

BQP Qualification Program Cover Letter

Date: November 1, 2018

Subject: DDT QUALIFICATION SUBMISSION

DDT Type: Biomarker Qualification

ATTN: CDER-Biomarker Qualification Program

C/O CDER Document Room: Upon receipt notify:

CDER-BiomarkerQualificationProgram@fda.hhs.gov

Biomarker DDT Tracking Number: (in bold print), if previously assigned

Check Here	Submission Type
✓	Letter of Intent
	Qualification Plan
	Full Qualification Package
	Update of Above (Check two, this box and one above)
	Other (please specify):

Biomarker Name(s): N170 to upright human faces

Context of Use: Describe the intended drug development use for the biomarker named above (1 to 2 sentences, see the graphic below for how to write the context of use.)

Diagnostic biomarker (identifying a biologically homogeneous subgroup within autism spectrum disorder) to enrich clinical trials by reduction of 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 controls.

Contact Information: Complete contact information including name(s), affiliation, mailing address, email address, phone and fax numbers.

1. James McPartland, Co-chair, Biomarkers Consortium ABC-CT Project Team

Associate Professor; Yale Child Study Center
230 South Frontage Road, New Haven, CT 06520
(203) 785-7179 james.mcpartland@yale.edu

2. Linda Brady, Co-chair, Biomarkers Consortium ABC-CT Project Team

Director, Division of Neuroscience and Basic Behavioral Science (DNBBS)
6001 Executive Boulevard, Room 7204/MSC 9645, Bethesda, MD 20892
(301) 443-3563 lbrady@mail.nih.gov

BQP Qualification Program Cover Letter

3. FNIH Biomarkers Consortium, Neuroscience Steering Committee, ABC-CT Project Team

FNIH Biomarkers Consortium

<https://fnih.org/what-we-do>

<https://fnih.org/what-we-do/biomarkers-consortium/programs>

Purpose Statement: Describe the purpose of the submission in 3-5 sentences.

To obtain formal feedback from the FDA regarding a brain-based EEG biomarker (*N170 to human faces*) as an enrichment/stratification biomarker for the core social communication symptoms of ASD. The N170 to human faces is proposed for use in future clinical trials as an enrichment measure. The N170 biomarker is being studied in two major consortia efforts and in a project spearheaded by Janssen R&D, which is why it is being prioritized for submission to the FDA for feedback: 1) this project, the ongoing FNIH Biomarkers Consortium Autism Biomarkers Consortium for Clinical Trials (ABC-CT) study; 2) the Innovative Medicines Initiative (IMI) EU-AIMS Longitudinal European Autism Project (LEAP) study (in Europe); and 3) JAKE (the Janssen Autism Knowledge Engine). The purpose of this submission is to solicit feedback from the FDA regarding the potential viability of the N170 to human faces measure as an enrichment biomarker, the proposed data analytic plan, and next steps for confirmatory studies.

In addition to the EEG N170 response to faces, these programs are studying other objective measures that may have utility for discrimination, as well as measurement of change and additional contexts of use, in individuals with ASD. The applicant intends to explore the approach to early evaluation and consideration of multiple potential biomarkers, including both EEG endpoints and eye-tracking endpoints, in conjunction with computer-administered stimuli designed to evoke biological responses.

Submission Statement: Include a statement in the cover letter that: “The physical media submission is virus free with a description of the software (name, version and company) used to check the files for viruses.”

The physical media submission is virus free and has been checked for viruses with ESET Endpoint Antivirus software.

Additional Instructions for LOI/QP/FQP¹ submissions: For every electronic submission, a comprehensive table of contents should be submitted containing three or four levels of detail, with the appropriate bookmarks to key referenced sections in the document.

¹ LOI: Letter of Intent; QP: Qualification Plan; FQP: Full Qualification Plan

Biomarker Qualification Letter of Intent (LOI) Content Elements

NOTE TO REQUESTORS: FDA is currently developing its policies for submissions under section 507 and expects to issue guidance to aid in the development of submissions. In the interval, the agency has assembled this resource to help requestors. These content elements are informed by 10 years of experience with the legacy qualification process, input from multiple public meetings, comments to the docket and collaborative public partnerships. Given the changes to the process as defined in the 21st Century Cures Act, we expect to see further development of this content based on continued feedback.

For additional resources on submission content, please see prior BQP submissions that we have accepted into the program under section 507 [HERE](#). Please also note that certain information contained in submissions will be made publicly available as per the 21st Century Cures Act, as described in greater detail [HERE](#).

Should you have any questions or want to provide feedback on this or other BQP resources, including the content and format of submissions and the transparency provisions under section 507, please contact us at CDER-BiomarkerQualificationProgram@fda.hhs.gov

COMMENTS: The following information will be made publicly available as per the 21st Century Cures Act, described in greater detail [HERE](#)

Table of Contents

ADMINISTRATIVE INFORMATION	5
DRUG DEVELOPMENT NEED.....	5
BIOMARKER INFORMATION	5
BIOMARKER NAME.....	5
<i>Biomarker description</i>	<i>5</i>
<i>Biological rationale</i>	<i>6</i>
CONTEXT OF USE	6
PROPOSED CONTEXT OF USE (COU) STATEMENT.....	6
BIOMARKER MEASUREMENT (ANALYTICAL).....	7
<i>A standard operating procedure (SOP) for sample collection, storage and test/assay methodology</i>	<i>7</i>
<i>An analytical validation plan or data.....</i>	<i>7</i>
BIOMARKER MEASUREMENT (CLINICAL).....	8
<i>Description of Clinical Decision Process and Tool</i>	<i>8</i>
SUPPORTING INFORMATION.....	9
SUMMARY OF EXISTING PRECLINICAL OR CLINICAL DATA	9
SUMMARY OF ANY PLANNED STUDIES TO SUPPORT THE BIOMARKER AND COU	9
ALTERNATIVE/COMPARATOR/CURRENT STANDARD(S) APPROACHES.....	9
PREVIOUS QUALIFICATION INTERACTIONS AND OTHER APPROVALS	10
<i>Letter of Support (LOS) issued for this biomarker on date:</i>	<i>10</i>
<i>Discussed in a Critical Path Innovation Meeting (CPIM) on date:</i>	<i>10</i>
<i>Previous FDA Qualification given to this biomarker with DDT Tracking Record Number</i>	<i>10</i>
<i>Qualification submissions to any other agencies with submission number</i>	<i>10</i>
<i>Prior clearances or approvals:</i>	<i>10</i>
<i>Prior or current Regulatory submissions.....</i>	<i>10</i>
ATTACHMENTS.....	
ABC-CT EEG Acquisition Protocol	12
ABC-CT EEG Manual	44
ABC-CT EEG Quality Control	66
ABC-CT ERP Pipeline and Derived Results Manual	109
Publications Relevant to Biomarker Development Proposal	123
Draft ABC-CT Objectives and Analysis Plan.....	131
FDA Involvement in Biomarker Development Proposal.....	139
ABC-CT Interim Analysis N170 Experiment and Data	140
ABC-CT Study Protocol	146
ADDITIONAL INFORMATION & SUBMISSION INFORMATION:.....	n/a

Administrative Information

Requesting Organization:

FNIH Biomarkers Consortium, Neuroscience Steering Committee, ABC-CT Project Team

FNIH Biomarkers Consortium

<https://fnih.org/what-we-do>

<https://fnih.org/what-we-do/biomarkers-consortium/programs>

1. Primary contact

James McPartland, Co-chair, Biomarkers Consortium ABC-CT Project Team

Associate Professor; Yale Child Study Center

230 South Frontage Road, New Haven, CT 06520

(203) 785-7179

james.mcpartland@yale.edu

2. Alternate contact

Linda Brady, Co-chair, Biomarkers Consortium ABC-CT Project Team

Director, Division of Neuroscience and Basic Behavioral Science (DNBBS)

6001 Executive Boulevard, Room 7204/MSC 9645, Bethesda, MD 20892

301-443-3563

lbrady@mail.nih.gov

Submission Date: **November 1, 2018**

Drug Development Need

Describe the drug development need that the biomarker is intended to address, including (if applicable) the proposed benefit over currently used biomarkers for similar COUs (limited to 1,500 characters).

There are no FDA-approved drugs for the core symptoms of Autism Spectrum Disorder (ASD). Trials of novel agents in ASD have been difficult to interpret based on a variety of factors, including the wide heterogeneity in the spectrum of individuals who meet DSM-5 syndromal ASD diagnostic criteria and a high placebo response (due to expectation bias). Controlling for clinical variables, such as sex, age, IQ and severity of core symptoms, has had limited utility in reducing the variability observed in clinical trials. A quantitative biomarker could allow for the selection of a subgroup with a potentially shared underlying pathophysiology that may be more likely to respond to pharmacologic interventions or respond more robustly or quickly to targeted agents. A more homogenous group identified by one or more brain-based biomarkers of social communication function would permit more efficient evaluation of interventions targeted to deficits in this domain.

Biomarker Information

Biomarker name

N170 to upright human faces (N170)

Biomarker description (source, composition and decision process).

If biomarker is an index/scoring system, please provide information on how the index/composite or final decisional criteria is/are derived (e.g., algorithm), the biologic rationale for inclusion of each of the components, the rationale for any differential weighting of the elements, and the meaning/interpretation of the index/score (limited to 1,500 characters).

Individuals with ASD have been shown in multiple studies to have a deficit in visual processing of the human face, leading to difficulties with social communication and formation of social relationships. The N170, recorded over scalp corresponding to 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. Longer N170 latency relative to age-matched typically developing (TD) individuals reflects decreased processing efficiency of structural encoding of the human face in ASD (McPartland et al., 2004).

Biological rationale (underlying biological process) reflected on the measurement if available.

Convergent evidence from lesion studies, non-human primate research, and functional magnetic resonance imaging (fMRI) indicates that face processing relies upon a specific network of specialized brain regions, with particular reliance upon occipitotemporal regions, such as the fusiform gyrus and superior temporal sulcus. Electroencephalographic (EEG) and event related potential (ERP) studies of face perception, which provide acute temporal resolution, enable imaging of brain activity in real time. ERP paradigms are more robust to variation in attention than other neuroimaging methods and reveal a distinct component associated with face processing. The N170, a negative-going voltage deflection recorded over the occipitotemporal scalp approximately 170 milliseconds (ms) after viewing a face, indexes the earliest stages of face-specific processing (i.e., structural encoding). Neural generators of the N170 have been localized to occipitotemporal sites, including the fusiform gyrus and superior temporal sulcus (Itier & Taylor, 2004; Shibata et al., 2002). Studies analyzing both fMRI and ERP data indicate covariation between N170 latency and amplitude and hemodynamic activity in the fusiform gyrus and superior temporal gyrus (Corrigan et al., 2009; Iidaka et al., 2006). The latency of the N170 reflects faster, more efficient, or expert processing of visual information.

Review of published research in ASD and TD indicates that N170 variability appears to associate with social-emotional function in typical and atypical development in areas such as social competence, distress, empathy, emotional sensitivity, anxiety, introversion, shyness, and social withdrawal (Kang et al., 2018). Across studies of groups of individuals with ASD and TD, N170 latency to faces is, on average, delayed in individuals with ASD and associates with severity of the condition. N170 latency is interpreted as an index of severity of ASD neuropathology, with higher latency values (i.e., longer latency) indicating more severe neuropathology and less efficient, temporally slowed neural activation.

Additional considerations for radiographic biomarkers

N/A

Context of Use

Proposed Context of Use (COU) Statement: Complementary to the stated Drug Development Need (limited to 500 characters see [BEST Glossary](#))

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 TD controls.

Biomarker Measurement (Analytical)

Provide a general description of what aspect of the biomarker is being measured and by what methodology (e.g., radiologic findings such as lesion number, specific measure of organ size, serum level of an analyte, change in the biomarker level relative to a reference such as baseline) (limited to 1,500 characters).

In the ABC-CT study, which is the reference study for this LOI, N170 latency was measured by EEG recording over predefined regions of interest over the right occipitotemporal scalp (EGI channels 89, 90, 91, 95, and 96). The experimental paradigm presented upright faces, inverted faces, and upright houses. Signal was averaged across the channels to provide an ERP for N170 to faces. The N170 peak amplitude (microvolts) and latency to peak (ms) were identified using a series of automated algorithms in which the negative component (N170) was identified as the most extreme negative peak following the P100 (a positive peak within the 80-180 ms window). Visual inspection of the N170 for each individual participant was confirmed via graphs of the waveform using a manualized process.

A standard operating procedure (SOP) for sample collection, storage and test/assay methodology

ABC_CT EEG Standard Operating Procedures are attached.

- 1) [ABC-CT EEG Acquisition Protocol \(page 12\)](#)
- 2) [ABC-CT EEG Manual \(page 44\)](#)
- 3) [ABC-CT EEG Quality Control \(page 66\)](#)
- 4) [ABC-CT ERP Pipeline and Derived Results Manual \(page 109\)](#)

An analytical validation plan or data (e.g., sensitivity, specificity, accuracy, and/or precision of the assay or method) (limited to 1,500 characters).

Prior to interim analysis, N170 latency to upright faces was identified as one of three primary outcome measures to be assessed for suitability as stratification/discrimination biomarkers. The pre-specified directional hypothesis was that latency would be delayed in ASD compared to TD. First, core viability was assessed in terms of (i) successful acquisition across demographic/clinical characteristics, (ii) consistency across sites, (iii) distributional properties (e.g. absence of severe non-normality, skew, zero-inflation; sufficient variability to show correlations with clinical factors or subgroup differences), (iv) test-retest reliability, and (v) construct validity (appropriate differential response to experimental conditions in TDs). Second, we performed a set of tailored analyses to examine group discrimination and identify potential subsets/cutoffs for stratification. Specifically, we used a combination of histograms, descriptive statistics, general linear models, ROC/sensitivity/specificity curves and cluster analysis to look for (i) significant mean differences between ASD and TD groups, (ii) regions of substantial non-overlap (or very different probability concentrations) between the ASD and TD distributions (diagnostic stratification) and (iii)

multi-modality (indicating a natural separation into subgroups within the ASD group). Details of statistical plan and summary of interim results are provided as attachments. These analyses will be applied to the full sample.

Biomarker Measurement (Clinical)

Description of Clinical Decision Process and Tool

At the time of this submission, ABC-CT study data collection is ongoing. Data presented here are from interim analyses (described in the attached Analysis Plan) including partial data from Time 1 (Baseline) and Time 2 (6 weeks). At the time of final analyses, which will include complete data with the addition of Time 3 (24 weeks), we will undertake determination of clinical decision making. The intention is to use our complete data set to identify a cutoff score(s) on the N170 latency (or series of scores based on covariates such as age or gender) to guide inclusion in a clinical trial. Our objective is to utilize FDA written feedback solicited from this LOI and discussion to inform this process.

Characterization of Biomarker for COU

To be determined with complete dataset.

Calculation/Modeling/Construction of Biomarker into a Decision Tool

To be determined with complete dataset.

Expected Distribution of Decision Criteria for COU

To be determined with complete dataset.

Decision Criteria Limits/Cut-offs and Application to COU

To be determined with complete dataset.

Clinical Validation

To be determined with complete dataset.

Benefits and Risks of Applying Clinical Decision Tool

To be determined with complete dataset.

Describe Knowledge Gaps, Limitations and Assumptions

To be determined with complete dataset.

Additional Considerations for Radiographic Biomarkers

N/A

How has the method for image acquisition, analysis, and integration of the data been optimized?(Limited to 1,000 characters.)

Details are provided in the attached Manuals of Procedures.

Does data currently exist to support the proposed cutoff point(s), if imaging results are not reported as a continuous variable?

N/A

Provide the name and version of the software package to be used for image acquisition and analysis (limited to 500 characters).

N/A

Supporting Information

Summary of existing preclinical or clinical data to support the biomarker in its COU (e.g., summaries of literature findings, previously conducted studies) (limited to 2,000 characters).

The N170 is a promising neural marker of ASD and has been investigated in more than 23 published pediatric and adult studies since 2004, in both adult and pediatric studies, and across a range of cognitive abilities. A recent meta-analysis (Kang et al., 2018) reviewed these studies (N ASD=374, N TD=359) and concluded that N170 latencies to faces were delayed in individuals with ASD vs. TD controls, while N170 amplitude was not significantly different. Atypical N170 latency to faces has been observed across a broad developmental range (age 3 years through adulthood) and across the range of cognitive ability from disability to normative intellectual ability.

The ABC-CT study selected four EEG measures (N170, Visual Evoked Potentials, Resting EEG, ERP to biological motion) based on extant EEG ASD studies in the literature which identified these as potential EEG biomarkers; the four measures were evaluated to determine their performance and reproducibility in a prospective five-site data collection study. In an interim analysis of baseline and 6 week data, N170 latency to faces demonstrated the best separation between TD controls and ASD subjects and identified a potential ASD subgroup that discriminated from TD subjects through a delayed N170 ERP. N170 biomarker data were acquired on 179 (out of 225) 6-11 year old children with TD (N=59) and ASD (N=120); thus 79.6% of the sample (92.2% TD and 74.5% ASD) provided a N170 latency score for the right region of interest. Right hemisphere N170 latency to faces in the ASD group (Mean=208.2ms; SD=31.0) was significantly longer [$F(1,177)=8.8, p<.01$] than in the TD group (Mean=194.2ms; SD=27.1; Area under Curve =.65 (95% CI: .56-73, $p<.01$)). Across two measurements separated by 6 weeks, in a subsample of subjects (N=145), the test-retest reliability (ICC) equaled .69 overall (TD=.65, ASD=.68). These data will be augmented with the full sample; data collection will be completed in June, 2019.

Summary of any planned studies to support the biomarker and COU. How will these studies address any current knowledge gaps? (Limited to 2,000 characters.)

The ABC-CT is designed to examine N170 latency to faces in 200 children with ASD and 75 TD children across three time points (T1=Baseline, T2=6 weeks, T3=24 weeks). Analyses will examine N170 latency in terms of: (1) Successful acquisition across sites and across key demographic and clinical factors (e.g., females, lower IQ), including age, sex, and functional level; (2) Appropriate distributional properties; (3) Test-retest (T1 / T2) reliability and stability; (4) Discrimination between ASD and TD. These analyses seek evidence for establishing utility in denoting a more biologically homogeneous subgroup of individuals with ASD as evidenced by manifestation of N170 latency longer than in other individuals with ASD and not commonly observed in TD subjects.

Alternative/comparator/current standard(s) approaches

Given the absence of quantitative biomarkers for the proposed context of use, there are currently no alternative approaches.

Previous Qualification Interactions and Other Approvals

Letter of Support (LOS) issued for this biomarker on date:

N/A

Discussed in a Critical Path Innovation Meeting (CPIM) on date:

N/A

Previous FDA Qualification given to this biomarker with DDT Tracking Record Number

N/A

Qualification submissions to any other agencies with submission number

The submitters have not submitted to any other agency; however, a collaborating study, the EU-AIMS Consortium (IMI), submitted a request for scientific advice to the EMA in December 2013, Submission #EMA/H/SAB/045/1/QA/0000/PED (upon receipt of feedback #EMA/H/SAB/045/1/QA/2014/PED)

Prior clearances or approvals: Laboratory Developed Test (LDT), Research Use Only (RUO), FDA Cleared/Approved Provide 510(k)/PMA Number, Clinical Laboratory Improvement Amendments (CLIA)

N/A

Prior or current Regulatory submissions to Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH)

N/A

Attachments

Please provide a list of publications relevant to this biomarker development proposal.

[Publications Relevant to Biomarker Development Proposal \(page 123\)](#)

Optional* – If this biomarker development effort is part of a longer-term goal, please summarize your long-term objectives.

[Draft ABC-CT Objectives and Analysis Plan \(page 131\)](#)

Optional* – If you have other supporting information you would like to provide, please submit as attachment(s).

[FDA Involvement in Biomarker Development Proposal \(page 139\)](#)

Attachments

[ABC-CT Interim Analysis N170 Experiment and Data \(page 140\)](#)

[ABC-CT Study Protocol \(page 146\)](#)

Additional Information & Submission Information:

Please refer to the [Resources for Biomarker Requestors](#) for the mailing address and other important submission-related instructions. For more about Biomarker Qualification see our program's [Home Page](#). If you have any questions about submission procedures, please contact via email; CDER-BiomarkerQualificationProgram@fda.hhs.gov.