LOI DECISION LETTER

DDTBMQ000079

November 08, 2018

Nerve Unit, Massachusetts General Hospital
Anne Louise Oaklander, MD, PhD
275 Charles Street, Warren Building Room 806
Boston, MA 02114

Dear Dr. Oaklander:

We are issuing this Letter of Intent (LOI) Decision Letter to the Nerve Unit, Massachusetts General Hospital, 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 August 1, 2018 and have concluded to **Accept** it into the CDER BQP.[1] We support and encourage your ongoing study of this promising biomarker.

You have proposed qualification of Epidermal Neurite Density (END) as a diagnostic biomarker, along with other clinical indicators, to confirm a diagnosis of small fiber polyneuropathy (SFPN) for use as an inclusion criterion in drug development clinical studies. Based on our review of the LOI, we agree there is an unmet drug development need. As this biomarker development effort is refined in subsequent submissions, the submitted data, the specifics of your context of use (COU), (including the target patient population), and the design of study(ies) used in the clinical validation of the biomarker will ultimately determine which of the recommendations below are most applicable.

For the 507 DDT qualification process, please prepare a Qualification Plan (QP) submission that addresses the scientific considerations and recommendations outlined below. A QP contains details of the analytical validation of the biomarker measurement method, detailed summaries of existing data that will support the biomarker and its 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.

[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.

In addition to the qualification effort, we encourage further study of your biomarker including collection of specified exploratory information from the proposed clinical trials. When evaluating biomarkers prospectively in drug development studies, requestors 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 requestors 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 (academic, industry, government or patient interest groups) that would like to join in this effort or have information or data that may be useful may contact Dr. Anne Louise Oaklander (aloaklander@mgh.harvard.edu), the point of contact for this project.

Biomarker Considerations

Requestor's Description: END measures the neurite density per skin surface area, often per mm^2 skin surface area. END measurements quantitate degeneration of the farthest ends of small-fiber axons emerging from the dermal-epidermal junction in full-thickness punch skin biopsies removed from 10 cm above the lateral malleolus. A skilled morphometrist counts the individual neurites (aka nerve fibers, axon twigs) that ascend into the epidermis by established rules.

FDA's Recommended Description: Neurite density per skin surface area, in mm^2

Type of biomarker: Histologic (manual enumeration of small-fiber axons emerging from the dermal-epidermal junction in biopsy preparations of a specified thickness)

Matrix: full-thickness punch skin biopsies removed 10 cm (less in children) above the lateral malleolus.

To better understand the benefits of the identified biomarker as a DDT, and to continue to refine the COU, please see these recommendations and requests for the following information;

FDA's questions for continued development of the biomarker description:

1. There is a need to standardize the biomarker name. If END is the same as IENFD used in European and American Guidelines, then the biomarker name should be IENFD to avoid confusion. Please use nomenclature consistent with consensus activities currently underway.

2. Please indicate how the enumeration of small-fiber axons emerging from the dermal-epidermal junction in full-thickness punch skin biopsies is a two-dimensional surface area measurement (mm^2) versus a linear measurement (per mm)?

3. Please describe if the staining method you propose is specific to the neurites whose loss characterizes SFPN pathology? Are there relative differences in staining or the visibility of neurites undergoing pathological processes?

Context of Use (COU) Considerations

Requestor's COU: *Diagnostic biomarker to be used with clinical indicators to identify SFPN. END measurement from punch skin biopsies taken 10 cm above the outer ankle, less in children, is the gold-standard objective test for diagnosing SFPN for clinical use and enrollment in clinical trials.*

FDA's suggested COU for continued biomarker development: Diagnostic biomarker, to be used in conjunction with other clinical indicators, to confirm a diagnosis of SFPN for use as an inclusion/exclusion criterion in drug development clinical trials.

Analytical Considerations

4. Pre-Analytical Process: Please provide information on Sample Collection, Fixation, Handling, Processing, Staining, Background, Positive and Negative Controls for IHC, Stability and Supporting Standard Operating Procedures. The biomarker description should address additional information including; SOPs for staining, enumeration and ensuring consistent, accurate and reliable values.

5. Analytic Method:

    - Please provide clear definition of a "skilled morphometrist" and describe procedures for minimizing inter- and intra-reader as well as intra- and inter-laboratory variability.
    - Please provide a description of the measurement method including details on rules for counting so that implementation by different labs may generate reproducible results (topics would include: section selection, validation, # of sections, manual versus computational analysis.
        - If manual, how will variability between labs be addressed and how will variability by morphologist be addressed?

6. Analytical Method Description: Please describe the process used to analyze collected samples and, if needed, computations and procedures used to produce the information.[2]

7. Analytical Method Performance*:* Please provide the impacts of Variability, Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value, and Comparative Value in nonclinical studies. In your next step of the qualification process, please provide descriptions of how accuracy and reproducibility of counts will be established.

8. Analytical Method Validation: Please provide details on Calibration, Controls, and Verification of Repeat Measures (Variability) and Demonstration of Capability for Full Parameter Range. Please describe the methods you will use to assess whether or not there is such variability? Please address potential for false positives or false negatives using the proposed approach and what you will do to minimize potential for false results.

9. Confirmation of Transparency of Analytics Technical Parameters: Section 507 of the FD&C Act includes transparency provisions that apply to your submission. Certain information about the analytical assay may be publicly posted. Please confirm technical parameter and other pertinent information about the assay 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 or qualify a specific assay for use with the biomarker.

Clinical Considerations

10. Intended population for COU: In which specific populations do you see this biomarker being useful? Please describe the benefits and risks of using this procedure and test for drug development in that specified population. Please provide the background prevalence of SFPN in the populations of interest.

11. You indicate in the abstract titled, "Diagnostic performance of a multivariate model of normal epidermal nerve fiber (ENF) density for skin-biopsy diagnosis of SFPN" that you collected biopsies from 373 normal volunteers (8-92 years) including 42 children. Please describe the process/demographics for selection of volunteers and provide descriptive statistics of the volunteer population (by age, race, sex, condition or other) that you describe as normal. Are there additional factors that may influence END which you need to study further? How do you propose to group ages given the rapid rate of decline in END by age in children?

[2] Mangus LM, Dorsey JL, Weinberg RL, Ebenezer GJ, Hauer P, Laast VA, Mankowski JL, Tracking Epidermal Nerve Fiber Changes in Asian Macaques: Tools and Techniques for Quantitative Assessment. Toxicol Pathol. 2016 Aug;44(6):904-12.

12. In what types of studies and types of new drugs (e.g., mechanisms of action) do you envision this biomarker and COU would be applicable?

13. In your next step of the submission, please specify the exact clinical indicators and process to be used along with END biomarker for diagnosing SFPN.

Considerations on Inclusion or Exclusion Criteria

14. The proposed biomarker appears to be used as a confirmatory tool for the identification of SFPN, after ruling out the presence of other conditions and confirmation of specific symptoms, diagnoses or identification of a specific population. Please describe the clinical, diagnostic and safety considerations that will be taken into account prior to performing the biopsy procedure. For example, what conditions are ruled out or ruled in using what types of testing, etc. (e.g., rule outs; mixed fiber neuropathy by EMG, immune disorders, inflammatory, thrombotic or other conditions which could result in complications, etc. rule in: diabetes, etc.)?

Interpretive Criteria (Cut-off points/Thresholds/Boundaries), Application & Validation in population

15. You indicate that the values stratified by age, race, sex, etc., vary. You further indicate that cutoffs for the abnormal END that use a single threshold (e.g., 3.8 ENF/linear mm) to determine normality of ENF results in false negative results in approximately 75% of cases. Your abstract indicates that different models yield contradictory interpretations of the same biopsies and incorporating demographic covariates improves diagnostic sensitivity, especially for young patients. Please provide the approach you plan to use in developing END values for each subgroup for which you plan to identify cut-off point(s), e.g. an END value $\leq 5^{th}$ centile of the population distribution indicates a high likelihood of SFPN; values in the 5^{th} - 15^{th} centiles are indicative of borderline SFPN. In addition, provide a rationale/basis for why that subgroup and cut-off point are needed. Do you propose one set of standard cut-off point(s) stratified by demographic covariates or will the cut-off point(s) be based on laboratory-based populations or do you propose another approach? What is the potential for misclassification using the proposed approach? What is the impact of misclassification for the patient and for drug development?

16. To have a biomarker that indicates abnormal END, the cut-off point needs to be identified and validated. For example, the 5^{th} centile needs to be demonstrated as a valid representation of a condition, the 5^{th} to 10^{th} or 15^{th} centiles as borderline for SPFN. Differences in counts or count cut-off point(s) based upon underlying disease or condition or stage of disease/condition, age, race, and sex needs to be evaluated.

Gaps and Proposed Studies

17. Identify gaps and assumptions in your proposal and propose studies with study descriptions that are needed to fill these scientific gaps.

Statistical Considerations

Interpretive Criteria & Cut-off point Validation

18. Advantages and disadvantages of use: Please provide data on the application of the proposed cut-off point(s) and the sensitivity, specificity. You indicate there are "no standards available for Positive Predictive Value and Negative Predictive Value calculations." Please indicate a standard that may be used for comparison and where there is no available standard for direct estimation please provide a surrogate or current standard(s) that may be used for estimation, i.e., a constellation of symptoms, etc. for comparison purposes.

19. Please provide sensitivity analyses, identifying and ranking factors most influential in setting the cut-off points for persons 23 years old and under and those over 23.

20. In response to your statement, "no recommendations on whether labs can just use published norms, and how big and representative the normative database should be, and what statistical analysis should be applied." There are insufficient data in your submission to provide feedback on this aspect of your project. Understanding more about the variability (intra and inter patient, intra and inter reader, etc.), the types and levels of stratification, may aid our understanding. Please provide your thoughts on what the normative database should look like, including the subsets of the population that should be represented.

21. Please describe the cut-off point(s) or the 5th centiles, how they were established and how you plan to validate them.

Please note that section 507 of the FD&C Act includes transparency provisions that apply to your submissions. Information about 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]

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

If you have questions, please contact Chris Leptak (christopher.leptak@fda.hhs.gov) through email. We look forward to working with you on this beneficial project.

Sincerely,

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

Sharon Hertz, M.D./ Sharon Hertz, M.D.
Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Office of New Drugs/CDER