LETTER OF INTENT
DETERMINATION LETTER
DDTBMQ0000103

May 28, 2020

Professor Tyrone Cannon
North American Prodrome Longitudinal Study (NAPLS) Research Consortium
Yale University, P.O. Box 208205
2 Hillhouse Avenue, New Haven, CT 06520

Dear Professor Cannon:

We have completed the review of the Letter of Intent (LOI) for Drug Development Tool (DDT) BMQ0000103 received on March 19, 2020 by the CDER Biomarker Qualification Program (BQP), submitted for qualification under section 507 of the Federal Food, Drug, and Cosmetic Act.

The LOI is for "*Individualized Risk Calculator for Psychosis (IRC-P),"* and the proposed context of use (COU) is "Prognostic biomarker intended for use in clinical trials. It will be used in conjunction with clinical high-risk for psychosis (CHR-P) or Attenuated Psychosis Syndrome (APS) diagnosis in young people aged 15-35 years of age, to enrich for individuals most likely to progress to full psychosis and poor long-term functional outcomes."

FDA has completed its review and has agreed to accept your LOI into the CDER Biomarker Qualification Program. In preparing to submit a Qualification Plan (QP), please ensure that the QP submission addresses the scientific issues and the recommendations outlined below.

Drug Development Needs:

1. We agree that there is an unmet need in drug development for the CHR-P/APS patient population. A clinical trial enrichment strategy targeting patients at high risk for full psychosis would benefit trial design by increasing study power.

2. By calculating an individual risk of conversion for each CHR-P/APS patient during screening for a study, the IRC-P may provide a more targeted assessment of risk of conversion than the CHR-P/APS diagnosis alone.

3. For the higher-risk patients identified for study inclusion by the IRC-P, the absence of conversion to psychosis may support interpretation as an effect of the treatment intervention used in the trial.

4. The benefit/risk balance for patients may be improved by reducing the likelihood that patients who are unlikely to convert will be exposed to potential adverse effects of investigational drugs.

Context of Use (COU):

5. We recommend changing the description of the IRC-P from “prognostic biomarker” to “prognostic assessment tool” because no biological signal is detected or interpreted in the course of collecting the data that serve as inputs to the IRC-P.

6. We recommend that you generate a more precise, clearly defined definition for the context of use for the IRC-P.

    a. The target patient population should be clarified. Would “CHR-P or APS” or just CHR-P (or APSS) be more appropriate? CHR-P includes the SIPS diagnosis of APSS, which is similar to the DSM-5 diagnosis of APS but not identical. Patients with the DSM-5 APS diagnosis may not exactly match the patient population on which the IRC-P model was built.

    b. The definition of “progress to full psychosis and poor long-term functional outcomes” should be clarified. Would “full psychosis” be defined by SIPS “current psychosis” or by a set of corresponding diagnoses in DSM-5 that may give clinicians and researchers a clearer picture of the clinical state(s) that the IRC-P is intended to predict?

Clinical Considerations:

7. In the absence of a universally accepted approach to predict disease progression for psychosis, we are supportive of your proposal to calculate the risk of disease progression based on a broad aspect of conditions and backgrounds. However, we are concerned about the reliability of this predictive tool considering the heterogeneity of the illness. In addition, this prognostic assessment tool does not appear to have clear links to biological signals or patient physiology, and few of the raw input variables are specific to psychosis. You may wish to consider including other types of biological assessments such as genomic markers, eye movement tracking, or EEG data into the tool if appropriate.

Statistical Considerations: We recommend that you take into account these comments while preparing your statistical analysis plan (SAP), which needs to be included in your qualification plan submission.

8. The risk calculator may affect the interpretability and validity of any efficacy results of future trials based on NAPLS reference data criteria.

9. The criteria for the risk calculator (i.e., individuals meeting CHR-P or APS diagnosis) were based on NAPLS-2 reference database; the 1-year and 2-year risk estimates were computed using NAPLS-2 database; the same reference database is used to justify validity and replicability of the IRC-P. To learn more about IRC-P as a prognostic biomarker, please share with us results from the ongoing multi-consortia international effort called HARMONY (Harmonization of At Risk Multisite Observational Networks for Youth), the collaborative effort involving NAPLS, PRONIA (https://www.pronia.eu), and PSYSCAN (http://psyscan.eu) consortia studies.

10. The degree of prognostic enrichment depends on the prediction performance compared to current clinical trial enrollment criteria (e.g., DSM-5 diagnosis of APS) for identifying subjects with greater likelihood of conversion to psychosis. Therefore, instead of comparison to SIPS items P1 and P2, the prediction performance of IRC-P with multiple thresholds should be compared to current clinical trial enrollment criteria.

11. Statistical validity, including several aspects of the IRC-P, needs to be assessed and needs to demonstrate acceptable performance.

    a. We recommend correlation analysis among the components of the IRC-P be performed on all datasets you plan to use to support your proposed context of prognostic enrichment.

    b. We are aware of NCT03230097, a phase 2 controlled trial to investigate treatment effect in patients with APS, a 52-week study. We recommend that you use the data from the placebo arm of this trial to assess the added value of the prediction performance of IRC-P as a one-year risk calculator.

    c. We recommend that you propose a separate trial that allows you to assess the added value of the prediction performance of IRC-P as a two-year risk calculator.

When you prepare for your QP submission, thoroughly review the questions above and address them line by line following the numbering above or you may refer to the sections in your QP where your responses are found. The summary of your responses may be added to the appendix section of your QP.

The following weblinks contain the contents to include in your submission to reach the next milestone (Qualification Plan): https://www.fda.gov/drugs/cder-biomarker-qualification-program/resources-biomarker-requestors and the submission portal: CDER NET GEN Portal. Please Contact **CDER's Biomarker Qualification Program (BQP)** (**CDER-BiomarkerQualificationProgram@fda.hhs.gov)** should you have any questions (refer to **DDTBMQ0000103**).

Sincerely,

Christopher L. Leptak -S

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