U.S. FOOD & DRUG ADMINISTRATION

LETTER OF INTENT
DETERMINATION LETTER
DDT-BMQ000114

June 4, 2021

David Vaillancourt, PhD
Professor and Chair
University of Florida
1864 Stadium Road
Gainesville, FL 32611

Dear Dr. Vaillancourt:

We are issuing this letter to notify you of our determination on the project submitted to the Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (BQP) on 2/1/2021 (BMQ000114). We have completed our review of the Letter of Intent (LOI) deemed reviewable on February 16, 2021 and have determined to accept the LOI into the CDER[1] Biomarker Qualification Program.

Your LOI submission proposes "Web-based Automated Imaging Differentiation of Parkinsonism" with the proposed COU:

> Differential diagnosis of PD, MSAp, and PSP which are forms of Parkinsonism. The use can be in clinical drug trials to diagnose patients for entry into study and/or enrich the cohort in the clinical drug trial.

Your next submission, a Qualification Plan (QP), contains details of the analytical validation plan for the biomarker measurement method, detailed summaries of existing data that will support the biomarker and its context of use (COU), and includes descriptions of knowledge gaps and how you propose they will be mitigated. If future studies are planned, please include detailed study protocols and the statistical analysis plan for each study as part of your QP submission.

Below, we provide you with specific considerations and recommendations to help improve your preparation for, and submission of the QP. As this biomarker development effort is refined, the submitted data, the specifics of your context of use (including the target patient population), and the design of study(ies) used in the clinical validation of the biomarker will

[1] In December, 2016, the 21st Century Cures Act added section 507 to the Food, Drug, Cosmetic Act (FD&C Act). FDA is now operating its drug development tools (DDT) programs under section 507 of the FD&C Act.

ultimately determine which of these considerations and recommendations are most applicable. For more information about your next submission and a QP Content Element outline, please see the BQP Resources for Biomarker Requestors web page.[2]

CONSIDERATIONS & RECOMMENDATIONS

1. Drug Development Need

Requestor's Drug Development Need Statements:

Parkinson's disease (PD), multiple system atrophy Parkinsonian variant (MSAp), and progressive supranuclear palsy (PSP) are neurodegenerative forms of Parkinsonism which can be difficult to diagnose as they share similar motor and non-motor features. Since the treatment, prognosis (often more rapid in atypical Parkinsonism), and pathology of these diseases differs, developing a biomarker to distinguish these disorders would be greatly beneficial for drug development and clinical trials.

We agree there is a need to improve diagnosis of PD, MSAp, and PSP to facilitate drug development for these diseases.

2. Biomarker Name & Description

The biomarker name is free-water and fractional anisotropy of human brain based on diffusion MRI (dMRI) and a machine learning algorithm, which shows anatomical structures of key regions in the basal ganglia, cerebellum, midbrain, thalamus, corpus callosum, and cortex.

2.1 As your biomarker development effort continues, please provide more specific descriptions of the anatomic structures and how the biomarker will be assessed (e.g., interpretation of individual findings or integration into a multi-component algorithm).

3.COU Considerations

We have the following suggestions for your proposed COU "Differential diagnosis of PD, MSAp, and PSP which are forms of Parkinsonism. The use can be in clinical drug trials to diagnose patients for entry into study and/or enrich the cohort in the clinical drug trial"

3.1 Please focus on one context that this tool is most useful (e.g. enrichment of cohorts) in clinical trials.
3.2 Please clarify how the AID-P tool might be used, either in combination with expert clinical impression or as a stand-alone diagnostic tool.

[2] https://www.fda.gov/drugs/cder-biomarker-qualification-program/resources-biomarker-requestors

4. Analytical Considerations

4.1 You should compare your imaging tool to standards of truth including autopsy examination and diagnosis by experts who follow patients prospectively for at least 2 years after their initial presentation of early symptoms.

4.2 If you are interested in using the AID-P as a diagnostic tool (i.e. clinical care outside of clinical trials), you may submit your application to our device center within FDA--- Center for Devices and Radiological Health (CDRH). You can engage CDRH in parallel to the biomarker qualification program.

4.3 Please describe the weights of the brain regions and tracts that lead to the categorization of the patients by AID-P. Do you expect the weights to be stable across the stages of the disease, demography of the patients, the acquisition system (i.e. MRI systems other than 3T) etc.?

5. Clinical Considerations

5.1 You should demonstrate AID-P can accurately differentiate parkinsonian syndromes in early stages of disease.

5.2 In the future, the clinical diagnosis should be determined using broadly accepted, disease-specific diagnostic criteria. The UPDRS Part III score (including the Movement Disorders Society update) is not intended to diagnose Parkinson's disease nor the other parkinsonian syndromes of interest.

5.3 You should address whether the tool can differentiate patients with variant forms of PSP and MSA from each other and from Parkinson's disease.

5.4 You should address whether AID-P can differentiate other neurodegenerative disorders that present with parkinsonism and/or cerebellar symptoms (e.g., Lewy body disease, spinocerebellar ataxias, Corticobasal syndrome and dementia [e.g. Alzheimer's disease]).

5.5 Describe whether cerebrovascular disease (e.g. subcortical and cortical ischemic disease, amyloid angiopathy and previous intracranial hemorrhage) would impact the accuracy of the AID-P tool.

5.6 Describe the potential impact of treatment with dopaminergic medications, for example levodopa products, might have on the accuracy of the AID-P tool.

6. Statistical Considerations

6.1 In the paper titled "Development and Validation of the Automated Imaging Differentiation in Parkinsonism (AID-P): A Multi-Site Machine Learning Study",

6.1.1 It described that age and sex variables were included in all analyses. Please specify all covariates to be considered in the new prospective study (U01 grant).

6.1.2 Supplementary table 1 shows that the study duration is over 10 years (December 2008 to November 2018). Please clarify if there was any major change in technology (or software of reading MRI) of dMRI which could make direct comparisons invalid.

6.1.3 Analytical Methods and Measurement Units section noted that two stages of the biomarker are used. The first stage is to differentiate PD vs Atypical Parkinsonism, and the second stage is to differentiate MSA vs PSP. Please clarify if subjects will go through the first stage and only those who are categorized to atypical parkinsonism will move to the second stage.

6.2 You noted that dMRI data are acquired using a 3 Tesla MRI machine including Siemens, Philips, or General Electric machines. Is there a machine-specific effect evaluated on generating dMRI data? If so, specify how it was managed in analyses.

6.3 In your qualification plan, please include the statistical analysis plan (SAP). The SAP should address statistical related comments mentioned above. Please provide detailed information of machine learning algorithm including the methodology, equations, program codes, etc. (i.e. full technical manual). Please also provide primary statistical analysis method and statistical criteria for showing biomarker's utility based on the one context of use you will pursue.

Please address each of the specific considerations and recommendations and any data requests cross-referencing the numbered list above in a separate addendum to your QP submission.

When evaluating biomarkers prospectively in clinical trials, requesters are encouraged to submit study data using Clinical Data Interchange Consortium (CDISC) standards to facilitate review and utilization of data. Data sharing and the capability to integrate data across trials can enhance biomarker development and utilization. If sponsors plan to use the biomarker prior to qualification to support regulatory review for a specific Investigational New Drug (IND), New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) development program, they should prospectively discuss the approach with the appropriate CDER or CBER division.

The BQP encourages collaboration and consolidation of resources to aid biomarker qualification efforts. Any individuals or groups (academia, industry, government) that would like to join in this effort, have information or data that may be useful can contact Dr. Vaillancourt.

Should you have any questions or if you would like a teleconference to clarify the content of this letter, please contact the CDER Biomarker Qualification Program via email at CDER-BiomarkerQualificationProgram@fda.hhs.gov with reference to DDT-BMQ000114 in the subject line. For additional information and guidance on the BQP please see the program's web pages at the link below.[3]

[3] https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/cder-biomarker-qualification-program

Sincerely,

Christopher L. Leptak -S

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Christopher Leptak, MD, PhD
Director, CDER Biomarker Qualification Program
Office of New Drugs
Center for Drug Evaluation and Research

Eric P. Bastings -S

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Date: 2021.06.04 09:43:24 -04'00'

Eric Bastings, M.D.
Division Director, Division of Neurology (DN I)
Office of Neuroscience, Office of New Drugs
Center for Drug Evaluation and Research

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov