans with CBER's Office of Tissues and Advanced Therapies.