DEPARTMENT OF HEALTH & HUMAN SERVICES PUBLIC HEALTH SERVICE

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: March 10, 2015

ATTN: Diane Stephenson, Ph.D.
Executive Director, Coalition Against Major Diseases (CAMD)
Critical Path Institute
1730 E River Rd.
Tucson, Arizona 85718

Subject: Biomarker Letter of Support

Dear Dr. Stephenson:

We are issuing this Letter of Support to the Critical Path Institute's Coalition Against Major Diseases (CAMD) to encourage the further study and use of low baseline hippocampal volume (HV) measured by magnetic resonance imaging (MRI) as an exploratory prognostic biomarker for enrichment in clinical trials for Alzheimer's disease (AD).

The current view is that early intervention in Alzheimer's disease may be essential to achieve a large treatment benefit. This concept is clearly recognized by FDA in the 2013 Draft Guidance for Industry, entitled "Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease."[1] Identifying patients with Mild Cognitive Impairment (MCI) that are likely to develop further cognitive impairment within the time frame of a clinical trial could lead to therapies that have greater impact on the disease. Scientific evidence supports the view that the earliest biomarker changes may precede the onset of clinical symptoms.

We support CAMD's proposed study of HV measured by MRI as an exploratory biomarker to identify patients likely to have progression of their MCI symptoms during the course of a clinical trial. CAMD's literature review and preliminary data suggest that the extent of hippocampal atrophy as demonstrated on volumetric MRI, along with clinical diagnostic criteria and other covariates, may provide evidence of neurodegeneration early in Alzheimer's disease, predict clinically relevant cognitive deterioration trajectories, and help predict development of dementia in patients with MCI. Patients with less hippocampal atrophy appear less likely to show clinically-relevant cognitive deterioration over the course of a clinical trial of reasonable duration. Likewise, inclusion of these patients may dilute the potential to observe statistically significant beneficial effects of novel therapeutic agents. Such application is consistent with the FDA's draft guidance "Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products."[2] Greater experience with the use of HV as a neuroimaging biomarker in clinical trials may be useful to more accurately determine its clinical utility for prognostic enrichment, drug development decisions, and study design considerations.

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[1] http://www.fda.gov/RegulatoryInformation/Guidances/
[2] *Ibid.*

No specific hippocampal image analysis algorithm is endorsed by FDA. Because the analysis algorithm may introduce uncertainty in the hippocampal volume measurement, strong emphasis on applying good scientific, laboratory, and software development practices for quality control and validation of the specific hippocampal volume measurement algorithm is imperative. Furthermore, the adoption of standardized MRI acquisition protocols including phantom-based quality control and data standards are strongly encouraged to facilitate future analyses across studies. We are aware that the CAMD team is currently aligning with other consortia focused on standardization of hippocampal volume measures and planning the integration of additional biomarker data to support qualification in the future.

We encourage exploration of the possible use of low baseline hippocampal volume (as measured by MRI) to identify patients likely to show clinical progression of their MCI symptoms for the purpose of clinical trial enrichment. We will consider data collection on this biomarker to be exploratory in nature. When including this biomarker in clinical trials, sponsors are encouraged to employ consensus AD Clinical Data Interchange Consortium (CDISC)[3] standards for data harmonization. We believe data sharing and integrating data across trials can foster an accelerated path for AD drug development programs. If sponsors intend to include analyses of this biomarker to support regulatory decision making for a given Investigational New Drug (IND) development program, they should prospectively discuss the approach to these analyses with the Division of Neurology Products in CDER.

Any groups (academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Dr. Diane Stephenson (dstephenson@c-path.org), the CAMD point of contact for this project, or view the Critical Path Institute website.

Sincerely,

Janet Woodcock, M.D.

Director, CDER

U.S. Food and Drug Administration

[3] http://www.cdisc.org/therapeutic#alzheimers