Early Alzheimer's Disease: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of the stages of sporadic Alzheimer's disease (AD) that occur before the onset of overt dementia (i.e., Stages 1 through 3; discussed in section III). These stages are collectively referred to as "early AD" in this guidance; however, it is recognized that AD occurs on a continuum and patients in the last stage of early AD (i.e., late Stage 3) and patients with AD in the earliest stages of overt dementia (i.e., early Stage 4) may not differ significantly in clinical presentation. This guidance is intended to serve as a focus for continued discussions among representatives of the Office of Neuroscience in the Center for Drug Evaluation and Research or the Office of Therapeutic Products in the Center for Biologics Evaluation and Research, as appropriate, pharmaceutical sponsors, the scientific community, and the public about the development of drugs for the treatment of early AD.[2]

This guidance revises the draft guidance for industry *Early Alzheimer's Disease: Developing Drugs for Treatment* (February 2018). This revision, when finalized, will represent FDA's current thinking regarding the selection of subjects with early AD for enrollment in clinical trials and the selection of endpoints for clinical trials in this population.[3]

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.

[1] This guidance has been prepared by the Office of Neuroscience in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration (FDA).

[2] In addition to consulting guidances, sponsors are encouraged to contact the Office of Neuroscience or the Office of Therapeutic Products to discuss specific issues that arise during the development of drugs to treat early AD.

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

II. BACKGROUND

Historically, clinical criteria that defined later stages of AD, after the onset of overt dementia, were used for enrollment in clinical trials. Accordingly, subjects 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.

As the scientific understanding of AD has evolved, efforts have been made to incorporate in clinical trials the use of biomarkers reflecting underlying AD pathophysiological changes and the enrollment of subjects with AD at earlier stages of the disease, in which there may be minimal or no detectable abnormality on clinical assessments. These efforts are particularly important because there may be an opportunity to intervene very early in the disease process of AD, given the slowly progressive course of AD and the development of characteristic pathophysiological changes that greatly precede the development of clinically evident findings. 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 or very early symptomatic intervention, and treatment directed at this goal must begin before there are overt clinical symptoms. This opportunity carries with it the need to understand ways to assess treatment benefit in these earlier stages of disease.

This document provides an overview on the Agency's current thinking on diagnostic criteria and clinical staging of AD to inform enrollment in clinical trials and the selection of appropriate endpoints for the stage(s) of disease proposed to be enrolled in a clinical trial. The design of clinical trials that are specifically focused on the treatment of patients with AD who have developed overt dementia (i.e., Stages 4 through 6; discussed in section III), 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 does not discuss treatment of dementias other than AD.

III. DIAGNOSTIC CRITERIA FOR EARLY AD

Eligibility for enrollment in trials intended to support an application for approval for treatment of early AD should be based on current consensus diagnostic criteria intended to establish the true biological presence of AD rather than criteria based on syndromic or other definitions; this approach is intended to avoid enrollment of a substantial number of subjects who would not actually have AD.

FDA supports the use of biologically based diagnostic criteria that are grounded in a contemporary understanding of the pathophysiology and evolution of AD. The characteristic pathophysiological changes of AD precede, often by many years or even decades, the development of clinically evident findings and progress as a continuous disease process that can be categorized into stages. Those stages are defined below, initially only by those

pathophysiological changes and then by the development of subtle clinical abnormalities, detectable using sensitive neuropsychological measures. These initial clinical findings are followed by the development of more apparent cognitive abnormalities, accompanied by initially mild and then more severe or more extensive functional impairment. Based on knowledge gained from previous clinical trials and the evolving understanding of the pathophysiology 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 cognitive symptoms reported by patients or observers with the presence or absence of functional impairment manifested as meaningful impact on daily activities. Although FDA recognizes that variations in the selection and application of clinical characteristics and biomarkers may lead to the enrollment of subjects in clinical trials who are at slightly 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 pathophysiological 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 pathophysiological changes are typically demonstrated by assessment of various biomarker measures.

- **Stage 2: Patients with characteristic pathophysiological changes of AD and subtle detectable abnormalities on sensitive neuropsychological measures or subjective complaints of mild cognitive symptoms but no functional impairment.** This may be considered a transitional stage in which slight cognitive symptoms first appear. The emergence of subtle functional impairment signals a transition to Stage 3.

- **Stage 3: Patients with characteristic pathophysiological changes of AD, generally 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. This stage roughly corresponds with the syndrome of "mild cognitive impairment"; however, it is noted that the term "mild cognitive impairment" may also encompass patients in late Stage 2 or early Stage 4.

- **Stages 4, 5, and 6: Patients with overt dementia, progressing through mild, moderate, and severe stages.** This diagnosis is made as functional impairment worsens from that seen in Stage 3. A discussion of these three disease stages is not the focus of this guidance.

For study design, it is important to define the study population using 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, 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 study population at the time of primary outcome assessment.

As discussed above, it is expected that biomarker evidence of disease will establish the reliable diagnosis of subjects in trials of early AD. As copathology is common in AD, sponsors may consider including assessments of other copathologies in their clinical trials to inform exclusion criteria or for preplanned analyses of safety and efficacy in subgroups of the enrolled population. If biomarker evidence will be needed to adequately define the anticipated indicated population and an FDA-approved or cleared diagnostic test is not available, sponsors should engage early in development with the appropriate review division at FDA to discuss the potential need for the codevelopment of a companion diagnostic device.

IV. OUTCOME MEASURES

Both clinical outcome assessments and biomarkers[4] should be included in clinical trials enrolling subjects with AD Stages 1-3; however, the approval pathway may differ based on the selection of the primary endpoint and its ability to measure a clinically meaningful change. Direct measures of clinical benefit or validated surrogate endpoints may support a traditional approval.[5] Surrogate endpoints or intermediate clinical endpoints that do not directly measure clinical benefit but that are considered reasonably likely to predict clinical benefit may support an accelerated approval[6] (see section IV. C.). Under the accelerated approval pathway, postapproval trials have been required to verify and describe clinical benefit.

A. Clinical Endpoints

Historically, studies to support approval for drugs in the overt dementia stages of AD (Stages 4 through 6) have used an approach which required the assessment of both cognitive and functional (or global) measures as co-primary endpoints. The co-primary endpoint approach was used, in part, because the cognitive assessments used in the studies were not considered inherently clinically meaningful. Conventional approaches to assessing the cognitive deficits of AD use highly sensitive formalized measures of neuropsychological performance directed at particular domains that are capable of discriminating small changes in cognitive measures that may be of uncertain clinical meaningfulness when assessed alone. This approach was typically used in the setting of a therapy intended to treat disease symptoms in later stages of AD (i.e., Stages 4 through 6) and was intended to ensure that a change on a cognitive assessment was accompanied by an observed functional benefit, and alternately, that any observed functional

[4] For definitions of clinical outcome assessments and biomarkers, refer to the BEST (Biomarker, EndpointS, and Other Tools) Resource, available at https://www.ncbi.nlm.nih.gov/books/NBK338448.

[5] For further discussion of surrogate endpoints generally, please see the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014).

[6] Section 506(c)(1)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356(c)(1)(A)).

benefit could be attributed to a benefit on cognition and was not attributable to changes in other conditions. This remains a generally acceptable approach for stages of AD with detectable cognitive and functional impairments (Stages 3 and higher). Using this approach, the typical duration of a clinical trial in the symptomatic stages of AD has been 2 years or less; however, FDA recognizes that it may take longer to establish a clinically meaningful treatment effect in early AD due to the minimal or absent cognitive and functional deficits seen in those stages of the disease. Additionally, many of the assessment tools typically used to measure functional impairment in patients with later dementia stages of AD (Stages 4 through 6) would not be sensitive to detect subtle functional changes in early AD. Therefore, FDA may consider other approaches, including endpoints based on cognitive assessments or surrogate endpoints, which may allow for shorter trial durations as a basis for approval in the earliest stages of AD (i.e., Stages 1, 2, and early 3).

Cognition, in its entirety, encompassing all its constituent processes and domains, is essential for daily functioning. As previously noted, it can be challenging to interpret the clinical meaningfulness of small changes detected on sensitive neuropsychological tests; however, more marked cognitive changes may represent a change that is clearly clinically meaningful. It follows, in concept, that cognitive changes of a particular magnitude, or breadth of effects across multiple domains, or change in trajectory over time, may represent clinically meaningful change, independent of measures of functional change.

In the setting of therapy that targets underlying disease pathophysiology, changes in the long-term course of core cognitive measures of AD relative to placebo may potentially provide evidence of clinically meaningful effect with respect to the clinical progression of the disease. It would generally be expected that such effects on cognitive measures would be supported by similarly persuasive effects on the characteristic pathophysiological changes of AD.

In patients in the earliest clinical stages of AD (refer to section IV. D., Considerations for Specific Stages of Early AD), FDA will consider strong justifications that a persuasive effect, considering both magnitude of effect and statistical robustness of the findings, on cognition alone as assessed by sensitive neuropsychological tests may provide adequate support for a marketing approval. Given the array 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. Whether effects on cognitive outcome measures would be capable of providing evidence of effectiveness in the absence of a meaningful change in function to support either traditional or accelerated approval would require detailed discussion with the Agency. However, in a trial with relatively short-term assessments, such as a trial for a therapy intended to treat symptoms of AD, an effect on sensitive measures of neuropsychological performance of uncertain independent clinical meaning (e.g., a word-list recall test) would generally not allow for an overall finding of efficacy in the absence of meaningful functional benefit.

B. Time-to-Event Analysis

The use of a time-to-event 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 cognition or daily function, perhaps represented by certain disease stage transitions) would generally 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.

C. Surrogate Endpoints

Clinical trials showing an effect on a surrogate endpoint that is determined to be "reasonably likely to predict clinical benefit" can be the basis for accelerated approval,[7] including for drugs intended for the treatment of AD. For example, in certain circumstances, FDA has considered a reduction of the brain amyloid beta burden, as assessed by positron emission tomography, to be a surrogate endpoint that is "reasonably likely to predict clinical benefit." That endpoint, in clinical trials that enrolled participants with Stage 3 and 4 AD, has thus been used as a basis for accelerated approval for monoclonal antibodies directed against aggregated forms of amyloid beta, with postapproval trials required to verify and describe clinical benefit.

The acceptability of a surrogate endpoint for use in a particular therapeutic development program for early AD may depend on the stage of disease, population enrolled in trials, therapeutic mechanism of action, and availability of current treatments. A surrogate endpoint that is determined to be appropriate for use in a particular therapeutic clinical development program should not be assumed to be appropriate for use with a different product or trial population. Sponsors considering the use of a biomarker as the primary measure of effect should discuss their plans with FDA early in development. In general, even if accelerated approval is considered as the initial approval pathway, clinical outcome assessments should be included in clinical trials for early AD to assess early clinical changes that may potentially provide support for any changes observed on biomarkers. Evolution of the scientific understanding of AD may also influence these considerations.

FDA strongly supports and encourages continued research in understanding the role of biomarkers in AD and stresses the potential importance of biomarkers 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.

D. Considerations for Specific Stages of Early AD

Stage 1

Because it is highly desirable to intervene as early as possible in AD, it follows that patients with characteristic pathophysiological changes of AD but no subjective complaint, functional impairment, or detectable abnormalities on sensitive neuropsychological measures (Stage 1 AD

[7] Section 506(c)(1)(A) of the FD&C Act (21 U.S.C. 356(c)(1)(A)).

patients) are an important target population for enrollment in clinical trials. It can be challenging in trials of a typical duration (e.g., 2 years or less) to demonstrate a clinically meaningful benefit in these patients because there is no clinical impairment to assess at baseline and patients may have variable latency to the onset of symptoms. It is anticipated that at this stage of disease, an effect on the characteristic pathophysiological changes of AD, as demonstrated by an effect on various biomarkers, may be an appropriate measure. 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. Whether effects on biomarkers would support accelerated approval would require detailed discussion with the Agency, including a plan for subsequent confirmation of clinical benefit. However, another approach to Stage 1 patients might be to conduct a study of sufficient duration to allow the evaluation of clinical outcomes, as discussed for Stage 2 patients below. As subjects transition to Stage 2 during participation in the trial, the principles applicable to outcome assessment for Stage 2 would apply. A time-to-event analysis approach could also be considered (see section IV. B.).

Sponsors considering these issues should meet with FDA early in development to discuss the evidence that would be needed to support a marketing application. Evolution of the scientific understanding of AD may also influence these considerations.

Stage 2

In patients with Stage 2 AD, who have only subtle cognitive deficits detected on sensitive measures of neuropsychological performance and no evidence of functional impairment, it may be difficult to establish a clinically meaningful benefit on subtle cognitive deficits unless the trial has a long duration. One possible approach would be to conduct a study of sufficient duration to allow the evaluation of the clinical measures that assess cognition and function, as discussed below for Stage 3 patients. A time-to-event analysis approach could also be considered (see section IV. B.).

Alternatively, as discussed in section IV. A., FDA will consider strong justifications that a persuasive effect on cognition as measured by sensitive neuropsychological tests may provide adequate support for a marketing approval. It would generally be expected that such effects on cognitive measures would be supported by similarly persuasive effects on the characteristic pathophysiological changes of AD. Whether effects on cognitive outcome measures would, in the absence of a meaningful change in function, support either traditional or accelerated approval would require detailed discussion with the Agency.

As patients transition to Stage 3 during participation in the trial, the principles applicable to outcome assessment for Stage 3 would apply.

Sponsors considering these issues should meet with FDA early in development to discuss the evidence that would be needed to support a marketing application. Evolution of the scientific understanding of AD may also influence these considerations.

Stage 3

Patients with Stage 3 AD approaching the onset of overt dementia have relatively mild but noticeable impairments in their daily functioning. As patients have detectable cognitive and functional impairment at this stage of disease, it is important to demonstrate that a therapy favorably affects the observed impairments in both cognition and daily functioning. The independent assessment of daily function and cognitive effects remains an acceptable approach. However, it is important to note that many of the assessment tools typically used to measure functional impairment in patients with later dementia stages of AD (Stages 4 through 6) may not be suitable for use in early AD patients. An integrated scale that adequately and meaningfully assesses independent effects on both daily function and cognition is also acceptable as a single primary efficacy outcome measure in early AD patients. FDA encourages the development of novel approaches to the integrated evaluation of subtle functional impairment that arise from early cognitive impairment (e.g., facility with financial transactions, adequacy of social conversation).

In early Stage 3 AD (which may be difficult to distinguish from late Stage 2 AD), FDA will consider strong justifications that a persuasive effect on cognition as measured by sensitive neuropsychological tests may provide adequate support for a marketing approval. It would generally be expected that such effects on cognitive measures would be supported by similarly persuasive effects on the characteristic pathophysiological changes of AD, and positive trends on functional outcome assessments. As previously described, a time-to-event analysis approach could also be considered (see section IV. B.). Whether effects on cognitive outcome measures would, in the absence of a meaningful change in function, support either traditional or accelerated approval would require detailed discussion with the Agency.