LETTER OF INTENT
DETERMINATION LETTER

DDTBMQ000115
July 27, 2021

Dr. Maureen Kane, PhD
University of Maryland, Baltimore
School of Pharmacy
20 N. Pine Street
Baltimore, MD 21201

Dear Dr. Maureen Kane:

We are issuing this letter to the University of Maryland, Baltimore, School of Pharmacy, to notify you of our determination 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 Letter of Intent (LOI) deemed reviewable on March 30, 2021, and have concluded to **Not Accept** it into the CDER BQP[1]. You have proposed qualification of a panel of biomarkers that may help diagnose and enrich traumatic brain injury (TBI) drug clinical trials by providing a quantitative measure of phospholipid markers in conjunction with currently used TBI diagnostic tests. Please note that the 21st Century Cures Act was signed into law in December 2016 and adds the new section 507 to the Federal Food, Drug, and Cosmetic Act (FD&C Act) concerning the qualification of drug development tools (DDTs). FDA now operates its DDT program under the section 507 provisions. As stated in section 507(a)(2)(B), an LOI submission may not be accepted based upon factors which include scientific merit.

We have provided comments and recommendations for further improvement of your proposed project. We recommend revising and resubmitting this LOI based on the following considerations:

Drug Development Need Considerations:

You have not adequately established the need for the development of these biomarkers within the proposed context of use (COU). The drug development need should clearly identify how these biomarkers will improve drug development for TBI. It is unclear how these biomarkers will change or improve diagnoses and enrich clinical trials from the current standard of using a clinical history, clinical exam (such as Glasgow Coma Scale (GCS)), and radiographic criteria (such as head computed tomography (CT)). The LOI states these biomarkers will provide a quantitative value but it does not identify what additional information such a value will add to the current standard. You provide examples of patients being unconscious, or unable to complete the GCS, and assert that CT scans lack diagnostic utility as a reason to measure your proposed

[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.

biomarkers; however, your submission does not indicate how your proposed biomarkers would overcome such issues and subsequently facilitate enrollment into a clinical trial.

The proposed biomarkers may also be able to distinguish between mild, moderate, and severe TBI, but it is unclear how this distinction would be made and its ultimate utility in improving drug development for a specific severity of TBI.

Based on your LOI, there may be related unmet needs that could be appropriate for the proposed biomarkers. We acknowledge that these biomarkers are in early development and encourage you to continue developing these biomarkers. In addition to the animal studies that are in progress, collecting human data may help address a specific drug development need and formulate a revised COU.

Context of Use (COU) Considerations

Requestor's COU: *Diagnostic enrichment biomarker, in conjunction with other clinical factors, based on the plasma biomarker level to identify patients with traumatic brain injury by blunt mechanism head injury appropriate for inclusion in drug-development clinical trials.*

Biomarker Considerations:

Requestor's Description: *Individual or composite biomarkers that includes all or a subset of biomarkers listed below:*

Biomarker matrix: Plasma
Biomarker type: Molecular

PE(38:6)
1-hexadecanoyl-2-(docosahexaenoyl)-sn-glycero-3-phosphoethanolamine
PE(38:6)
PE(16:0/22:6)
HMDB ID: HMDB0008946; HMDB08946, Pubchem ID: 9546799, LMID: LMGP02010095

PC(38:8)
1-a-Linolenoyl-2-eicosapentaenoyl-sn-glycero-3-phosphocholine
PC(38:8)
PC(18:3/20:5)*
HMDB ID: HMDB0008215, PubchemID: 52922865, LMID: LMGP01011693

TG(60:12)
1-Oleoyl-2-eicosapentaenoyl-3-docosahexaenoyl-glycerol
TG(60:12)
(18:1/20:5/22:6)*
HMDB ID: HMDB0050239, Pubchem ID: 9545994, LMID: LMGL03012033

Clinical Considerations

1. Your future protocols should consider the following:
    a. Your proposed biomarkers, as described, would not change or replace the certainty of a diagnosis of TBI, since clinical history, clinical exam, and imaging would still be required. We recommend that you clearly state in which situations the proposed biomarkers could be used to improve the conduct of clinical TBI trials.
    b. You state the biomarkers will "enrich" the patient population with TBI. Enrichment is the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population. It is not clear at this time in what way your proposed biomarkers would enrich a clinical trial in patients with TBI. Please make this clear in any future submission. We refer you to the Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Effectiveness of Determination of Human Drugs and Biological Products.
    c. Your proposed biomarker measurements may vary with time depending on when the measurement was taken in relation to the TBI event. Head CT scans should be obtained at the same time intervals as the biomarker measurements are taken, to evaluate the time dependent relationship of these two measurements. It is known that head CT scans performed immediately after injury may not demonstrate the same changes as a head CT at later time points such as, 3, 6, 12, 24, 48, or 72 hours after injury as edema and tissue injury evolve. Time dependent changes should be considered when interpreting results of any biomarker assays and attempts should be made to correlate these changes with TBI severity.
    d. The clinical study protocol states that patients must have a "positive" head CT; however, the abnormal findings should be specified (e.g., intracranial hemorrhage). In addition, since head CT scans along with other measures will be used to differentiate patients with mild, moderate, and severe TBI, your protocol should clearly describe the imaging criteria used for this purpose.

2. You propose that these biomarkers may be able to distinguish between mild, moderate, and severe TBI. Clearly define how patients will be categorized by severity level, and collect data on your biomarkers in a sufficient number of patients in each of these categories to establish whether the biomarkers are able to differentiate these levels. Please include plans to provide quantitative data on the variability within each severity level and the magnitude of change between each severity level. Please also justify the use of the chosen scales to clinically identify TBI severity.

3. You estimate that a minimum of 15 patients in each group will be needed for the human study. Given the evidence is to be generated from animal study, we recommend a study with a minimum of 15 patients in each group (mild, moderate, severe) be a pilot human study. For any future clinical validation study, please include the parameter assumptions in the sample size planning. We recommend that you plan a sample size that could accommodate analyses of important subgroups such as sex, age, in addition to disease severity.

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 next LOI 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 groups (academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Dr. Maureen Kane (mkane@rx.umaryland.edu), the point of contact for this project.

We recommend scheduling 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 DDTBMQ000115 in the subject line. For additional information and guidance on the BQP please see the program's web pages at the link below.[2]

Sincerely,

Jeffrey N. Siegel -S

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Jeffrey Siegel, M.D.
Director, Office of Drug Evaluation Science
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Nicholas Kozauer -S

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Nick Kozauer, M.D.
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[2] https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/cder-biomarker-qualification-program