
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DRAFT GUIDANCE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)**

**February 2018
Clinical/Medical**

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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).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. 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 This draft guidance is intended to serve as a focus for continued discussions among the Division of Neurology Products, pharmaceutical sponsors, the academic community, and the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.³ 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*

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.

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37 *Clinical Evidence of Effectiveness for Human Drug and Biological Products*⁴ and the draft
38 guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics*,⁵ respectively.
39 This guidance also does not contain discussion of the general issues of statistical analysis or
40 clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical*
41 *Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical*
42 *Trials*, respectively.

43
44 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
45 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
46 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
47 the word *should* in Agency guidances means that something is suggested or recommended, but
48 not required.

49
50

II. BACKGROUND

52
53 ALS is a motor neuron disease that occurs most often as a sporadic disease with no known cause
54 or inheritance pattern. However, in a minority of patients, the disease has a clear familial
55 inheritance pattern that may be associated with an identified gene. ALS can present with
56 weakness and muscle atrophy in different areas of the body, with about 75 percent of patients
57 first experiencing weakness in the limbs, and about 25 percent of patients presenting with
58 difficulty swallowing and/or speaking (bulbar-onset ALS). ALS is a heterogeneous disease, but
59 all forms of the disease share the defining features of degeneration of both upper and lower
60 motor neurons. The diagnosis of ALS is based on the identification of its characteristic clinical
61 symptoms and signs, along with the exclusion of other diagnostic possibilities. ALS is also
62 considered a multisystem neurodegenerative disorder that can include cognitive and behavioral
63 changes in addition to muscle weakness.

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III. DEVELOPMENT PROGRAM

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68

A. General Considerations

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70

1. Early Phase Clinical Development Considerations

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72

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

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.

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77 2. *Drug Development Population*

78
79 Sponsors should base eligibility for enrollment in efficacy trials in ALS on current consensus
80 diagnostic criteria, with a focus on history, physical exam, and objective tests appropriate for
81 determining the presence of ALS and for excluding conditions that can mimic ALS.

82
83 ALS drug development can be targeted to an identified ALS patient subgroup(s) or to ALS
84 variant(s) when scientifically justified (see the draft guidance for industry *Enrichment Strategies*
85 *for Clinical Trials to Support Approval of Human Drugs and Biological Products*⁶). However, if
86 sponsors expect an investigational drug to be generally effective in ALS, studies should include a
87 broader ALS population.

88 89 3. *Efficacy Considerations*

90
91 Efficacy should be established by demonstration of a clinically meaningful effect on symptoms
92 or function, or of a favorable effect on survival. Effects on mortality, either positive or negative,
93 should be characterized in all ALS development programs, because they are important to the
94 consideration of the overall safety and effectiveness profile.

95 96 4. *Safety Considerations*

97
98 Clinical trials in ALS generally should be conducted under the oversight of a data monitoring
99 committee (DMC). The DMC should look at frequent intervals for emerging safety signals and,
100 if necessary, take appropriate measures to ensure that patients are not placed at unreasonable risk
101 of harm.⁷ It is important to recognize that a relatively high percentage of patients will have
102 serious adverse events or will die in studies of ALS, especially in trials of relatively longer
103 duration, and those events should be monitored to distinguish effects of the investigational drug
104 from effects of the underlying disease.

105
106 To support marketing approval, drug safety must be supported by an adequate number and
107 duration of patient exposures to characterize drug risks.⁸ FDA generally will consider the
108 serious and life-threatening nature of ALS and the treatment benefit when determining the
109 minimum number and duration of patient exposures needed.⁹

110

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.

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111 **B. Specific Efficacy Trial Considerations**

112

113 *1. Study Design*

114

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

121

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

125

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

131

132 *2. Efficacy Endpoints*

133

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

137

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

146

147 *3. Study Procedures and Timing of Assessments*

148

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

154

155 For trials based on functional endpoints, the first in-treatment assessment should be within a few
156 months of randomization so that at least one on-drug assessment can be recorded for all or most

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157 patients. Second and even third measurements should be performed at appropriate reasonably-
158 spaced intervals, to reduce the effect of random variation and more reliably verify that
159 progression has occurred. Use of the mean measurement obtained on two or more occasions may
160 decrease the effect of random variation. Variability may also be decreased by obtaining baseline
161 assessments on more than one occasion.

162
163 For safety monitoring, we also recommend early assessment of efficacy endpoints, which may
164 identify adverse effects on disease progression earlier than mortality endpoints or analyses of
165 adverse events.

166 167 4. *Statistical Considerations*

168 169 a. Prognostic factors

170
171 Although mean survival in ALS is 3 years after symptom onset, survival time varies greatly.
172 Also, an increasing number of clinical prognostic predictors are being identified in ALS. FDA
173 recommends that sponsors use randomization methods that help ensure that treatment arms are
174 balanced with respect to key prognostic factors.

175 176 b. Integrated assessment of function and survival

177
178 Functional endpoints can be confounded by loss of data because of patient deaths. To address
179 this, FDA recommends sponsors use an analysis method that combines survival and function into
180 a single overall measure, such as the joint rank test.

181 182 5. *Accelerated Approval Considerations*

183
184 Given the typically rapid progression of disease in ALS patients (recognizing that there is
185 considerable heterogeneity in the course of individual patients), it is generally feasible to
186 establish a clinical benefit in clinical studies of practicable duration, even if the benefit is
187 modest. This feasibility, in addition to the current state of scientific understanding of ALS,
188 which has not identified credible surrogate endpoints, leads FDA to advise sponsors to study
189 clinical endpoints capable of supporting full approval in studies intended to establish clinical
190 benefit. In the future, greater scientific understanding of ALS may provide opportunities for
191 discussion of surrogate endpoints that are reasonably likely to predict clinical benefit and that
192 might serve as a basis for accelerated approval. Sponsors considering a development program
193 intended to support an accelerated approval in ALS should discuss this approach and the overall
194 development program with FDA early in drug development.

195 196 6. *Risk-Benefit Considerations*

197
198 When making regulatory decisions about drugs to treat ALS, FDA will consider patient tolerance
199 for risk, and the serious and life-threatening nature of the condition.

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201 **C. Other Considerations**

202

203 1. *Relevant Nonclinical Safety Considerations*

204

205 Nonclinical studies provide important information based on which it can be determined whether
206 clinical trials are reasonably safe to conduct, and to inform clinical dose selection and safety
207 monitoring. For serious and life-threatening diseases for which treatments are not available or
208 are inadequate, as a general matter, it may be appropriate to permit clinical trials to commence
209 based on less than usual nonclinical testing if scientifically justified.¹⁰ In certain cases, the
210 duration of dosing in humans may exceed that of the nonclinical studies, if justified based on the
211 available nonclinical and clinical data.¹¹ Sponsors are encouraged to discuss this approach with
212 the Division of Neurology Products early in clinical development. Carcinogenicity studies
213 generally can be conducted after approval for drugs intended to treat ALS, given the unmet need
214 for effective therapies.

215

216 2. *Pharmacokinetic/Pharmacodynamic Considerations*

217

218 Given the serious and life-threatening nature of ALS, the full array of typically required clinical
219 pharmacology studies may not be needed prior to approval.¹² For example, studies of effects of
220 renal or hepatic impairment potentially may be able to be deferred until after approval or waived
221 if the patient population and metabolic pathways of the drug, considered together, suggest a low
222 likelihood of clinically meaningful pharmacokinetic and pharmacodynamic effects. Sponsors are
223 encouraged to discuss this approach with FDA early in clinical development.

224

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

¹⁰ Ibid.

¹¹ Ibid.

¹² Ibid.