

# The Long and Winding Road Toward Alzheimer Prevention

## *FDA offers new guidance on developing drugs for early-stage AD; seeks input*

BRIAN R. OTT, MD

DIRECTOR, ALZHEIMER'S DISEASE & MEMORY DISORDERS CENTER, RHODE ISLAND HOSPITAL

ON FEBRUARY 7, 2013, the U.S. Food and Drug Administration (FDA) issued a "guidance for industry" proposal titled, "Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease."<sup>1</sup> An accompanying press release<sup>2</sup> stated that, "This proposal is part of U.S. Department of Health and Human Services' (HHS) efforts under the National Plan to Address Alzheimer's Disease,<sup>3</sup> which calls for both the government and the private sector to intensify efforts to treat or prevent Alzheimer's and related dementias and to improve care and services. It responds to recommendations from a May 2012 HHS and National Institutes of Health Alzheimer's research summit to conduct clinical trials in at-risk individuals without symptoms and to develop and validate new measures so that Alzheimer's can be measured at the earliest possible time in the course of the disease."

At the core of the FDA guidance are proposals that a drug for Alzheimer's disease (AD) can be approvable based on relatively new criteria.<sup>4</sup> Typically to get approval for a treatment for AD, a pharmaceutical company must provide evidence from two separate large-scale clinical trials showing safety as well as efficacy on both a cognitive and a functional or global assessment scale. This approach, however, can't be practically applied to interventions aimed at treating patients at a very early or preclinical stage of their illness, when there is little if any functional impairment in daily living to improve. For clinical trials



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targeting prodromal AD or mild cognitive impairment (MCI), the guidance suggests that a composite measure that includes both cognition and function may be appropriate as a single primary outcome measure. For clinical trials targeting preclinical AD, since by definition there is no functional impairment

to assess, initial approval could be made upon demonstration of significant reduction in decline on a valid and reliable cognitive measure. Given the current state of our knowledge about AD biomarkers, these types of additional tests may provide supportive evidence of a "disease modifying" effect but could not be used as a surrogate primary efficacy measure at any stage.

There is now a wealth of research supporting the view that the pathology of Alzheimer's begins decades before the onset of symptoms, with amyloid deposition being the most widely recognized biomarker of the early pathologic cascade. With the help of insights gained from large longitudinal biomarker and brain imaging studies like the Alzheimer's Disease Neuroimaging Initiative, it is now possible to design prospective clinical trials whose goal is primary or secondary prevention of AD. The implications for controlling AD are substantial. It has been estimated that a treatment breakthrough that delays the age of onset of AD by five years would reduce the prevalence in Americans age 65 and older from 10 percent to 7 percent in 2020, and from 16 percent to 9 percent in 2050.<sup>5</sup>

Efforts to carry out studies using

conversion to AD as an endpoint, however, are limited in their power by the fact that AD is a disease that steadily progresses from a long asymptomatic period through a symptomatic period on a continuum rather than in discrete stages. The FDA guidance wisely proposes that future studies demonstrate change in the rate of cognitive decline as the clinical outcome rather than delay to conversion to disease stage. This should allow for trials of shorter

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duration and smaller sample sizes, two factors of major importance for the feasibility of prevention designs.

Despite such advances in our understanding of AD pathogenesis and clinical trial designs, unfortunately amyloid-modifying clinical trials to date have been unsuccessful. The past year has witnessed announcements that two large-scale, multicenter, multi-trial programs using anti-amyloid antibodies failed to show differences from placebo on prespecified endpoint analyses of cognition and function in patients with mild to moderate AD. Secondary analyses of one of these agents, solanezumab, however, suggest that a significant effect on slowing cognitive decline occurred for the milder cases, sparking hopes that this approach may be more effective when applied to upcoming trials enrolling subjects with prodromal or preclinical AD.

## Considerations

So the question arises whether a drug or biological agent should be approved for early treatment of AD if it shows significant effects on highly sensitive cognitive measures, supported by effects on biomarkers of the disease such as cerebrospinal fluid amyloid and tau levels or amyloid PET, in the absence of a global or functional outcome. The FDA guidance provides a potential roadmap to such approval, prompting some concern that approval based on marginal effects on sensitive disease markers in the end may be very costly, along with producing adverse effects in some people, without providing the clinically significant outcome of delaying the onset of dementia.<sup>6</sup> There are checks and balances that should preclude a premature rush to approval. First of all, approval of new therapies requires consideration of risks as well as benefits, and the balance of these two would no doubt be thoroughly weighed in FDA deliberations. The guidance states that even if a drug for slowing disease progression at the preclinical stage were to get initial accelerated approval based on demonstration of significant effects on cognition, the pharmaceutical company would still have to continue with longer-term studies to prove benefits in the overall course of patients with AD.

## Costs, reimbursement

Furthermore, if a new treatment is approved by the FDA, there is no guarantee that insurance carriers would agree to pay for such treatments, based on their own cost/benefit analyses. An example of potential progress in AD care that is currently bogged down by such cost-effectiveness considerations is the recently approved Amyvid® (florbetapir) PET imaging agent. On April 10, 2012, this imaging agent was approved for clinical use by the FDA, yet it is still not covered by Medicare and other insurers. On January 30, 2013, a panel convened by the Centers for Medicare & Medicaid Services recommended against coverage of

amyloid PET, citing only “intermediate” confidence that results affect health outcomes. While a final decision on whether to cover AV-45 amyloid PET will not take place until July, based on the panel’s review, a negative response is expected, while it awaits results of ongoing research studies aimed specifically at demonstrating significant effects on clinical decision making.

Overall, the recent FDA guidance on development of AD drugs has been welcomed by researchers in the field, because it provides a scientifically reasonable roadmap to at least weigh the evidence that will be coming from upcoming clinical trials of potentially disease-modifying therapies. The new day is dawning when a more enlightened approach to dealing with the huge and impending problem of AD is becoming a reality. In this regard, Rhode Island physicians will be interested to know that the Lieutenant Governor’s office in concert with the Department of Elderly Affairs is having regular meetings with health care professionals as well as town meetings with community members to design a statewide plan for AD care as part of the national AD plan. Interested people should contact Lindsay McAllister, Esq, Director of Health Policy, Office of the Lt. Governor, 82 Smith Street, Providence, RI 02903-1105; 222-2371, [lmcallister@ltgov.state.ri.us](mailto:lmcallister@ltgov.state.ri.us).

Also, by the end of this year, a multicenter secondary AD-prevention trial, called Anti-amyloid Treatment in Asymptomatic Alzheimer’s Disease (A4), will be starting. In this study 1,000 people at risk for developing dementia of the AD type by virtue of having a positive amyloid PET scan will be assigned to placebo vs. solanezumab anti-amyloid antibody infusions and followed for three years for evidence of reduced cognitive decline along with effects on biomarkers. People interested in prevention trials such as A4 can enroll now in the Rhode Island Alzheimer Prevention Registry (“Prevent AD”) by calling 401-444-0789 or

emailing to [memory@lifespan.org](mailto:memory@lifespan.org). In addition to being notified about current and upcoming prevention trials, registry participants receive quarterly newsletters about the latest news in brain health.

The FDA is seeking public comment on the draft guidance for 60 days. Instructions on how to submit comments are included in a Federal Register notice.

## References

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## Author

Brian R. Ott, MD, is a professor of neurology at The Warren Alpert Medical School of Brown University.

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## Correspondence

Brian R. Ott, MD  
Alzheimer’s Disease & Memory Disorders Center  
Rhode Island Hospital – APC 7  
593 Eddy Street, Providence RI 02903  
401-444-6440  
Fax 401-444-6858  
[BOtt@lifespan.org](mailto:BOtt@lifespan.org), [BOtt@brown.edu](mailto:BOtt@brown.edu)