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 16, 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 molecular neuroimaging of the dopamine transporter (DAT) as an exploratory prognostic biomarker for enrichment in trials for Parkinson's disease (PD).

Significant challenges exist in assessing the effects of therapies in patients with early PD based upon clinical evaluations alone. Because the early symptoms of PD are subtle and gradually progressive, early identification of patients likely to develop PD could facilitate drug development programs and could lead to therapies that have greater impact on the disease. Patients with PD have a progressive loss of DAT that can be assessed by single-photon emission computed tomography (SPECT) neuroimaging. In conjunction with clinical assessments, reduction in DAT may serve as an exploratory prognostic biomarker to help identify patients with increased likelihood of having progression of their PD symptoms. The goal is to enrich PD clinical trials by reducing the enrollment of patients who are less likely to show clinical disease progression. Exclusion of patients without evidence of dopamine deficit may improve statistical power and target the patients most likely to respond to 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 Such application is consistent with the FDA's draft guidance "Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products."[1]

We support CAMD's proposed study of DAT as an exploratory prognostic biomarker for identification of patients for enrollment in PD clinical trials. DAT levels can be measured by FP-CIT ([^{123}I]N-omega-fluoropropyl-2β-carbomethoxy-3β-{4-iodophenyl}nortropane, DaTscan™, GE Healthcare), a SPECT ligand approved for use in a clinical setting by both the FDA and EMA. Reduction in DAT assessed by DaTScan neuroimaging in patients with parkinsonian syndromes may precede the onset of clinical symptoms. Patients presenting with two or more motor signs of PD, plus reduction of DAT expression as visually assessed of DatScan™ SPECT images, may be more likely to progress clinically.

CAMD's literature review, preliminary data, and presented analysis plan suggest that this biomarker, in conjunction with clinical criteria (presence of at least two motor features characteristic of PD) and patient factors (baseline age, baseline disease severity, etc.) may be helpful to identify patients who are more likely to show symptomatic progression during the course of a clinical trial. Greater experience with the use of this exploratory biomarker in clinical trials is needed to more accurately determine its clinical utility for prognostic enrichment.

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

We encourage the use of this biomarker in clinical trials to evaluate its utility for the identification of patients likely to show clinical progression of Parkinson's motor symptoms. We will consider data collection on this biomarker to be exploratory in nature. When including this biomarker in clinical trials, sponsors will be encouraged to employ consensus PD Clinical Data Interchange Standards Consortium (CDISC) standards[2] for data harmonization. We believe that sharing and integrating data across trials can foster a more efficient path to biomarker qualification. If sponsors intend to include analyses of this biomarker to support regulatory decision making for a given IND drug development program, they should prospectively discuss their plan 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#parkinsons and http://www.commondataelements.ninds.nih.gov/PD.aspx#tab=Data_Standards