LOI DECISION LETTER

DDTBMQ000083

May 6, 2019

James McPartland, Ph.D.
Associate Professor
Yale Child Study Center
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 November 1, 2018 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 N170 to upright human faces (N170) as a tool to identify a homogenous subgroup within ASD for use in enrichment of 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 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.

Based on our review of the LOI, we agree there is an unmet need, and the development of N170 to upright human faces (N170) as a biomarker, with consideration to other clinical characteristics, may be helpful in clinical drug development trials.

When you are prepared to make a submission to the next stage in the 507 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 initial QP submission.

When evaluating biomarkers prospectively in clinical trials, sponsors are encouraged to submit study data

[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.

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. 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: **N170 to upright human faces (N170)[2]**

The N170, recorded over the scalp corresponding to the right occipitotemporal cortex, will be used for quantitative measurement of the latency, in milliseconds, of peak neural response to visual presentation of a human face.

- Please specify which aspects of N170 will be utilized to describe the biomarker (e.g., latency, amplitude, or other).

Context of Use (COU) Considerations

Requestor's COU: Diagnostic biomarker (identifying a biologically homogeneous subgroup within autism spectrum disorder) to enrich clinical trials by reduction of ASD-associated heterogeneity. It should be considered along with (a) clinical and demographic characteristics, such as DSM-5 diagnosis of ASD, age, and IQ and (b) relative to latency in age-matched typically developing (TD) controls.

1. The COU also does not differentiate how the population identified with this biomarker differs from other patients who have ASD. Will this patient subpopulation be more likely to respond to

[2]The N170 is an early face-sensitive ERP component that was first reported in the mid-1990s (Bötzel et al., 1995; Bentin et al., 1996), and has now become the most widely used ERP marker of face perception. (Eimer 2011)

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pharmacologic interventions or respond more robustly or quickly to targeted agents? Will N170 be an inclusion criterion in clinical trials?

Analytical Considerations

Pre-Analytical Sample Collection, Handling, Stability and Supporting Standard Operating Procedures

2. Please provide a full description of any signal processing procedure used to remove noise, correct the signal, or make any modification to the original signal obtained during the trial. Please explain how this processing will not affect the time differential between typically developing (TD) children and children with ASD or between different subgroups of children with ASD.

Validation: Calibration, Controls, and Verification of Repeat Measures (Variability) and Demonstration of Capability for Full Parameter Range (Performance)

3. You have stated that a net will be used to measure the N170 signal. You have not stated if these nets are 510K cleared. Please provide more information on the nets used to measure the signal. Please state if the net and software have 510K clearance.

4. Additionally, we understand that the EEG nets identified in the submission are all high-density EEG nets. It is unclear whether the N170 evoked response measurement would be generalizable to more common (non-high density) EEG nets and other EEG amplifier systems. Please provide a discussion as to whether this measurement would be generalizable to other (non-high density) EEG systems. Alternatively, please provide a clear discussion that identifies the requirements and limitations for making this measurement on other EEG nets and EEG amplifier systems.

5. It is unclear if the same net and software are used at the different sites in the study. Please state if the same system will be used at all sites throughout the study. If different nets and software are used, please describe the differences between the nets and software, and if this could affect how the response signal is analyzed.

6. In the DAAC EEG QC manual on page 15 of 43, the manual states that, if the signal quality is "good," the data will be considered valid; if the signal quality is "bad," the data file should be marked for follow-up review.. Please specify how a signal is determined to be good or bad.

Confirmation of Transparency of Analytics Technical Parameters

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 parameter and other pertinent

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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

Background

8. In the Background section of your QP or as an attachment, please describe the body of scientific literature necessary to support your COU.

Interpretive Criteria (Cut-offs/Boundaries), Application & Validation in population

9. The supporting documentation for this submission describes the full ABC-CT trial with multiple potential biomarkers for detecting group differences in ASD compared to typically developing youth (TD). The EEG pre-processing steps described in the ABC-CT methods appear to use pre-processing tools designed for large-scale EEG analysis. However, the COU describes clinical trials and the N170 values will presumably be obtained from individuals. Please describe how you will develop the N170 biomarker to establish two or more subgroups of individuals with ASD (e.g., cut-off scores, validity of subtypes), and how you will use the biomarker to establish the subgroup to which an individual study subject belongs, within the clinical trials setting.

Gaps and Proposed Studies

10. In your QP, please summarize the ongoing debate regarding N170 (e.g., Thierry et al 2007 paper describing poorly controlled inter-stimulus perceptual variability). Please describe how you will overcome established limitations regarding N170 measurement and interpretation, such as how you will specify tight experimental controls suitable for drug development trials.

11. The submission states that N170 latency can inform the severity of ASD neuropathology, with higher latency values indicating more severe neuropathology and less efficient, temporally slowed, neural activation. It is unclear how your proposed studies will demonstrate this index severity. The submission proposes to use N170 latency to diagnosis a subgroup of patients with the ASD. Will this biomarker also be used to assess severity in ASD patients or this subgroup of ASD patients?

12. We note that N170 to upright faces has not been validated for clinical use or subtyping of any conditions, including ASD. Greater research and clinical experience will be needed to understand if and how N170 to upright faces may be useful for diagnosing and subtyping ASD or be of added benefit to drug development programs.

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Statistical Considerations

13. For your proposed biomarker N170 to upright faces, we recommend that your data analysis plan and statistical analysis plan consider:

    - How the proposed EEG pre-processing with PREP pipeline affects the estimation variability of time to N170 and P100.

    - How the choice of smoothing parameters in the peak finding algorithm changes the variability of N170 latency and its ability to distinguish between ASD and TD children.

    - Characterizing the within subject variation in N170 ERP shape and phase both within an experimental visit and between visits and if this variation affects estimation of N170 to upright face amplitude and latency.

14. If you decide to pursue N170 as a diagnostic biomarker for qualification, please submit the statistical analysis plan for the validation study on how you will validate the N170 cut-off score and the diagnostic performance.

Other:

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.

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

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Sincerely,

Christopher L. Leptak -S

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Christopher Leptak, M.D., Ph.D.
Director, CDER Biomarker Qualification Program
Office of New Drugs/CDER

Tiffany Farchione -S

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