

May 17, 2018

Billy Dunn, M.D.
Center for Drug Evaluation and Research,
Food and Drug Administration,
10903 New Hampshire Ave.,
Bldg. 22, Rm. 4339,
Silver Spring, MD 20993-002

RE: [Docket No. FDA-2013-D-0077] "Early Alzheimer's Disease: Developing Drugs for Treatment; Draft Guidance for Industry; Availability."

Dear Dr. Dunn,

The coalition to Accelerate Cure/Treatments for Alzheimer's Disease (ACT-AD) is comprised of more than 50 national organizations representing patients, caregivers, researchers, health professionals, and other health advocates. Our mission is to support efforts to expedite the development, review, and approval of transformational therapies for Alzheimer's disease.

ACT-AD appreciates the opportunity to comment on the February 2018 revised draft "Guidance for Industry on Early Alzheimer's Disease: Developing Drugs for the Treatment" and on behalf of the coalition, we would like to thank you for issuing this guidance at a critical time. We would also like to thank you in advance for considering our comments and through this process will help our members with drug development programs and the future of research in this field.

- We appreciate the division's clarification on the co-primary endpoint approach. This guidance clarifies that cognition as an entity is meaningful, but the existing assessments used to measure changes in cognitive domains may not be able to demonstrate clinical meaningfulness. It is the method of assessment that must be further developed for the measure to yield meaningful results regardless of functional measures. We support public and private efforts to prioritize development of better cognitive measures.
- For Stage 1, ACT-AD supports the use of biomarkers to measure pathophysiological changes as a primary efficacy measure and its use as a basis for accelerated approval. The draft guidance finds "at present no sufficiently reliable evidence that any observed treatment effect on such biomarker measures would be reasonably likely to predict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)." We support FDA's fervent plea for continued research on biomarkers as a basis for successful clinical development. The lack of data to fully evaluate the predictive ability of biomarkers is discouraging for the entire Alzheimer's disease research field. We hope the National Institutes of Health and other public health organizations continue to prioritize the development of biomarkers for Alzheimer's disease after reading this draft guidance. Additionally, the call for a persistent treatment effect on disease course is valid, and we understand the candid appraisal of existing biomarkers as currently insufficient for predicting clinical benefit.
- For Stage 2, it would be elucidating if the guidance included the characteristics and features of independent measures of cognition and function or integrated scales that the agency would constitute as "sensitive measures of neuropsychological performance." This suggestion comes with the understanding that examples provided in the final guidance are merely illustrative and do not ensure approval.

- For Stage 3, we note the call for clinically meaningful measures, either independent measures of cognition and function, or an integrated scale. It would be informative to have more detail on characteristics of tests that are not considered clinically meaningful measures of cognition or function (the “word-list recall test” is mentioned for cognition, but that is the only example, and nothing is offered for function). We understand clinical meaningfulness is not simply defined, but this is a consistent query from sponsors and more detail will be effectual toward designing programs aligning with the new thinking of the Agency. We understand the FDA will not advocate for a test, but the more detail the agency can provide on this point will be helpful to the field.
- ACT-AD requests clarification on the section alluding to subjective complaints from subjects reporting a change in cognition and behavior. This mostly occurs in Stage 3, but it might also occur in late Stage 2, with subtle changes like difficulty balancing a checkbook or subtle changes in behavior like reduced interest and increased apathy.
- Combination therapy may be necessary for the effective treatment of Alzheimer’s disease. Guidance for this treatment approach would be valuable as sponsors consider the study design components for these types of trials. The ACT-AD coalition requests the finalized version of the guidance include the FDA’s considerations and recommendations on a multi-drug approach in clinical trials for early stage Alzheimer’s disease.
- Many ongoing and future studies in Alzheimer’s disease will include patient populations spanning multiple stages of the disease. We request the FDA provide guidance on studies in which it is expected the majority of patients move through the continuum of the disease while enrolled in a trial.
- While the focus of the guidance is on early stage Alzheimer’s disease, it would be helpful if the FDA provided guidance on studies with patient populations in Stage 3 and Stage 4. We propose Stage 4 should be included in the scope of this guidance with similar outcome measure expectations as Stage 3. Patients in Stage 3 or Stage 4 can be difficult to clinically differentiate, particularly in research populations using cognitive or functional measure. The overlap between these populations is underscored by ongoing research combining both Stage 3 and Stage 4 patients. As such, within a study, a common primary outcome should be applied to the entire population.

We want to recognize FDA for its leadership in issuing guidance that opens to door to earlier treatment of Alzheimer’s disease and begins to clear a path for more effective drug development in the future. Thank you for your careful consideration of the points expressed above and if ACT-AD can be of assistance to the division as it considers revisions to the draft guidance, please contact Ryne Carney on the coalition staff at rcarney@agingresearch.org or (202) 293-2856.

Sincerely,

Alliance for Aging Research

Alzheimer’s Drug Discovery Foundation

Alzheimer’s Foundation of America

American Association for Geriatric Psychiatry

American Federation for Aging Research

Anavex Life Sciences Corp.

Biogen

Brain Injury Association of America

BrightFocus Foundation

Cognition Therapeutics

Cure Alzheimer's Fund

Eli Lilly & Company

Gerontological Society of America

Global Coalition on Aging

HealthyWomen

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