LOI DECISION LETTER

DDTBMQ000093

March 17, 2020

James McPartland
Biomarkers Consortium ABC-CT Project Team
230 South Frontage Road New Haven, CT 06520

Dear Dr. McPartland,

We are issuing this Letter of Intent (LOI) Decision Letter to notify you of our decision on your proposed qualification project submitted to the Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (BQP). We have completed our review of your LOI submission of January 16, 2020 and have concluded to **Accept** it into the CDER BQP.[1] We support and encourage the study of biomarkers for autism spectrum disorder (ASD).

You have proposed qualification of Oculomotor Index of Gaze to Human Faces as a tool to reduce heterogeneity within the DSM-5[2] diagnosis of ASD for use in enrichment of clinical drug development trials. Based on our review of the LOI, we agree there is an unmet need, and the development of oculomotor index of gaze to human faces as a biomarker, with consideration of other clinical and demographic characteristics, may be helpful in clinical drug development trials.

As this biomarker development effort is refined in subsequent BQP submissions, the submitted data, the specifics of your context of use (including the target patient population), the specific analytics, and the design of the study(ies) used in the clinical validation of the biomarker will ultimately determine which of the comments below may be the most applicable to your qualification effort.

When you are prepared to make a submission to the next stage in the 507 drug development tool (DDT) qualification process, please prepare a Qualification Plan (QP) submission that addresses the scientific issues and the recommendations outlined below. A QP contains details of the analytical and software validation of the biomarker measurement method, detailed summaries of existing data that will support the biomarker and its context of use (COU), and 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. We have provided initial comments based on your LOI and hope these comments may be useful as you proceed with the preparation of your QP submission.

[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.

[2] American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub; 2013.

When evaluating biomarkers prospectively in clinical trials, sponsors 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 intend to include analyses of these biomarkers to support regulatory decision making for a specific Investigational New Drug (IND) development program, they should prospectively discuss the approach with the appropriate CDER division. 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. James McPartland (james.mcpartland@yale.edu), the primary point of contact for this project.

To better understand the benefits of the identified biomarker as a DDT, and to continue to refine the COU, please provide the information requested below in your QP submission. We acknowledge that some of the responses to questions and comments below may already be included in your publications or other publicly available resources, (such as the Epitope Registry or at www.epitopes.net). However, for completeness, we recommend that they be adequately summarized in the QP.

Biomarker Considerations

Requestor's Biomarker Description: *Oculomotor Index of Gaze to Human Faces ("Oculomotor Index")*

Atypical activity in brain circuitry in ASD, relative to TD, is reflected in reduced foveation to people. The Oculomotor Index was developed to quantify visual attention to human faces across three assays in an ET biomarker battery: Activity Monitoring (videos and images of two adults engaged in a shared play activity), Social Interactive Scenes (silent videos of two school-age children playing cooperatively or in parallel), and Static Social Scenes (naturalistic, static photographs of adults and/or children accompanied by a soundtrack). A composite was selected (versus metrics derived for individual assays) to capture interrelationships among multiple dependent variables and to reduce measurement error and context effects specific to any single ET assay. This allows us to measure a latent construct that may underlie performance differences both within and between groups. Lower Oculomotor Index scores reflect diminished attentional prioritization for human faces.

1. When thinking about expanding this eye-tracking setup into the field (i.e. a non-lab/ less controlled environment), please consider whether all three assays are necessary.

2. In your QP describe how the "latent construct that may underlie performance differences both within and between groups" is linked to a biological causal pathway that differs between the identified subgroup and the rest of ASD, as well as TD controls. Specifics on this requirement can be found in the clinical considerations section.

Context of Use (COU) Considerations

Requestor's COU: *Diagnostic enrichment biomarker, intended for stratification in clinical trials. It will be*

used, in conjunction with clinical and demographic characteristics, to obtain a subgroup with reduced DSM-5 ASD-associated heterogeneity.

FDA suggested COU for continued biomarker development: *Diagnostic biomarker to be used in conjunction with clinical and demographic characteristics to select a less heterogeneous subgroup within subjects with autism spectrum disorder (ASD) for clinical trial enrichment.*

1. As more information is known, please specify the "clinical and demographic characteristics" that will be used in conjunction with the oculomotor index biomarker for the purposes of diagnostic enrichment.

2. The proposed COU was updated in several ways. First, we removed the word "stratification," because you proposed to delineate a subgroup within a larger population, not to stratify the to-be- studied population. Second, we removed the DSM-5 specifier because diagnostic criteria change over time. Also, you describe reduced DSM-5 ASD-associated heterogeneity; however, there were no data to support that the identified subgroup has reduced heterogeneity in DSM-5 ASD symptoms compared to the entire sample. Therefore, we rephrased the statement about to reduced heterogeneity so as not to imply clinical heterogeneity.

3. It is important to demonstrate that the biomarker is accurate and reliable for the COU. Currently the proposed biomarker utility is "diagnostic enrichment"; however, it is possible that the type of enrichment could change to predictive or prognostic as you obtain more data and better define what differentiates the identified subgroup from other ASD patients and how this difference will be used in clinical trials.

Analytical Considerations

1. Is the eye tracking device to be used 510K cleared? If yes, please provide the 510K number.

2. Please provide the validated performance specifications for your eye tracker. It should include, but should not be limited to, the following specifications:

    a. Eye position sampling frequency
    b. Beam position adjustment frequency
    c. Acceptable tracking range
    e. Acceptable range of pupil diameters
    f. Maximum beam positional error during trackable eye movements

3. Please validate overall eye tracker performance with an eye movement simulation platform that can accurately reproduce actual eye movements recorded during your proposed test procedures.

4. Please demonstrate optical radiation safety for SR Eyelink 1000 Plus. For example, show compliance with optical radiation safety standard ANSI Z80.36:2016 for the duration of the measurements.

5. What are the soundtracks used for some of the assays (e.g., activity monitoring)? How does the combination of the selected visual and audio stimuli relate to ASD?

6. We note that an oculomotor index using eye-tracking is primarily a research tool and has not been validated for clinical use or subtyping of any conditions, including ASD. There are many environmental factors that can affect the eye-tracking data (e.g., vibrations in the surroundings, age, IQ, and movement). How do you plan to control for these environmental factors to ensure reproducibility of the experiments, especially outside of a well-controlled environment? Please see the clinical considerations section for suggestion of a field trial to support the ABC-CT lab trial data and the finding.

7. Section 507 of the FD&C Act includes transparency provisions that apply to your submission. Certain information about the analytical assay and software may be publicly posted if the biomarker is successfully qualified by the Agency. Please confirm technical parameters and other pertinent information about the assay and software that may be made public to ensure the biomarker can be used as a drug development tool by any interested party. The biomarker qualification process does not endorse the use of any specific device, assay, or software with a qualified biomarker.

Clinical Considerations

1. In the clinical considerations section, you state that "The intention is to use our complete dataset to obtain preliminary estimates of the cutoff score on the Oculomotor Index (or a series of scores based on covariates such as age or gender)." In your QP, please consider the following:

    a. Please explain how the data from typically developing controls will be used to inform a subgroup of the ASD patients in a clinical trial. Please detail how you plan to create standardized cutoff scores that will be meaningful in the clinical trial setting.

    b. What method will you use to determine which demographic and clinical covariates to include for use alongside the oculomotor index to create the final biomarker? The added information that these covariates provide will better refine how best to use the biomarker i.e., will it be a diagnostic, prognostic or predictive biomarker.

    c. Currently there are no clinical metrics to confirm the clinical meaningfulness of possible subgroups. How will you demonstrate construct validity of the mathematically derived subgroup? You need a better understanding of the biological plausibility (i.e., the biomarker's relationship to the clinical outcome of interest). In order to do this, you would need to identify and link the underlying biological and clinical characteristic of the identified subgroup. By integrating this information, you can reconstruct the causal pathway by which the subgroup differs from other ASD patients and predict how they will respond in a clinical trial. This knowledge is necessary for you to determine how to enrich the treatment groups in the trial.

2. The subgroup is based on the Oculomotor Index, which is described as a composite based on weighting of the three social scenes. The scenes take several minutes to view after setup and instruction and the assessment is completed in a specialized eye-tracking laboratory environment. It is unclear how practical it is to obtain the eye tracking data and high intraclass correlations in the real-world setting.

    a. Will weighting of the three scenes be part of the biomarker? If so, how will the weighting be determined? There may be a simpler approach than using all three scenes; for example, can the subgroup be determined using less data acquisition so that the time for testing is shorter in the field (e.g., testing with shorter scene lengths or only the static scene)?

    b. The research protocol is very extensive and implemented by highly trained research personnel. How will the protocol be updated for implementation in the clinical trial setting, keeping in mind the necessity of portability to clinical practice?

    c. A field study will be necessary to show reproducibility outside of a highly controlled laboratory setting (e.g., clinical trial setting vs. real-world clinical setting). In your QP please outline the study design for at least one field study and describe how it will be informed by the current eye-tracking laboratory design.

3. You mention "The Oculomotor Index can be interpreted as an index of severity of ASD neurobehavioral pathology, with lower scores indicating more severe neurobehavioral pathology." In your QP, please plan for and provide analyses demonstrating the correlation of the index to clinical severity. Do you anticipate that the ASD subgroup identified below the cutoff score will have a more severe form of ASD? How will you determine ASD severity?

4. The intention of the biomarker is to reduce heterogeneity of ASD within clinical trials. As you develop your QP:

    a. In your background justification, consider describing how the biomarker ties to an underlying mechanism that would be meaningful in clinical trials. For example, can the mechanism associated with the biomarker be linked to the pharmacological action of a drug?

    b. Please describe how you will use the biomarker to establish the subgroup for an individual study in the clinical trial setting, keeping in mind the need for real-world clinical translation.

    c. Explain how the Oculomotor Index or associated biomarkers would be used in clinical trials (e.g., an inclusion criterion based on cut-off scores).

    d. Describe what existing databases you plan to use to validate the subgroup as potentially meaningful for use in clinical trials. Also, see comments under statistical considerations.

    e. Consider linking the biomarker to a clinical outcome of relevance to the target population (e.g., learning, aggression, repetitive behaviors, social communication).

Statistical Considerations

1. If you decide to pursue oculomotor index as a diagnostic biomarker for clinical trial enrichment, please ensure a statistical analysis plan (SAP) for the validation study is included in your Qualification Plan.

2. In the SAP for QP, include mathematical details of how the composite Oculomotor Index is formed from the three video/image type indices. Specifically, what are the quantitative or qualitative measures you plan to use to measure the three paradigms (Activity Monitoring, Social Interactive Scenes, and Static Social Scenes) involved in the composite Oculomotor Index biomarker.

3. If the Oculomotor Index biomarker will be used to select patients into a clinical trial for treatment efficacy assessment in ASD patients, it is important to validate your proposed threshold selection algorithm's operating characteristics in the context of use with subgrouping ASD children with a clinical diagnosis of ASD. In the SAP, provide the details of how statistical validation will be performed and what pre-specified statistical criteria you will consider as evidence of diagnostic enrichment. You should also pre-specify what constitute your validation dataset(s) with description.

4. A separate SAP for a field study is also needed.

Please note that section 507 of the FD&C Act includes transparency provisions that apply to your submissions. Certain information contained within your submissions may be made publicly available on the Internet, as required by section 507. For examples of transparency and prior submissions see the Biomarker Qualification Submissions webpage[3].

If you have questions, please contact the CDER Biomarker Qualification Program (CDER-BiomarkerQualificationProgram@fda.hhs.gov) via email. We look forward to working with you on this beneficial project.

Sincerely,

Christopher L. Leptak -S
Digitally signed by Christopher L. Leptak -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300421152, cn=Christopher L. Leptak -S
Date: 2020.03.19 07:49:21 -04'00'

Christopher Leptak, M.D., Ph.D.
Director, CDER BQP
Office of New Drugs/CDER

Tiffany Farchione -S
Digitally signed by Tiffany Farchione -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000459254, cn=Tiffany Farchione -S
Date: 2020.03.18 22:11:56 -04'00'

Tiffany R. Farchione, M.D.
Director (Acting), Division of Psychiatry
Office of New Drugs/CDER

[3] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535881.htm