Guidance for Industry

Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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 http://www.regulations.gov. Submit written comments to the Division of Dockets Management (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 Nicholas Kozauer at 301-796-2250.

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

February 2013
Clinical/Medical

Guidance for Industry

Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
Tel: 301-796-3400; Fax: 301-847-8714; E-mail: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

February 2013
Clinical/Medical

TABLE OF CONTENTS

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

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of the various stages of Alzheimer's disease (AD) that occur before the onset of overt dementia.[2] Specifically, this guidance addresses the FDA's current thinking regarding the selection of patients with early AD, or patients who are determined to be at risk of developing AD, for enrollment into clinical trials. The guidance also addresses the selection of endpoints for clinical trials in these populations, as well as the manner in which disease modification might be demonstrated. This draft guidance is intended to serve as a focus for continued discussions among representatives of the Division of Neurology Products, pharmaceutical sponsors, the academic community, and the public.[3] The design of clinical trials that are specifically focused on the treatment of patients with established Alzheimer's disease dementia (i.e., dementia of the Alzheimer's type), or any of the autosomal dominant forms of AD, is not explicitly discussed, although many of the principles in this guidance will be pertinent.

FDA's guidance documents, including this guidance, 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 Division of Neurology Products in the Center for Drug Evaluation and Research (CDER) 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 a given drug product.

II. BACKGROUND

The diagnosis of AD for the purpose of clinical trial enrollment is generally based on consensus diagnostic criteria developed by the National Institute of Neurologic and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (now the Alzheimer's Association) that were proposed in 1984. These criteria are clinical in nature (with the exception of the diagnosis of definite AD that also requires histopathologic confirmation via autopsy or, rarely, brain biopsy) and require that patients must exhibit impairments in both cognitive and functional domains. Therefore, the NINCDS-ADRDA criteria restrict themselves to the diagnosis of patients in the dementia stage of AD where functional impairment must be evident by definition.

The underlying anatomical and pathophysiologic changes in AD begin many years before clinical symptoms emerge. A variety of biomarker measures have shown some promise with respect to their ability to reflect reliably the biological hallmarks of AD well before there is any evidence of clinical impairment. Levels of β-amyloid and tau proteins in the brain and cerebrospinal fluid, as well as markers of neuronal degeneration, are among the leading candidates in this respect. In the earliest clinical stages of AD, subtle cognitive deficits may be evident only through use of sensitive measures of neuropsychological performance. Thereafter, but before developing overt dementia, patients proceed through a clinical phase where cognition becomes increasingly affected and relatively mild but detectable impairments in some functional abilities emerge as well (sometimes referred to as mild cognitive impairment (MCI)). The development of drugs for the treatment of AD has increasingly focused on this entire range of disease states that occur before the onset of overt dementia because the benefits of a disease-modifying therapy are presumed to be the greatest in these stages, although no drugs have yet been shown to be effective in such populations.

We recognize that the standard approaches to the selection of outcome measures historically used in the development of treatments for dementia of the Alzheimer's type have major limitations when applied to clinical trials enrolling patients in the early clinical stages of the disease, or before clinical impairment has emerged at all. This guidance addresses some possible adaptations of the current approach to drug development for the treatment of the dementia stage of AD that appear more appropriate for clinical trials in the early stages of the illness.

III. DIAGNOSTIC CRITERIA FOR EARLY ALZHEIMER'S DISEASE

The diagnosis of MCI, particularly the amnestic subtype, has often been used to identify patients in the early stages of AD, although not all patients with this diagnosis progress to develop dementia. In recent years, the research community has actively sought to develop improved diagnostic guidelines for the accurate identification of these patients, primarily through the incorporation of various biomarker-based criteria into their framework (i.e., to add anatomic evidence to the somewhat uncertain characterization of MCI). Leading examples of such efforts are the research criteria for *prodromal AD*, published by the International Working Group for

New Research Criteria for the Diagnosis of AD (Dubois, Feldman, et al. 2010), and *MCI due to AD* by a National Institute on Aging — Alzheimer's Association working group (Albert, DeKosky, et al. 2011).

Research diagnoses such as *preclinical AD* have also been developed by these same groups in an attempt to identify patients even earlier in the disease continuum who are considered at-risk for developing AD dementia because of the presence of certain AD biological hallmarks. Although these criteria rely primarily on the presence of biomarker changes, they also allow for the use of sensitive (albeit yet undeveloped) clinical measures to detect subtle evidence of cognitive decline.

We acknowledge that many similarities exist between the leading diagnostic guideline proposals for the earliest stages of AD, and we support the concept of enriching trial populations with patients most likely to progress to more overt dementia, using both clinical and biomarker-based criteria. However, the need for an assessment of sensitivity and specificity in identifying patients who do have actual AD in clinical trials, as well as for the validation of the respective component methodologies (e.g., the selection of appropriate cut-points, assessment of assay variability), does not allow the FDA to formally endorse any specific diagnostic frameworks at this time.

IV. CLINICAL OUTCOME MEASURES

A. General Comments

Clinical trials in the dementia stage of AD should use a co-primary outcome measure approach in which a drug demonstrates efficacy on both a cognitive and a functional or global assessment scale. The intent of this dual measurement is to ensure the clinical meaningfulness of a cognitive benefit that may be observed. Before the onset of overt dementia, however, milder functional and/or global impairments become more challenging to assess accurately, especially for patients early in the spectrum of the illness. Therefore, although the principle behind the co-primary outcome measure approach still holds, the application of this approach in practice may be impractical in these cases and clear evidence of an effect on delaying cognitive impairment may provide sufficient evidence of effectiveness.

The following subsections specifically address potential strategies for demonstrating clinical efficacy in trials conducted in patients in the early stages of AD. We also acknowledge that many sponsors are seeking to develop drugs for the treatment of AD that have the ability to modify the course of the underlying disease process. Section V of this guidance addresses how a sponsor may support an argument that a clinical efficacy benefit is the result of disease modification.

B. Clinical Measures That Combine Assessments of Cognition and Function

Patients on the AD continuum closest to the onset of overt dementia (i.e., prodromal AD or MCI due to AD) are likely to have relatively mild but noticeable impairments in their daily functioning. It is therefore important to demonstrate that a drug favorably affects these deficits,

in addition to showing an improvement in cognition, to establish the clinical value of a given treatment. However, because many of the assessment tools used to measure functional or global impairment in patients with dementia have not been validated for use in these early stage patients, we consider the use of a composite scale, validated in early stage patients to assess both cognition and function as a single primary efficacy outcome measure, to be appropriate. The Clinical Dementia Rating scale, specifically the Clinical Dementia Rating – Sum of Boxes (CDR-SB) score, is an example of a suitable tool. The CDR-SB is a widely used scale that has demonstrated validity and reliability in the longitudinal assessment of patients with cognitive and functional deficits that do not rise to the level of a diagnosis of overt dementia. Additional assessment scales also may be appropriate for use in clinical trials in this population and we are open to considering other such proposals as well.

C. Isolated Cognitive Measures

We recognize that it is desirable to demonstrate efficacy in the earliest clinical stages of AD (i.e., preclinical AD) where only subtle cognitive deficits are present in the absence of any detectable functional impairment. In these cases, it would be difficult to establish a clinical consequence of any cognitive benefit during the course of a trial of reasonable duration. Assuming that these patients can be reliably identified, we can use the accelerated approval mechanism (21 CFR 314.510) to consider an effect on a valid and reliable cognitive assessment used as a single primary efficacy measure as support for a marketing approval.[4] Following the initial approval, a sponsor would then be required to demonstrate, in additional adequate and well-controlled studies or continuation of the initial studies, that the observed benefit persists and positively affects the overall course of a patient's condition.[5]

D. Time to a Dementia Diagnosis

The use of a time-to-event survival analysis approach (e.g., time to a diagnosis of dementia) is a particularly appealing primary efficacy measure in clinical trials in early AD. For practical reasons, trials designed with this endpoint have been generally conducted in the stages of the illness nearest to the onset of dementia (i.e., MCI). Sponsors may, however, find the use of a single composite scale that assesses both cognition and function in these patients more attractive because it presumably would allow for trials of a shorter duration and smaller sample size. The composite approach also circumvents the inherent challenges of applying a dichotomous time-to-event analysis to two disease stages that in actuality exist on a continuum.

[4] Accelerated approval allows the FDA to grant the marketing approval of certain drugs based on an effect on a clinical endpoint that is reasonably likely to predict the ultimate clinical outcome of interest (e.g., persistent improvement in cognition).

[5] See § 314.510.

V. DEMONSTRATING DISEASE MODIFICATION

A. General Comments

As already noted, we acknowledge that many sponsors are seeking to develop drugs that will alter the course of AD through a direct effect on the underlying disease pathophysiology (i.e., that will provide more than an improvement in cognition and functioning). Although it is tempting to consider a demonstration of a divergence of slopes (change with respect to time) between treatment arms on a given clinical outcome measure as evidence of disease modification in AD, we have concerns that a pharmacologically reversible effect that increases over time could also lead to such an outcome. It may be possible, however, that a claim of disease modification could be supported by evidence of a meaningful effect on a biomarker in combination with a clinical benefit, or through the use of a clinical trial design suited to demonstrate a lasting effect on the disease course. Both of these approaches are outlined in more detail below.

B. The Role of Biomarkers

1. Use of Biomarkers as Single Primary Outcome Measures

The approval of a drug for the treatment of AD based on the use of a biomarker as a single primary surrogate efficacy measure can be considered under accelerated approval. However, no reliable evidence exists at the present time that any observed treatment effect on such a measure is reasonably likely to predict ultimate clinical benefit (the standard for accelerated approval), despite a great deal of research interest in understanding the role of biomarkers in AD. Until there is widespread evidence-based agreement in the research community that an effect on a particular biomarker is reasonably likely to predict clinical benefit, we will not be in a position to consider an approval based on the use of a biomarker as a surrogate outcome measure in AD (at any stage of the illness).

2. Use of Biomarkers as Supportive Secondary Outcome Measures

We are open to considering the argument that a positive biomarker result (generally included as a secondary outcome measure in a trial) in combination with a positive finding on a primary clinical outcome measure may support a claim of disease modification in AD. For this to be the case, however, there should be widespread evidence-based agreement in the research community that the chosen biomarker reflects a pathophysiologic entity that is fundamental to the underlying disease process.

There is currently no consensus as to what particular biomarkers would be appropriate to support clinical findings in trials in early AD. For this reason, we recognize that 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. Therefore, we encourage sponsors to analyze the results of these biomarkers independently 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 new drug application or biologics license application submission.

213
214 **C. Alternative Trial Designs**
215
216 As already noted, we have not yet reached a conclusion that a comparison of the rate of change
217 in key clinical efficacy parameters (based on slopes) between active treatment and control
218 groups, using a standard parallel-arm study design, could provide the sole support for a claim of
219 disease modification. A randomized-start or randomized-withdrawal trial design (with clinical
220 outcome measures) appears to be a more convincing means of demonstrating such an effect. For
221 ethical reasons, a randomized-start design would be most appropriate for use in AD. In this
222 study design, patients are randomized to drug and placebo, and at some point, placebo patients
223 are crossed over to active treatment. If patients in the trial who were initially on placebo then
224 assigned to active treatment fail to *catch up* (after a reasonable period of time) to patients who
225 received active treatment for the entire duration of the trial, a disease modifying effect of
226 treatment would have been shown. We are unaware of any instances to date where this design
227 has been successfully used in a clinical trial to establish a disease modifying effect.
228

REFERENCES

Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, and Phelps CH, 2011, The Diagnosis of Mild Cognitive Impairment due to Alzheimer's Disease: Recommendations From the National Institute on Aging — Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease, *Alzheimer's Dement*, 7(3):270-9.

Albert MS, Moss MB, Blacker D, Tanzi R, and McArdle J, 2007, Longitudinal Change in Cognitive Performance Among Individuals With Mild Cognitive Impairment, *Neuropsychology*, 21(2):158-169.

Berg L, Miller JP, and Storandt M, 1988, Mild Senile Dementia of the Alzheimer Type, 2: Longitudinal Assessment, *Ann Neurol*, 23(5):477-484.

Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, Barberger-Gateau P, Delacourte A, Frisoni G, Fox NC, Galasko D, Gauthier S, Hampel H, Jicha GA, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Sarazin M, de Souza LC, Stern Y, Visser PJ, and Scheltens P, 2010, Revising the Definition of Alzheimer's Disease: A New Lexicon, *Lancet Neurol*, 9(11):1118-27.

Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, and Scheltens P, 2007, Research Criteria for the Diagnosis of Alzheimer's Disease: Revising the NINCDS-ADRDA Criteria, *Lancet Neurol*, 6(8):734-46.

Hughes CP, Berg L, Danziger WL, Coben LA, and Martin RL, 1982, A New Clinical Scale for the Staging of Dementia, *Br J Psychiatry*, 140:566-572.

Jack CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, and Trojanowski JQ, 2010, Hypothetical Model of Dynamic Biomarkers of the Alzheimer's Pathological Cascade, *Lancet Neurol*, 9(1):119-28.

Lynch CA, Walsh C, and Blanco A, 2006, The Clinical Dementia Rating Sum of Box Score in Mild Dementia, *Dement Geriatr Cogn Disord*, 21(1):40-43.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, and Stadlan EM, 1984, Clinical Diagnosis of Alzheimer's Disease: Report of the NINCDS-ADRDA Work Group Under the Auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease, *Neurology*, 34:939-44.

Petersen RC, 2004, Mild Cognitive Impairment as a Diagnostic Entity, *J. Intern. Med.*, 256:183-194.