Migraine: Developing Drugs for Acute Treatment

Guidance for Industry

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

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Clinical/Medical

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Contains Nonbinding Recommendations

Migraine: Developing Drugs for Acute Treatment Guidance for Industry[1]

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 prescription drugs for the acute treatment of migraine.[2] Specifically, this guidance addresses FDA's current thinking regarding the overall development program and clinical trial designs to support approval of prescription drugs for the acute treatment of migraine.[3] This guidance does not apply to over-the-counter drug products. This guidance also does not address the development of drugs indicated to reduce the frequency of migraine attacks. Such development will be addressed separately in a future guidance.

This guidance 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.[4]

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

[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 approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and therapeutic biological products licensed under section 351 of the Public Health Service Act unless otherwise specified. When used in this guidance, the term drugs refers to prescription drugs 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 acute treatment of migraine.

[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.

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Migraine is a chronic neurovascular disorder characterized by recurrent attacks of often severe headache, typically accompanied by nausea and sensitivity to light and/or sound. In adults, migraine attacks usually last from 4 to 72 hours. Migraine headache is typically throbbing, unilateral, and aggravated by physical activity. Criteria proposed by the International Headache Society (IHS) require a combination of some of these characteristics and associated symptoms in at least five attacks to establish a diagnosis of migraine.[5]

There are two major subtypes of migraine: migraine without aura (also called *common migraine*) and migraine with aura (also called *classic migraine*). Migraine with aura is characterized by focal neurological symptoms that typically precede, or sometimes accompany, the headache. These focal neurological symptoms are absent in migraine without aura. Some patients may present with both subtypes of migraine.

Pharmacologic approaches to the treatment of migraine include drugs to treat acute migraine attacks as they arise (acute treatment of migraine), and drugs to reduce the frequency of migraine attacks (preventive treatment). This guidance addresses the development of drugs for the acute treatment of migraine.

III. DEVELOPMENT PROGRAM

A. Trial Population

Either healthy adult volunteers or migraine patients can be enrolled in initial phase 1 trials. Because migraine patients are predominantly female, it is important to enroll, early in development (i.e., by the beginning of phase 2), women of child-bearing potential who are practicing effective contraception.

Because migraine peak incidence is during adolescence, and onset in younger children is not uncommon, pediatric studies of children are required under section 505B of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355c). Sponsors are encouraged to begin discussions about their pediatric clinical development plan early in development because sponsors are required to submit pediatric study plans no later than 60 days[6] after an end-of-phase 2 meeting.[7]

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[5] See http://ihs-classification.org/en/.

[6] Or such other time as agreed upon.

[7] See section 505B(e)(2)(A)(ii)(I) of the FD&C Act (21 U.S.C. 355c(e)(2)(A)(ii)(I)).

B. Efficacy Considerations

Typically, at least two adequate and well-controlled trials are needed to support approval of a new molecular entity. A single adequate and well-controlled trial may be sufficient to support approval of a new route of administration for a drug already approved for the acute treatment of migraine, for treatment of a new subpopulation (e.g., for the pediatric population) or for a drug already approved for the prophylaxis of migraine (see the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*).

1. Trial Design

In general, efficacy trials should use a randomized, double-blind, placebo-controlled, parallel group design. Although a comparison of a single dose level with placebo can be used to support efficacy of a drug, it is usually preferable to study at least two doses.

The timing of drug administration should be defined in the protocol. Although drug administration as early as practicable during the course of acute migraine is typically recommended by migraine experts, evidence should be obtained that the investigational drug is able to treat a migraine headache of moderate or severe intensity, because many patients reach that level of pain. Therefore, in efficacy trials intended to support approval, migraine patients should take the investigational drug as soon as they experience a migraine headache of moderate or severe intensity. It is also important to collect sufficient baseline information about the headache (i.e., headache intensity, presence or absence of associated symptoms, unilaterality or bilaterality of the headache, aggravation by exercise, throbbing or nonthrobbing) to be able to verify that the headache treated was, in fact, acute migraine. Additional trials assessing drug response after treatment of acute migraine at the mild pain stage can be conducted, and can be described in labeling.

Typically, efficacy trials should assess the effectiveness of a single administration of the investigational drug to treat a single acute migraine episode. To assess the safety and efficacy of redosing (e.g., in case of recurrence of migraine symptom(s) or an incomplete response), patients should be re-randomized to investigational drug or control.

2. Trial Population and Entry Criteria

Patients enrolled in clinical trials should have a diagnosis of migraine, with or without aura, according to established IHS criteria. The age at the time of initial migraine diagnosis should be younger than 50 years, to decrease the chance of enrolling patients with other disorders.

The time since initial diagnosis should be at least 1 year. Patients with coexisting types of headaches (e.g., tension-type headaches) can be included in the trial if the other headaches are distinguishable from migraine headache by the patient.

3. Dose Selection

The first controlled trials should explore a range of doses to assess the dose-response relationship and provide a basis for dose selection in definitive efficacy trials. Some data should be collected on doses above and below what appears to be the optimal dose, and an effort should be made to identify the lowest dose that provides a desirable treatment effect. It is advisable, whenever feasible, to obtain plasma drug level data in patients. Establishing a plasma concentration (exposure)-response relationship can be useful to support dosing recommendations based on specific patient characteristics (e.g., body weight, renal function).

4. Concomitant Medications

During the conduct of early trials, and until the drug's metabolism is adequately understood, concomitant medications should be avoided. Assuming no important drug-drug interactions are anticipated, concomitant medications to reduce the frequency of migraine episodes can be used in later stage trials, but only if the dosage of those concomitant medications has been stable for at least 3 months before inclusion into the trial. If the trial population includes patients with and without concomitant treatment to reduce the frequency of migraine episodes, randomization should be stratified by use/non-use of such concomitant treatment. If drugs used for the preventive treatment of migraine have been withdrawn, withdrawal should be complete at least 1 month before trial entry.

It is important that patients avoid any analgesic or other acute migraine medication(s) for at least 24 hours before treatment with the investigational drug to reduce confounding factors. Use of rescue medication must be allowed, but patients should be encouraged to wait at least 2 hours after initial treatment before using rescue medication. Rescue medication can consist of the patient's usual acute treatment of migraine, unless this treatment has the potential for an adverse interaction with the investigational drug (e.g., 5-HT_1 agonist or ergot alkaloid medications should be avoided within 24 hours of any investigational 5-HT_1 agonist or vasoactive drug use).

5. Efficacy Endpoints

Because migraine is a complex disorder characterized by several associated symptoms (i.e., nausea, photophobia, and phonophobia) in addition to headache, a drug effect on headache pain alone is not considered sufficient to grant a claim for the acute treatment of migraine. In the past, approval of drugs for the acute treatment of migraine was based on the demonstration of an effect on four co-primary endpoints: pain, nausea, photophobia, and phonophobia. This approach remains acceptable.

A preferred approach, which aims to better align the study outcome with the symptom(s) of primary importance to patients, is to demonstrate an effect on both pain and the patient's most bothersome symptom. Patients are asked to identify their most bothersome migraine-associated symptom in addition to pain. The identification can take place either before the attack is treated (e.g., at the baseline visit), or at the time of the attack, but before administration of the study drug. Using this approach, the two co-primary endpoints are (1) having no headache pain at 2 hours after dosing and (2) a demonstrated effect on the most bothersome migraine-associated symptom

at 2 hours after dose. Regardless of the associated symptom identified as most bothersome, all three important migraine-associated symptoms (i.e., nausea, photophobia, and phonophobia) should be assessed separately as secondary endpoints.

Migraine-associated headache pain and associated symptoms should be measured by asking patients to self-report the current status of their headache pain and associated symptoms. A four-point Likert scale should be used for headache pain (i.e., 0=none, 1=mild, 2=moderate, 3=severe), and a binary scale (present or absent) should be used for associated symptoms.

The following additional secondary endpoints should be assessed in efficacy trials:

- The proportion of patients achieving "no headache pain" at various time points following treatment. For this analysis, it is especially useful to record the time that no headache pain is first noted.

- The proportion of patients requiring additional medication (either a second dose or rescue medication) within 24 hours of initial treatment.

- The proportion of patients who are "sustained pain-free," defined as having no headache pain at 2 hours after dose, with no use of rescue medication and no relapse of headache pain within 24 hours (24-hour sustained pain-free) or 48 hours (48-hour sustained pain-free) after administration of the investigational drug. The proportion of patients who are sustained pain-free should not be used as a primary endpoint, because it is possible to show a significant effect on the proportion of patients who are sustained pain-free without any significant drug effect on individual migraine symptoms (including pain) by the 2-hour time point.

- The incidence of pain relapse, defined as the return of headache of any severity within 48 hours after administration of the investigational drug, when the patient was pain-free at 2 hours after investigational drug administration.

6. Trial Procedures and Timing of Assessments

The treatment observation period should be at least 48 hours and include data collection at prespecified time points during the observation period (e.g., 0, 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24, and 48 hours). For outpatient trials, the patient should be instructed to record all data in a headache diary. The headache diary should be shown to be well defined and reliable for the target population based on the recommendations described in the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

7. Statistical Considerations

The typical primary efficacy analysis should compare, between treatment groups, the proportion of patients with no headache pain at 2 hours after dosing (i.e., going from a pain score of 2 or 3 at baseline to a score of 0 at 2 hours) and the proportion of patients with absence of the "most bothersome associated symptom" at 2 hours after dosing. No correction for multiple comparisons

is necessary for these two co-primary endpoints, because both must show a statistically significant effect of treatment.

Secondary endpoints expected by FDA in acute migraine trials are described under section III.B.5., Efficacy Endpoints. Additional secondary endpoints may be considered. Ordering of secondary endpoints should be based on the trial objectives and intended claims in labeling. Typically, secondary endpoints to be described in labeling should not be duplicative of the primary endpoints. It is important to define prospectively the secondary endpoints, and include a statistical plan to control the Type-I error rate for the multiple comparisons.

C. Safety Considerations

Acute migraine headaches are treated long term and intermittently. Therefore, the safety database intended to support approval should follow the same general paradigm as for chronic-use drugs, including the conduct of at least one long-term safety trial during which patients can treat all acute migraine episodes with the investigational drug.

Because phase 3 trials are typically conducted in the outpatient setting, phase 1 and early phase 2 trials, during which the investigational drug is administered under close medical supervision, provide the best opportunity to obtain vital sign and laboratory data at times close to investigational drug administration. These trials should include vital signs, hematology, serum chemistry, urinalysis, and 12-lead electrocardiogram at appropriate intervals. Vital signs and electrocardiography should be assessed around expected C_{max} for the investigational drug and major metabolites. During most short-term phase 2 and phase 3 outpatient trials, baseline and post-treatment vital signs and laboratory assessment should be conducted. Safety data during long-term phase 3 trials should be obtained at appropriate intervals, taking into consideration the results of nonclinical studies and earlier human experience with the investigational drug and with other drugs of the class.

New molecular entities should follow the safety recommendations in the ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions*. To be counted in the long-term safety database, adult patients should treat, on average, a minimum of two migraine attacks per month. The safety experience should be at relevant doses and frequency of administration, including a substantial experience at the highest dose and highest frequency of administration proposed for marketing.

If the drug has the potential to have adverse vascular effects, additional nonclinical studies (e.g., in vitro studies to assess coronary artery vasoconstriction) and safety studies in populations at risk (e.g., patients with known coronary artery disease) may be needed. Consultation with the Division is advised early in the development program.

D. Other Considerations

1. Pediatric Studies

Migraine is a relatively common disorder in children. There are reasons to believe that migraine in the adult and pediatric populations are substantially different clinical entities and one cannot assume that a drug effective in adults will also be effective in children. Therefore, studies in the pediatric population are needed. Because migraine is rare in children younger than 6 years old, a partial waiver for the conduct of studies in this age group generally will be granted. Sponsors are encouraged to begin discussions about their pediatric clinical development plan early in development because they are required to submit pediatric study plans no later than 60 days[8] after an end-of-phase 2 meeting.[9] Pediatric studies should evaluate patients aged 6 to 17 years. Because disease characteristics change with puberty, pediatric studies should include adequate numbers of patients to characterize safety and efficacy of the drug across the entire pediatric age range. Migraine diagnosis should be based on IHS criteria. We recommend that sponsors refer to the Pediatric Research Equity Act as amended by the Food and Drug Administration Reauthorization Act of 2017[10] to review requirements for submission of an initial pediatric study plan.[11]

Before initiation of a clinical efficacy trial, the pharmacokinetics of the drug in the pediatric population should be assessed and compared with the pharmacokinetics of the drug in adults. This permits proper dose selection for pediatric efficacy and safety studies. The development of an age-appropriate formulation should also be considered as needed.

Sponsors can consider the following two options for their pediatric efficacy studies programs:

(1) Conduct separate efficacy studies, one in patients aged 12 to 17 years and a second in patients aged 6 to 11 years (each powered to show efficacy).

(2) Conduct a single efficacy study in patients aged 6 to 17 years, with a sufficient number of patients in the 6- to 11-year and 12- to 17-year subgroups to be able to characterize the efficacy (and safety) of the drug in each subgroup adequately (but without a need to achieve statistical significance in each subgroup).

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[8] Or such other time as agreed upon.

[9] See section 505B(e)(2)(A)(ii)(I) of the FD&C Act (21 U.S.C. 355c(e)(2)(A)(ii)(I)).

[10] See section 505B of the FD&C Act (21 U.S.C. 355c).

[11] See also the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans*. When final, this guidance will represent the FDA's current thinking on this topic.

Because of the high placebo response rate in pediatric migraine studies, an enrichment strategy[12] should be considered to increase the chance of demonstrating a drug effect. An approach that has proven successful in several pediatric trials is, during a migraine attack, to first administer single-blind placebo to all patients, and then randomize only those patients who did not achieve freedom from pain at 30 minutes to the investigational drug or placebo. Also, only patients whose migraine attacks typically last at least 3 hours should be included. The proportion of patients pain-free at 2 hours after administration of the investigational drug should be the primary endpoint. An approach that evaluates pain and another symptom (i.e., co-primary endpoints) is not needed for pediatric studies. Migraine-associated symptoms should be evaluated as secondary endpoints. Other secondary endpoints as described above for adult trials also should be evaluated, again with control of the Type-I error rate.

A 1-year long-term pediatric safety study should be conducted. Generally, if the drug is already approved in adults, the pediatric safety database should include data on at least 200 patients treating, on average, one migraine attack per month for 6 months; and 75 patients treating, on average, at least one migraine attack per month for 1 year. That study should evaluate the effect of treatment on growth, cognition, and endocrine development. A juvenile animal toxicology study in a single species (typically rat) should be conducted prior to initiation of the long-term pediatric safety study.

2. Labeling Considerations

Over the past 2 decades, FDA has approved several new drugs indicated for the treatment of acute migraine for marketing in the United States. The majority of these are selective 5-$HT_{1B/1D}$ receptor agonists and thus belong to the drug class referred to as triptans. The principal safety concern with triptans relates to their ability to cause coronary or peripheral arterial constriction that may result in serious adverse cardiac or peripheral vascular events. As a result, FDA has adopted certain standard or class labeling for triptans. Future investigational drugs with similar pharmacological activity will be subject to this class labeling, unless it can be shown that the drug does not have vasoconstrictive effects. Also, new drugs of other pharmacological classes that also have the potential for vasoconstrictive effects probably would be subject to similar class labeling.

The latest approved labeling for a member of this class should form the basis, or template, for labeling of new drugs that share a similar mechanism of action, or have similar safety issues (e.g., coronary vasoconstriction). As is always the case, additional information regarding the safe use of a drug should be included in the appropriate sections of labeling, even though it may not be described in this guidance.

The recommendations for the following labeling sections apply to all new drugs indicated for the acute treatment of migraine.

[12] See the draft guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*. When final, this guidance will represent the FDA's current thinking on this topic.

- **INDICATIONS AND USAGE**

  This section should be brief and should state that the drug is indicated for the acute treatment of migraine with or without aura.

- **DOSAGE AND ADMINISTRATION**

  This section should include the following information:

  – The minimum interval between doses to treat the same acute migraine episode (i.e., if the migraine episode has not resolved by 2 hours after taking the drug, or returns after transient improvement). Re-dosing information should be described in labeling only if information supporting the safety and efficacy of re-dosing is included in the marketing application.

  – The average number of acute migraine episodes within a 30-day period that can be treated safely (based on data obtained from the long-term safety trials).

- **WARNINGS AND PRECAUTIONS**

  This section should include a description of medication overuse headache as follows:

  Medication Overuse Headache
  Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, or a combination of drugs for 10 or more days per month) may lead to exacerbation of headache (i.e., medication overuse headache). Medication overuse headache may present as migraine-like daily headaches or as a marked increase in frequency of migraine attacks. Detoxification of patients including withdrawal of the overused drugs and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

- **CLINICAL STUDIES**

  This section should describe the efficacy trials from which evidence of effectiveness was obtained.

  This section should include a figure derived using a Kaplan-Meier survival analysis method showing the estimated probability of achieving an initial headache response within the first 2 hours following the initial dose. Pooled efficacy data from similarly designed controlled trials can be used to generate these graphs. If there are dose-response data, these should be shown. A brief statement describing the dose-response relationship of the drug, as well as brief statements regarding efficacy in important subgroups (e.g., sex, age, and race) also should be included.

Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 4 Years of Age and Older

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Billy Dunn at 301-796-2250.

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Drugs for the Treatment of Partial Onset Seizures: Full Extrapolation of Effectiveness from Adults to Pediatric Patients 4 Years of Age and Older Guidance for Industry[1]

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I. INTRODUCTION

This guidance provides recommendations to sponsors on the clinical development of drugs for the treatment of partial onset seizures (POS) in pediatric patients. Specifically, this guidance addresses FDA's current thinking regarding clinical development programs that can support extrapolation of the effectiveness of drugs approved for the treatment of POS in adults to pediatric patients 4 years of age and older. This guidance does not address clinical development programs for the treatment of POS in pediatric patients less than 4 years of age. This guidance does not address the development of drugs to treat other types of seizures.

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II. BACKGROUND

Historically, because evidence adequate to support an extrapolation approach was not available, FDA has required, under section 505(d) of the Federal Food, Drug, and Cosmetic Act, that sponsors establish effectiveness for the treatment of POS in pediatric patients by performing one or more adequate and well-controlled clinical trials in pediatric patients. The doses in these pediatric trials were generally based on body weight and age, in an effort to attain blood

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

concentrations similar to those found to be effective in adults. Doses were also informed by safety and tolerability data from open-label studies in the pediatric population.

Efficacy can be extrapolated from adults to pediatric patients when it is reasonable to assume that children, compared with adults, have a similar progression of disease, similar response of disease to treatment, and similar exposure-response relationship.[2] After excluding children with POS associated with epileptic encephalopathies, such as Lennox-Gastaut syndrome, the pathophysiology of POS appears similar in adults and pediatric patients 4 years of age and older.[3] Clinical trials of drugs for the treatment of POS in pediatric patients 4 years of age and older have shown a response to treatment (reduction in seizure frequency) similar to the response to treatment seen in adults. Systematic and quantitative analyses conducted by FDA, using data from clinical trials of drugs approved for the treatment of POS in both adults and pediatric patients 4 years of age and older, have shown that the relationship between exposure and response (reduction in seizure frequency) is similar in adults and pediatric patients 4 years of age and older. These analyses, conducted for drugs with a variety of putative mechanisms of action, have allowed FDA to conclude that the efficacy of drugs approved for the treatment of POS can be extrapolated from adults to pediatric patients 4 years of age and older.

III. DEVELOPMENT CONSIDERATIONS

A. Formulation Development

Children may differ from adults in many aspects of pharmacotherapy including feasibility of routes of drug administration, drug-related toxicity, and taste preferences. It is therefore essential for sponsors to formulate pediatric drugs to best suit a child's age, size, and physiologic condition. FDA encourages sponsors to explore innovative approaches to pediatric formulation development and testing.

B. Efficacy Considerations

As noted above, FDA has concluded that the effectiveness of drugs approved for the treatment of POS in adults can be extrapolated to pediatric patients 4 years of age and older. This conclusion does not apply to the treatment of POS in pediatric patients less than 4 years of age or to the treatment of other types of seizures.

[2] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*. See also the pediatric study planning and extrapolation algorithm in the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[3] Pellock JM, Carman WJ, Thyagarajan V, Daniels T, Morris DL, and D'Cruz O, 2012, Efficacy of Antiepileptic Drugs in Adults Predicts Efficacy in Children: A Systematic Review, Neurology; 79(14):1482–1489.

C. Clinical Pharmacology/Dosing Considerations

To support extrapolation, blood concentrations of active drug/metabolites should be obtained from an adequately designed pharmacokinetic and tolerability study in which single and/or multiple doses of the investigational drug are administered in patients 4 to 16 years of age. The study should include an appropriate distribution of pediatric patients across this age range and be designed to characterize adequately the acute tolerability over a range of doses that covers drug concentrations known to be effective in adults.

Simulations should be performed to select doses expected to achieve exposures similar to those in adults. The sample size and sampling scheme should be planned carefully to enable characterization of pharmacokinetics with adequate precision.[4] Pharmacokinetic data from that study should be used to determine pediatric dosages and regimens that provide drug exposure similar to that known to be effective in adult patients with POS. Sponsors should share the results of this analysis with FDA before initiating the open-label safety studies described below.

D. Safety Considerations

Safety data generally cannot be extrapolated from adults to children. Therefore, sponsors should conduct clinical studies to characterize adequately the safety of the drug in pediatric patients 4 years of age and older with POS, with all ages well represented. Such studies can be open-label in design. In general, a minimum of 100 pediatric patients should be exposed to the drug for at least 6 months of treatment although the sponsor should determine the specific study characteristics on a case-by-case basis, depending on the expected and emerging safety profile of the drug. Dosing levels in these safety studies should be at or above those determined to be effective in the pediatric population, based on the extrapolation described above. Blood concentrations of the drug and its active major metabolites should be quantified whenever severe or serious adverse events occur in patients enrolled in the study.

[4] Wang Y, Jadhav PR, Lala M, and Gobburu JV, 2012, Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies, J Clin Pharmacol, 52(10):1601–1606.

Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment

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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.

Clinical Evidence of Effectiveness for Human Drug and Biological Products[4] and the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics*,[5] 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.

[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*[6]). 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.[7] 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.[8] 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.[9]

[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.[10] 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.[11] 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.[12] 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.

[10] Ibid.

[11] Ibid.

[12] Ibid.

Duchenne Muscular Dystrophy and Related Dystrophinopathies: 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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Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment

Guidance for Industry

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Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment Guidance for Industry[1]

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I. INTRODUCTION

This guidance addresses FDA's current thinking regarding clinical development programs and trial designs for drugs to support an indication for the treatment of one or more dystrophinopathies: Duchenne muscular dystrophy (DMD) and related dystrophinopathies including Becker muscular dystrophy (BMD), DMD-associated dilated cardiomyopathy (DCM), and symptomatic carrier states in females.[2, 3] The most prominent pathology in dystrophinopathies is degeneration of skeletal and cardiac muscle leading to progressive loss of muscle function, respiratory and cardiac failure, and premature death. This guidance does not address the development of drugs to treat secondary complications of muscle degeneration in dystrophinopathies (e.g., drugs specifically for heart failure or pulmonary infections).

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design, as these 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.[4]

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[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 (CBER), 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 dystrophinopathies.

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

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II. BACKGROUND

Dystrophinopathies result from genetic mutations in the dystrophin gene that decrease the amount of dystrophin protein and/or cause dysfunction of the protein. Protein dysfunction leads to muscle degeneration and, in many patients, downstream pathologies including inflammation and fibrosis that interfere with muscle regeneration and cause loss of movement, orthopedic complications, and, ultimately, respiratory and cardiac failure. The most common and generally most severe dystrophinopathy is DMD, with a birth prevalence of about 1 in 3,500 to 6,000 males. DMD causes delay and/or failure to reach developmental milestones, functional losses in the first decade of life, and greatly decreased life expectancy. BMD generally has later onset of symptoms and slower progression. BMD is characterized by wide interpatient variability in severity, with some patients having a clinical course similar to that observed for DMD, while other patients remain nearly, or in some cases completely, asymptomatic. The birth prevalence of BMD is about 1 in 20,000 males. DCM is less common and caused by dystrophin mutations that primarily affect cardiac muscle. Finally, some female carriers of dystrophin mutations experience muscle degeneration similar to that in males.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Early Phase Clinical Development Considerations

For a variety of reasons, communication between drug developers and those affected by dystrophinopathies is important during the development of drugs for these conditions, to discuss expectations with respect to both efficacy and safety.

- FDA recognizes that those affected by life-threatening and severely debilitating illnesses with unmet medical need are generally willing to accept greater risks and greater uncertainties about risks.[5] It is important that drug developers understand how affected individuals view treatment goals and risk tolerance as well the relationship between treatment goals and risk tolerance to a patient's specific circumstances. For example, tolerance for risk may differ between patients with the more severe and less severe dystrophinopathy phenotypes. As development proceeds and the potential benefits and risks of a drug become

[5] 21 CFR 312.80, subpart E.

more clearly understood, drug developers should elicit further input from patients and caregivers.

- Many patients with dystrophinopathies are children. Special considerations apply to the conduct of studies in children and the types and contexts of risks that are considered to be ethically acceptable.[6] Within the bounds of these ethical considerations, in studies where the risk to children is more than minimal, drug development studies may be allowed to proceed under FDA's regulatory framework if the risk is justified by the anticipated benefit to the child and the relation of the anticipated benefit to the risk is at least as favorable as that presented by available alternative approaches .[7] However, patients and caregivers can make appropriate decisions about participation in clinical studies only if provided with clear information about the potential risks and benefits. In addition to informed consent, and assent by children, if applicable, based on information available at the beginning of the study, it is critical that emerging safety information be communicated rapidly to study patients and their caregivers on an ongoing basis to allow them to reassess continued participation.

- Treatment goals similarly may differ, depending on patient-specific circumstances such as age and disease stage. Patients most severely affected by the disease, along with their caregivers, can provide insight into the outcomes that are most appropriate to designate as primary endpoints, how these outcomes might best be assessed, and the meaningfulness of treatment effects when considered in the context of the overall disease.

2. Drug Development Population

There is a need to understand the safety and efficacy of investigational drugs for dystrophinopathies across disease stages and phenotypes. Although drug developers 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), drug developers should not unnecessarily exclude patients from enrollment based on characteristics such as age or disease stage unless scientifically justified. Broader inclusion criteria allow more rapid trial enrollment, potentially accelerating drug development. Demonstrating safety and efficacy of an investigational drug generally involves several stages of development and a number of clinical trials, increasing the feasibility of including patients across different disease stages and phenotypes.

There is a strong rationale for treatment of patients at an early age because drugs that preserve muscle, in particular, may have the greatest effect on prognosis before muscle health has deteriorated. There is also a need to assess safety and efficacy of drugs at later phases of disease, however, including stages when respiratory and cardiac pathology is more pronounced.

[6] 21 CFR part 50, subpart D.

[7] 21 CFR 312.42.

3. Efficacy Considerations

The statutory standards for effectiveness apply to drugs for dystrophinopathies just as the standards apply for all other drugs. FDA has long stressed, however, that it is appropriate to exercise flexibility in applying the statutory standards to drugs for serious diseases with unmet medical needs, while preserving appropriate guarantees for safety and effectiveness.[8]

4. Safety Considerations

Trials in dystrophinopathies generally should be conducted under the oversight of a data monitoring committee (DMC). The DMC should look for emerging safety signals at frequent intervals and, if necessary, advise the sponsor regarding appropriate measures to ensure that patients are not placed at unreasonable risk of harm.[9]

To support marketing approval, drug risks must be characterized with an adequate number of patients and an adequate duration of exposure.[10] FDA generally will consider the serious and life-threatening nature of DMD and other severe dystrophinopathies when determining the minimum number and duration of patient exposures needed.[11] Drugs shown to provide an important benefit will generally need less safety data to provide adequate assurance that benefits outweigh risks. 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 efficacy studies but in whom, based on other data, the use of the drug following approval is likely. Safety data from a reasonable number of patients exposed to the drug for at least 1 year generally is appropriate to support approval of drugs intended for chronic use in treating DMD and other severe dystrophinopathies.

Adverse events of special interest for drugs for the treatment of dystrophinopathies include those related to immune responses to dystrophin or other muscle components. Exacerbation of cardiac disease may be a concern for drugs that increase physiological stress on the heart by increasing the amount or activity of skeletal muscle or for drugs that could directly affect cardiac dystrophin.

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[8] 21 CFR 312.80, subpart E, Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses.

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

[10] 21 CFR 314.125(b)(2).

[11] 21 CFR 314.105(c); FDA is required to exercise its scientific judgment to determine the kind 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 randomized placebo-controlled trials, which generally are the most efficient way to demonstrate efficacy of drugs to treat dystrophinopathies. In some circumstances, however, FDA may consider trials using external controls (historically controlled trials) to be adequate and well controlled studies that may contribute to evidence of efficacy to support approval. However, FDA recognizes that historically controlled trials lack important design features that reduce bias, such as randomization and masking of treatment assignment and generally are persuasive only when drug effects are large on objective endpoints that are less susceptible to bias.[12] (Expectation bias can increase motivation in patients who know they are receiving active treatment, thereby improving patient performance on functional tests.) To support reliance on externally controlled studies, a sponsor should present detailed evidence that the study design and conduct are adequately controlled for bias. For example, it would be critical to establish that the control group was prospectively well matched to the treatment group across important baseline and prognostic variables, including age, baseline value of the primary efficacy measure and other measures of disease stage, type and intensity of supportive care, dose and duration of concomitant pharmacotherapies, and genotype, among others. Potential sources of bias, such as differences in encouragement during tests of physical performance or function, should be eliminated or minimized. The disease course in an external patient cohort can be sensitive to the date of inception and the age of patients at inception. Thus, selection of these parameters with data in hand can introduce bias. Again, because of the inherent limitations of externally controlled trials, only large treatment effects are likely to be convincing.

2. Study Population

Although there is a need to characterize the safety and efficacy of investigational drugs for dystrophinopathies across multiple disease stages and phenotypes, a sponsor can target drug development to an identified disease subgroup when scientifically justified (e.g., drugs that are directed at specific dystrophin mutations). Similarly, sponsors can base enrollment on early biomarker data that suggest clinical benefit is likely to occur in only a subset of patients that can be identified using that biomarker.

For drugs that may slow clinical decline but are not expected to improve or reverse preexisting muscle dysfunction, it may be useful to consider prognostic enrichment (i.e., the use of inclusion criteria to select patients with characteristics that predict more rapid clinical decline during the planned study). Such criteria might include a history of rapid deterioration before study entry or more severe functional deficit at enrollment. For more information on prognostic enrichment, see the draft guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*.[13]

[12] See ICH E10.

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

For drugs targeted to specific mutations, sponsors need to identify accurately the dystrophin mutation(s) of each patient for enrollment. Even for drugs intended to have mutation-independent efficacy, FDA strongly recommends testing because knowledge of genotype-phenotype correlations may reveal differences in safety and efficacy across subgroups. For similar reasons, FDA also strongly recommends genotyping additional loci that modify phenotype.

For drugs in which efficacy or safety may be related to the patient's specific dystrophin mutation or to another type of finding related to a biomarker for which a suitable diagnostic device is not available, a sponsor should develop contemporaneously a companion diagnostic device. The sponsor should establish the clinical performance characteristics of the diagnostic device using data from the clinical development program of the drug. Given the serious and life-threatening nature of dystrophinopathies and the lack of satisfactory alternative treatments that currently exist, however, FDA may approve a drug even if a companion diagnostic device is not yet approved or cleared, if the benefits from the drug are so pronounced as to outweigh the risks from the lack of an approved or cleared in vitro companion diagnostic device.[14] During the drug review, FDA will determine the need for clearance or approval of the device. We encourage sponsors to engage early in development with the Division of Neurology Products or the Center for Devices and Radiological Health at FDA to discuss the potential need for the codevelopment of a companion diagnostic device

3. Efficacy Endpoints

FDA has no defined set of required or recommended clinical outcome measures for studies in dystrophinopathies. Although existing outcome measures developed for clinical trials and/or clinical care in dystrophinopathies or related conditions may be appropriate, FDA will also consider proposals for the use of novel outcome measures that are capable of measuring clinically meaningful effects in patients. FDA encourages sponsors to propose and, if necessary, develop endpoints that can validly and reliably assess patients with a wide spectrum of symptoms and disease stages. Sponsors should engage FDA early during the selection and/or development of efficacy endpoints. The sponsor should include an assessment of multiple efficacy endpoints, when feasible, to characterize the breadth of effects on dystrophin-related pathologies, including skeletal, respiratory, and cardiac muscle function, even if the primary endpoint is only one of these measures.

Efficacy endpoints that can measure change of function over a wide range of types and severity of deficits may offer a number of advantages in the development of drugs for dystrophinopathies. Such endpoints may increase the number of patients eligible for enrollment and may decrease possible loss of information from *floor* and *ceiling* effects that occur, respectively, when patients become unable to contribute data because they can no longer complete a function, or remain capable of performing a function throughout the study. For similar reasons, FDA encourages sponsors to use endpoints that can assess function across different stages of the disease (e.g., by

[14] See the guidance for industry and Food and Drug Administration staff *In Vitro Companion Diagnostic Devices* available at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081752.htm.

combining measures of ambulation and upper body function). Endpoints should have the ability to detect *improvement* from baseline, as well as decline, to capture the spectrum of possible beneficial drug effects.

Patient-reported outcomes (PROs),[15] 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. PROs can be useful to assess the clinical meaningfulness of an objective finding of relatively small magnitude and to contribute to assessments of benefit and risk. PRO instruments for dystrophinopathies generally 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. In cases where a patient is unable to report for himself or herself (e.g., a young child), the sponsor should base observer-reported outcomes on what a caregiver or other observer directly sees during a patient's daily activities.

Sponsors can measure efficacy endpoints based on function in a variety of ways, including performance-based outcome assessments that demonstrate the patient's ability to perform a specific activity or set of activities (e.g., ability to perform the activity(ies) (yes or no); time required to perform the activity(ies)) or as time to event for decline or loss of an ability. For young children in whom abilities are still developing, it may be appropriate to assess time to event in the positive sense (i.e., the time to reach a certain developmental milestone).

Additional considerations for endpoints include the following:

- In neonates, infants, and young children up to 4 years of age, developmental scales have been used in DMD (e.g., the Griffiths Scale of Mental Development or Bayley Scales of Infant and Toddler Development, Third Edition). However, sponsors should discuss with the FDA, and reach agreement on, the appropriateness of the use of such scales in clinical trials.

- In ambulatory children ages 3 years and older, the North Star Ambulatory Assessment or an age-appropriate modified North Star Ambulatory Assessment can provide a useful measure of gross motor function, as can timed function tests such as time to climb four stairs or time to walk or run 10 meters, among others.

- Myometry may be an appropriate endpoint for treatments that increase or preserve muscle strength, and it can be used to provide reliable measurements in children ages 5 years and older. The clinical meaningfulness of differences in muscle strength should be supported by the magnitude of the effect observed or by the demonstration of a drug effect on an appropriate functional measure. In some instances, a demonstrated effect on

[15] A PRO is a measurement based on a report that comes directly from the patient (i.e., study subject) about the status of the patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else.

muscle strength could be considered an *intermediate clinical endpoint* and be used to support accelerated approval.[16]

- The 6-minute walk test (6MWT) or shorter versions such as the 2-minute walk test, can measure both strength and endurance, and can be appropriate for patients as young as 5 or 6 years of age. There are challenges associated with the use of these tests. First, performance tends to improve with time in very young patients whereas performance tends to worsen with time in older patients. Second, there can be a floor effect of losing ambulation in older patients with more advanced disease. Analyses of change in 6MWT can be strongly influenced by the inclusion or exclusion of patients who lose ambulation during the trial; such patients contribute zero values. Third, considering the above, the data may not be normally distributed, which can have important analytical ramifications.

- For older nonambulatory patients, a number of outcome measures are available that measure primarily upper extremity function.

Many functional endpoints in clinical trials for dystrophinopathies include tasks performed by a patient in a clinical setting according to instructions administered by a health care professional. Such endpoints can be affected by the effort of the patient and/or coaching or encouragement by a family member, caregiver, or medical staff so that blinding to treatment is critical. Sponsors should consider other ways to minimize such influences. For example, sponsors should standardize the encouragement given to patients during testing, and whenever practicable, study personnel who are not aware of clinical course or potentially unmasking adverse events should administer tests of functional endpoints.

Efficacy in dystrophinopathies can also be demonstrated by an effect on respiratory and/or cardiac endpoints, with the following considerations:

- Specific clinical respiratory outcomes can include nocturnal desaturation, aspiration pneumonia, and progression to mechanically assisted ventilation. Additional measures of respiratory function, such as vital capacity, maximal inspiratory pressure, and maximal expiratory pressure can also be used. As with myometry, sponsors should support the clinical meaningfulness of differences in these additional measures by examining the magnitude of the effect observed (both mean effect and distribution of responses) or by the demonstration of a drug effect on an adequate functional measure. In some instances, a demonstrated effect on these measures could be considered an intermediate clinical endpoint and used to support accelerated approval.

- Evidence of effectiveness in chronic heart failure has traditionally relied on randomized, double-blind clinical trials in adult patients with documented heart failure and/or left ventricular dysfunction caused by common etiologies such as ischemic heart disease, hypertension, or myocarditis. Most of these trials have been designed to detect outcomes such as improved survival or a composite of improved survival and decrease in heart

[16] See the guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics*.

failure hospitalizations. These trials have not used improved exercise capacity alone as an endpoint, at least in part, because heart failure treatments that have improved exercise capacity have had adverse effects on survival. A treatment for DMD directed at the underlying disease pathology might pose fewer such concerns so that FDA could consider improved exercise capacity alone to be an appropriate endpoint. One obvious disadvantage of an approach demonstrating improvement in exercise capacity is that the effects of skeletal muscle function and cardiac muscle function might not be easily distinguished.

- Few natural history studies exist for patients with DMD cardiomyopathy, which increases the difficulty of developing measures that might predict disease progression or serve as endpoints for accelerated approval. FDA recommends that, whenever feasible, sponsors collect the following cardiac data during clinical trials: periodic evaluation of signs and symptoms of cardiac involvement or heart failure that are appropriate for the age and disease stage of the trial population, inventory of cardiac medications, serial electrocardiograms, and serial noninvasive imaging studies (e.g., echocardiography or cardiac magnetic resonance imaging).

Dystrophin is expressed in the brain, and dystrophinopathies can be associated with cognitive and behavioral effects. Although many drugs that affect behavior would not be considered dystrophinopathy-specific (e.g., drugs for attention deficit hyperactivity disorder), FDA could approve a drug for dystrophinopathies if a specific beneficial effect on the nervous system were demonstrated (i.e., the benefit would not be expected to occur in patients without dystrophin mutations).

4. Study Procedures and Timing of Assessments

Drugs that will be chronically administered to patients with dystrophinopathies should be shown to be effective for a period of at least 3 months. For drugs expected to slow functional decline, study length necessarily is affected by the rate of progression in addition to predicted drug efficacy. Although studies of 1 year's duration have been conducted in DMD, sponsors should base the duration of studies on scientifically justifiable sample size calculations that include, when appropriate, the predicted rate of functional decline in the placebo group, the anticipated effect size, the variability around these estimates, and the desired statistical power. Efficacy studies of 18 to 24 months' duration may substantially increase statistical power, while only modestly increasing overall development time.

5. Endpoint Adjudication

Blinded adjudication of cardiac endpoints has commonly been used in studies of cardiovascular drugs, and sponsors should consider this if cardiac endpoints (e.g., heart failure, cardiac hospitalizations) are used. Sponsors should also consider adjudication for complex respiratory endpoints (e.g., aspiration pneumonia) because equivocal cases may occur. Functional endpoints (e.g., the ability to rise from the floor, to walk) potentially may benefit from adjudication to address potential confounding factors such as reversible injury.

6. Statistical Considerations

In general, statistical approaches for dystrophinopathies should be similar to those used in other disease areas, as described in other guidances. Sponsors can use designs that increase the efficiency of studies (e.g., adaptive designs[17]).

For efficacy assessment based on a continuous measurement of functional capacity, sponsors generally should perform statistical analyses on the change from baseline for each treatment group, with the treatment effect assessed by comparing the mean changes between the treatment and control groups at one or more specific times. The mean changes would normally be adjusted for the baseline measurement to improve statistical power for detecting a treatment effect.

Overall, a study should be adequately powered to be able to detect a treatment effect in the study population taking into account the estimated effect size. Because of the limited number of patients with DMD, however, it may not be realistic or feasible to adequately power the study to attain statistically significant results for each distinct subpopulation of interest in the study. If the sponsor has obtained statistically significant results demonstrating efficacy in the overall target population, favorable trends in the efficacy results may support the inclusion of a description of subpopulations within the clinical trials section of labeling.

Sponsors can decrease variability by obtaining a baseline assessment on more than one occasion, if practicable (e.g., performing a 6MWT on two occasions, 1 week apart). For studies that require a specific degree of physical disability for enrollment (e.g., a 6MWT distance of less than 350 meters), the screening assessment used to qualify patients for study entry should not be used as the baseline assessment. A sponsor should obtain a separate baseline assessment after the screening assessment to limit regression to the mean. For dystrophinopathies, sponsors can also consider a variation of this approach that assesses the change from baseline in the slopes (or rates of change). Whereas the typical change from baseline assessment takes only two measurements into consideration (pretreatment and posttreatment at a particular time point), assessment of slope change takes multiple measurements into consideration for each patient, thereby possibly improving statistical power to show a treatment difference.

The likelihood that randomization will be fully successful in producing comparable study arms can be increased through stratified randomization based on one or more prognostic factors. For young children, stratification might be based on markers of lower-limb strength or ambulatory abilities, whereas for older children, pulmonary and cardiac status might be appropriate stratification factors. With small to moderate sample sizes, however, sponsors should limit such covariates to a few that are carefully chosen.

7. Accelerated Approval Considerations

In dystrophinopathies, biomarkers that reliably reflect the health and amount of skeletal muscle at a biochemical, cellular, or tissue level may be useful across the drug development process,

[17] See the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics*. When final, this guidance will represent the FDA's current thinking on this topic.

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. A single biomarker measure can, in different circumstances, serve different functions; for example, baseline dystrophin expression can be a marker of a patient's prognosis whereas an increase in dystrophin could reflect biological activity of a drug and guide key aspects of drug development such as dose selection and route of administration. Even if it cannot be concluded that a given biomarker can serve as a surrogate endpoint, positive findings based on a biomarker may help support the mechanism of action of a drug, help identify the appropriate patient population to study or treat, or support the validity of findings on other endpoints. To support continued progress in overall drug development for dystrophinopathies, trials with clinically meaningful endpoints should include a selection of relevant biomarkers to help establish the correlation between such biomarkers and clinical endpoints.

The potential for a biomarker to predict clinical benefit in dystrophinopathies could relate to the magnitude of change of the biomarker and tissue in which the biomarker is measured. The meaning of a change in a biomarker might also depend on the age or disease stage of a patient or on other patient factors such as inflammation or autoimmunity to dystrophin or other muscle components. When biomarkers are assessed, analytical validity should be demonstrated to the extent possible, and there should be adequate assessment of the performance characteristics of the biomarker assay, including quality-control measures and documentation of results.

Deficiency of functional dystrophin appears to be the proximate cause of the symptomatic and functional consequences of dystrophinopathies, justifying particular interest in dystrophin as a biomarker and as a potential surrogate endpoint for accelerated approval.

FDA also encourages sponsors to consider the use of other biomarkers, such as those measured with magnetic resonance imaging or magnetic resonance spectroscopy. Advantages of imaging include its noninvasiveness, its ability to assess large samples of muscle, the fact that it can be performed repeatedly at multiple time points, and its ability to assess multiple regions of the body, including cardiac muscle.

Sponsors considering a development program intended to support accelerated approval should discuss their development programs with the Division of Neurology Products early in drug development.

8. Benefit-Risk Considerations

When making regulatory decisions regarding drugs for dystrophinopathies, FDA will consider patient and caregiver tolerance for risk and the serious and life-threatening nature of these conditions. For example, patients may be willing to tolerate substantial risk of harm if a drug might delay loss of important abilities such as ambulation. However, tolerance for risk may vary among individuals and be affected by disease stage and severity; FDA would consider this heterogeneity in regulatory decisions.

C. Other Considerations

1. Relevant Nonclinical Safety Considerations

Nonclinical studies provide important information upon which it can be determined whether clinical trials are reasonably safe to conduct, and to inform clinical dose selection and 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 human studies may exceed that of the nonclinical studies if justified based on the available nonclinical and clinical data. Sponsors are encouraged to consult with the Division of Neurology Products early in clinical development.

Studies in juvenile animals, to assess the potential for toxicity to immature systems and developmental processes, should be conducted to support clinical studies in the pediatric population. The design of studies in juvenile animals[18] and timing of submission during clinical development should be discussed with the Division prior to study initiation. Carcinogenicity studies generally can be conducted after approval for drugs intended to treat most dystrophinopathies.

2. Pharmacokinetic/Pharmacodynamic Considerations

Given the serious and life-threatening nature of diseases such as DMD and other severe dystrophinopathies, the typical array of clinical pharmacology testing is unlikely to be needed to support a new drug's approval. For example, FDA can defer until after approval, or waive, studies of effects of renal or hepatic impairment if the patient population and metabolic pathways of the drug, considered together, suggest a low likelihood of clinically meaningful effects on pharmacokinetics or pharmacodynamics. FDA encourages sponsors to consult with the Division of Neurology Products early in clinical development.

Sponsors should define and evaluate as needed the pharmacokinetic and/or pharmacodynamic interactions between an investigational new drug and other drugs commonly used in dystrophinopathies during drug development as part of an adequate assessment of the drug's safety and effectiveness. Concomitant use of supplements, herbals, and dietary modifications is common in dystrophinopathies, and sponsors should consider the potential effects of these on the pharmacokinetics and pharmacodynamics of investigational drugs.

Sponsors should 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/dosing regimen(s) for confirmatory studies and the need for dose adjustment for various extrinsic/intrinsic factors such as drug-drug interactions, age, and renal function, among others. Importantly, exposure-response assessment can also contribute to evidence of effectiveness from confirmatory studies. The

[18] Such studies may not be needed for gene or cell therapy products regulated by CBER. Sponsors should consult with CBER early in clinical development to discuss the need for juvenile animal toxicology studies.

response variables used in the analyses should include prespecified primary and secondary endpoints, as well as results involving biomarkers collected in the studies for efficacy and safety.

3. Labeling Considerations

FDA encourages sponsors to enroll patients across disease stages and phenotypes. Data from even a relatively small number of patients across different disease subgroups may help to support an indication that includes broader groups of patients. In general, FDA will consider approval for a broader patient population unless issues (e.g., an unacceptable safety risk, an expected lack of effectiveness in certain subpopulations) exist that provide arguments against such an approach.

Early Alzheimer's Disease: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Billy Dunn at 301-796-2250 or (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

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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Early Alzheimer's Disease: Developing Drugs for Treatment

Guidance for Industry

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Contains Nonbinding Recommendations

Draft — Not for Implementation

Early Alzheimer's Disease: Developing Drugs for Treatment Guidance for Industry[1]

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 the stages of sporadic Alzheimer's disease (AD) that occur before the onset of overt dementia (collectively referred to as early AD in this guidance, though it is recognized that patients with later stage early AD and patients with AD in the earliest stages of dementia may not differ significantly).[2] This guidance is intended to serve as a focus for continued discussions among representatives of the Division of Neurology Products in the Center for Drug Evaluation and Research or the Office of Tissues and Advanced Therapies (OTAT) in the Center for Biologics Evaluation and Research, as appropriate, pharmaceutical sponsors, the scientific community, and the public.[3] The design of clinical trials that are specifically focused on the treatment of patients with AD who have developed overt dementia, or any of the autosomal dominant forms of AD, is not discussed, although some of the principles in this guidance may be pertinent.

This guidance revises the draft guidance for industry *Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease* issued in February 2013. This revision addresses the Food and Drug Administration's (FDA's) current thinking regarding the selection of patients with early AD for enrollment into clinical trials and the selection of endpoints for clinical trials in these populations.

[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 therapeutic biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the Division of Neurology Products or OTAT to discuss specific issues that arise during the development of drugs to treat early AD.

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

Historically, the use of clinical criteria that defined later stages of AD, after the onset of overt dementia, were used for enrollment into clinical trials. Accordingly, patients included in these trials exhibited both the cognitive changes typical of clinically evident AD and the degree of functional impairment associated with overt dementia. Drugs that were approved for dementia during that time were evaluated in that context. Studies supporting approval of those drugs used a co-primary approach to assessment of cognitive and functional (or global) measures. This approach ensured both that a clinically meaningful effect was established by a demonstration of benefit on the functional measure and that the observed functional benefit was accompanied by an effect on the core symptoms of the disease as measured by the cognitive assessment.

The co-primary endpoint approach was used, in part, because the cognitive assessments used in the studies were not considered inherently clinically meaningful. Such assessments typically measure the cognitive deficits of AD through the use of highly sensitive formalized measures of neuropsychological performance that are capable of discriminating small changes of uncertain independent clinical meaningfulness. This historical dichotomy of functional and cognitive assessments has led to common use of the terms *cognition* and *function* with respect to outcome assessment in AD clinical trials, with the implication that an effect on cognition is non-meaningful unless accompanied by a benefit on an independent endpoint assessing function in a meaningful manner. FDA rejects this dichotomy and finds such usage inappropriate, because it implies that an effect on cognition itself, regardless of the nature of the observed effect and the manner in which it is assessed, cannot be clinically meaningful. This is certainly not the case.

Cognition, in its entirety, encompassing all its constituent processes and domains, is most certainly meaningful in terms of daily function. Although small changes in various cognitive domains may be detected using sensitive neuropsychological tests that are capable of detecting changes of uncertain clinical meaningfulness, more marked cognitive changes may represent impairment that is clearly clinically meaningful. It follows, in concept, that cognitive changes of particular character, perhaps defined by magnitude or breadth of effect(s), may represent clinically meaningful benefit. The issue of concern with regard to considering the meaningfulness of cognitive measurements is the method of assessment, not the entity of cognition itself, especially for cognition taken as a whole. In short, cognition is meaningful, but when measured using conventional approaches with sensitive tools directed at particular domains, the meaningfulness of measured changes may not be apparent.

As the scientific understanding of AD has evolved, efforts have been made to incorporate in clinical trials, to varying degrees, the use of biomarkers reflecting underlying AD

pathophysiological changes and the enrollment of patients with AD at earlier stages of the disease, stages in which there may be no functional impairment or even no detectable clinical abnormality. These efforts are particularly important because of the opportunity to intervene very early in the disease process that AD provides, given the development of characteristic pathophysiological changes that greatly precede the development of clinically evident findings and the slowly progressive course of AD. It is obvious that delaying, or, preferably, halting or reversing, the pathophysiological process that will lead to the initial clinical deficits of AD is the ultimate goal of presymptomatic intervention, and treatment directed at this goal must begin before there are overt clinical symptoms. This opportunity carries with it the need to understand the optimum manner in which to assess treatment benefit in these earlier stages of disease.

III. DIAGNOSTIC CRITERIA FOR EARLY ALZHEIMER'S DISEASE

Eligibility for enrollment in efficacy trials in AD, including early AD, should be based on current consensus diagnostic criteria, with a focus on objective tests and, when appropriate, history and physical examination, to determine the presence or likely presence of AD, and to exclude other conditions that can mimic AD.

FDA supports and endorses the use of diagnostic criteria that are based on a contemporary understanding of the pathophysiology and evolution of AD. The characteristic pathophysiological changes of AD greatly precede the development of clinically evident findings and progress as a continuous disease process through stages defined initially only by those pathophysiological changes and then by the development of subtle abnormalities, detectable using sensitive neuropsychological measures. These are followed by the development of more apparent cognitive abnormalities, accompanied by initially mild and then more severe functional impairment. In part because of failures of clinical trials intended to alter disease progression in later stages of AD, there is an increased focus on evaluating drug treatments for AD in the earliest stages of the disease. Diagnostic criteria that reliably define a population with early AD, including the earliest stages characterized only by pathophysiological changes, are suited to the evaluation of drugs intended to delay or prevent the emergence of overt symptoms.

Important findings applicable to the categorization of AD along its continuum of progression include the presence of pathophysiological changes as measured by biomarkers, the presence or absence of detectable abnormalities on sensitive neuropsychological measures, and the presence or absence of functional impairment manifested as meaningful daily life impact that present with subjective complaints or reliable observer reports. Although FDA recognizes that variations in the selection and application of clinical characteristics and biomarkers may lead to the identification of patients who are at somewhat different stages of a progressive disease process, the following categories are conceptually useful for the design and evaluation of clinical trials in different stages of AD:

- **Stage 1: Patients with characteristic pathophysiologic changes of AD but no evidence of clinical impact.** These patients are truly asymptomatic with no subjective complaint, functional impairment, or detectable abnormalities on sensitive neuropsychological

measures. The characteristic pathophysiologic changes are typically demonstrated by assessment of various biomarker measures.

- **Stage 2: Patients with characteristic pathophysiologic changes of AD and subtle detectable abnormalities on sensitive neuropsychological measures, but no functional impairment.** The emergence of subtle functional impairment signals a transition to Stage 3.

- **Stage 3: Patients with characteristic pathophysiologic changes of AD, subtle or more apparent detectable abnormalities on sensitive neuropsychological measures, and mild but detectable functional impairment.** The functional impairment in this stage is not severe enough to warrant a diagnosis of overt dementia.

- **Stage 4: Patients with overt dementia.** This diagnosis is made as functional impairment worsens from that seen in Stage 3. This stage may be refined into additional categories (e.g., Stages 4, 5, and 6, corresponding with mild, moderate, and severe dementia) but a discussion of these disease stages is not the focus of this guidance.

It is vital to distinguish accurately these conceptual categories, even in the presence of a single continuous disease process, to allow and inform appropriate outcome measure selection. In descriptions of studies, both proposed and completed, sponsors should identify both the stage of AD defined for study eligibility and enrollment and the stage of AD anticipated for the majority of the enrolled patient population at the time of primary outcome assessment.

It is reasonable to expect that biomarker evidence of disease will play a role in the reliable identification of patients in trials of early AD. Indeed, it is unusual to encounter a proposed clinical trial that does not include in the enrollment criteria biomarker evidence of disease. If this evidence could be needed to adequately define the anticipated indicated population, we encourage sponsors to engage early in development with the Division of Neurology Products, OTAT, or the Center for Devices and Radiological Health as appropriate, at FDA to discuss the potential need for the codevelopment of a companion diagnostic device.

IV. OUTCOME MEASURES

A. Clinical Endpoints for Early AD Trials in Stage 3 Patients

Early AD patients approaching the onset of overt dementia (Stage 3 patients) are likely to have relatively mild but noticeable impairments in their daily functioning. Although studies in this stage of disease will generally include sensitive measures of neuropsychological performance of uncertain independent clinical meaningfulness, it is important to demonstrate that a drug favorably affects these functional deficits. Many of the assessment tools typically used to measure functional impairment in patients with overt dementia may not be suitable for use in these early stage patients. Ideally, the outcome measure used in this stage of disease will provide an assessment of meaningful cognitive function. An integrated scale that adequately and meaningfully assesses both daily function and cognitive effects in early AD patients is acceptable as a single primary efficacy outcome measure.

FDA encourages the development of novel approaches to the integrated evaluation of subtle early AD (predementia) functional deficits/impact that arise from early cognitive impairment (e.g., facility with financial transactions, adequacy of social conversation). The independent assessment of daily function and cognitive effects is also an acceptable approach. In this setting, an effect on a sensitive measure of neuropsychological performance of uncertain independent clinical meaning (e.g., a word-list recall test) should not allow for an overall finding of efficacy in the absence of meaningful functional benefit. For drugs with the potential to lead to measurable functional benefit without a corresponding cognitive benefit, assessment of an independent cognitive endpoint is important.

B. Clinical Endpoints for Early AD Trials in Stage 2 Patients

In patients in the earliest clinical stages of AD (Stage 2 patients), where only subtle cognitive deficits detected on sensitive measures of neuropsychological performance are present, and there is no evidence of functional impairment, it may be difficult to establish a clinically meaningful effect on those subtle cognitive deficits during the course of a trial of reasonable duration. Nonetheless, a possible approach is to conduct a study of sufficient duration to allow the evaluation of the measures discussed above for Stage 3 patients. As patients transition to Stage 3 during participation in the trial, the principles applicable to outcome assessment for Stage 3 would apply.

Alternatively, and in view of the rapidly and continually expanding body of knowledge concerning AD, FDA will consider strongly justified arguments that a persuasive effect on sensitive measures of neuropsychological performance may provide adequate support for a marketing approval. Given the panoply of available neuropsychological tests, a pattern of putatively beneficial effects demonstrated across multiple individual tests would increase the persuasiveness of the finding; conversely, a finding on a single test unsupported by consistent findings on other tests would be less persuasive. A large magnitude of effect on sensitive measures of neuropsychological performance may also increase their persuasiveness. It would generally be expected that such arguments would be supported by similarly persuasive effects on the characteristic pathophysiologic changes of AD, as discussed below for Stage 1 patients.

Importantly, such arguments should be predicated on the certainty of diagnosis of enrolled patients, the certainty of their future clinical course, and the certainty of the relationship of the observed effects on sensitive measures of neuropsychological performance and characteristic pathophysiologic changes to the evolution of more severe cognitive deficits and functional impairment. Whether such arguments, if convincing, would support full approval (i.e., the cognitive effects were found to be inherently clinically meaningful, either on face or because they reliably and inevitably are associated with functional benefit later in the course of the disease) or accelerated approval (i.e., the cognitive effects were found to be reasonably likely to predict clinical benefit, with a post-approval requirement for a study to confirm the predicted clinical benefit) would be a matter of detailed consideration. Sponsors considering these issues should discuss their plans with FDA early in development. Evolution of the scientific understanding of AD may also influence these considerations.

C. Endpoints for Early AD Trials in Stage 1 Patients

Because it is highly desirable to intervene as early as possible in AD, it follows that patients with characteristic pathophysiologic changes of AD but no subjective complaint, functional impairment, or detectable abnormalities on sensitive neuropsychological measures (Stage 1 patients) are an important target for clinical trials. A clinically meaningful benefit cannot be measured in these patients because there is no clinical impairment to assess (assuming that the duration of a trial is not sufficient to observe and assess the development of clinical impairment during the conduct of the trial). In Stage 1 patients, an effect on the characteristic pathophysiologic changes of AD, as demonstrated by an effect on various biomarkers, may be measured. Such an effect, analyzed as a primary efficacy measure, may, in principle, serve as the basis for an accelerated approval (i.e., the biomarker effects would be found to be reasonably likely to predict clinical benefit, with a post-approval requirement for a study to confirm the predicted clinical benefit). As with the use of neuropsychological tests, a pattern of treatment effects seen across multiple individual biomarker measures would increase the persuasiveness of the putative effect.

Although the issues and approaches discussed above for Stage 2 patients are relevant for Stage 1 patients, there is unfortunately at present no sufficiently reliable evidence that any observed treatment effect on such biomarker measures would be reasonably likely to predict clinical benefit (the standard for accelerated approval), despite a great deal of research interest in understanding the role of biomarkers in AD. FDA strongly supports and encourages continued research in this area and stresses its potential importance in the successful development of effective treatments appropriate for use in the earliest stages of AD. Precompetitive structured sharing across the AD scientific community of rigorously collected standardized data is a crucial component of this research. While research pursues the development of evidence sufficient to support the use of biomarker measures as the primary evidence supporting an accelerated approval, or perhaps a full approval if the fundamental understanding of AD evolves sufficiently to establish surrogacy, a possible approach to Stage 1 patients might be to conduct a study of sufficient duration to allow the evaluation of the measures discussed above for Stage 2 patients. As patients transition to Stage 2 during participation in the trial, the principles applicable to outcome assessment for Stage 2 would apply.

D. Time-to-Event Analysis

The use of a time-to-event survival analysis approach (e.g., time to the occurrence of a clinically meaningful event during the progressive course of AD, such as the occurrence of some degree of meaningful impairment of daily function) would be an acceptable primary efficacy measure in clinical trials in early AD. Sponsors considering such an approach should discuss their plans with FDA early in development.

E. Assessment of Disease Course

Although the demonstration of a substantial clinically meaningful treatment effect of any sort is of paramount importance, this may not be feasible in a clinical trial of reasonable duration, especially very early in the course of the disease, and clinical trials in early stage disease will

usually be intended to provide evidence that a drug has permanently altered the course of AD through a direct effect on the underlying disease pathophysiology, an effect that persists in the absence of continued exposure to the drug.

A randomized-start or randomized-withdrawal trial design (with clinical outcome measures) is the most convincing approach to demonstrating a persistent effect on disease course. Generally, a randomized-start design would be most appropriate for use in AD. In this study design, patients are randomized to drug and placebo, and at some point, placebo patients are crossed over to active treatment. If patients in the trial who were initially on placebo and then assigned to active treatment fail to catch up (after a reasonable period of time) to patients who received active treatment for the entire duration of the trial, a persistent treatment effect on disease course would have been shown.

Assessment of various biomarkers may provide supportive evidence for a drug that has an established clinically meaningful benefit, but the effects on biomarkers in AD are not sufficiently well understood to provide evidence of a persistent effect on disease course.

Currently, there is no consensus as to particular biomarkers that would be appropriate to support clinical findings in trials in early AD. For this reason, sponsors at present have insufficient information on which to base a hierarchical structuring of a series of biomarkers as secondary outcome measures in their trial designs. Sponsors are therefore encouraged to analyze the results of these biomarkers independently, though in a prespecified fashion, with the understanding that these findings will be interpreted in the context of the state of the scientific evidence at the time of a future marketing application.