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: February 26, 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 cerebrospinal fluid (CSF) analytes $A\beta_{1-42}$, total tau, and phosphotau, as exploratory prognostic biomarkers for enrichment in trials for Alzheimer's disease (AD).

The current consensus view in the field of AD is that early intervention may be essential to demonstrate clinically-relevant disease modification. This concept has been recognized by FDA in the 2013 Draft Guidance for Industry "Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease."[1] Identifying patients with Mild Cognitive Impairment (MCI)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. Strong scientific evidence appears to support the view that the earliest biomarker changes precede the onset of clinical symptoms

We support CAMD's proposed study of these exploratory CSF biomarkers to identify patients likely to have progression of their MCI symptoms during the course of a clinical trial. Baseline levels of these CSF biomarkers, along with clinical information, could be helpful as inclusion criteria for enrollment in AD clinical trials. Likewise, since biomarker-negative patients appear less likely to show clinically-relevant cognitive deterioration over the course of Phase 2 and Phase 3 clinical trials, inclusion of biomarker-negative 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 Such application is consistent with the FDA's draft guidance "Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products."[1]

CAMD's literature review and preliminary data describe the profile of these CSF biomarkers in MCI patients. CSF levels of $A\beta_{1-42}$, total tau, and phosphotau represent body fluid-derived biomarkers that may serve as indices of changes in brain pathology that occur in very early stages of AD. This information (along with additional patient factors) suggests that these biomarkers may have value in predicting the trajectory of the disease. Furthermore, reduced CSF $A\beta_{1-42}$, either alone

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

or in combination with increased CSF total tau and phosphotau, may predict the subsequent development of overt dementia in patients with MCI. Greater experience with the use of these exploratory biomarkers in clinical trials is needed to more accurately determine their clinical utility for prognostic enrichment, impacting drug development decisions and study design considerations.

No specific CSF biomarker test system or assay validation process is endorsed by FDA. Strong emphasis on the application of good scientific and quality control laboratory practices of the assay test system is imperative. The reference method for standardization should be described and the assay platform's performance characteristics with respect to the dynamic range, limit of detection, analytical specificity (selectivity, exclusivity, inclusivity), precision, lot-to-lot variability and reproducibility should be established in advance of analysis of clinical trial data. We support the development of standardized methods for sample collection, handling, and storage to improve reproducibility and reliability in ongoing and prospective clinical trials. We are aware that CAMD is currently aligning with other consortia focused on standardization of CSF biomarker assays.

We encourage the inclusion of these exploratory CSF biomarkers in clinical trials to evaluate their clinical utility for identifying patients likely to show clinical progression of their MCI symptoms for the purpose of clinical trial enrichment. We consider data collection on this biomarker to be exploratory in nature. When including these biomarkers in clinical trials, sponsors are encouraged to employ consensus AD CDISC[2] standards for data harmonization. We believe that sharing and integrating data across trials can foster an accelerated path for AD drug development programs. If sponsors intend to include analyses of these biomarkers to support regulatory decision making for a given IND drug development program, they should prospectively discuss 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. Dianne 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

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