Early Alzheimer's Disease: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)
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Contains Nonbinding Recommendations

Draft — Not for Implementation

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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 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This guidance revises the draft guidance for industry *Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease* issued in February 2013.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.