PIND 141250

MEETING PRELIMINARY COMMENTS

Broad Institute of MIT and Harvard
Attention: Eric Lander, PhD
President and Founding Director
415 Main Street
Cambridge, MA 02142

Dear Dr. Lander:[1]

Please refer to your pre-investigational new drug application (PIND) file for prion protein (PrP)-lowering antisense oligonucleotides.

We also refer to your June 19, 2019, correspondence, received August 19, 2019, requesting a meeting to discuss a proposed surrogate biomarker for your PrP-lowering antisense oligonucleotides development program.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to me, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call me at [redacted]

Sincerely,

{See appended electronic signature page}

Heather M. Bullock, RN, BSN, MSHS
Captain, United States Public Health Service
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: October 31, 2019 from 11:00 a.m. to 12:00 p.m. EST
Meeting Location: FDA White Oak Building 22, Room 1313
Silver Spring, MD

Application Number: PIND 141250
Product Name: Prion protein (PrP)-lowering antisense oligonucleotides

Proposed Indication: Genetic prion disease
Sponsor Name: Broad Institute of MIT and Harvard

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for October 31, 2019 from 11:00 a.m. to 12:00 p.m. EST at the FDA White Oak campus between Sponsor and the Division of Neurology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager [RPM]). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

On November 14, 2017, scientists from the Broad Institute of MIT and Harvard (Broad Institute) had a Critical Path Innovation Meeting (CPIM) with the Agency to discuss their preliminary work to develop a therapeutic strategy for genetic prion disease. On August 19, 2019, the Broad Institute submitted a meeting request to discuss a proposed surrogate biomarker for their PrP-lowering antisense oligonucleotides development program. The Agency's preliminary responses to questions contained in the sponsor's background materials follow.

2.0 DISCUSSION

Questions Regarding Biomarker Assessment

Question 1: What, if any, further analytical validation of the technical performance of the BetaPrion Human ELISA kit will be necessary to support its use as an assay for a surrogate biomarker endpoint?

FDA Response to Question 1:

Based on the information you submitted regarding the technical performance of the BetaPrion Human ELISA kit and the targeted mass spectrometry assay, please see below for aspects that we believe either require additional data or clarification. Where possible, we have provided recommendations to address the gaps.

1. In general, please provide detailed standard operating procedures (SOP) for the BetaPrion Human ELISA and mass spectrometry assays as per the modifications and optimizations you have performed leading up to your validation. These modifications should be described in detail with steps specific to your intended use, samples, instrumentation, and distinct from the commercially available method.
    a. Your SOPs should describe steps for any acceptance/rejection criteria for the samples and raw data at each key step, chain of custody of the CSF samples, blinding protocols for the samples, and roles/responsibilities for each analyst or laboratory involved in the procedures.
    b. The ELISA method SOP should have sufficient detail on the standard curve material, capture and detection antibodies, dilution steps, detection methods, and steps for calculating the final reported PrP value with appropriate units.
    c. Your procedures for rejected samples or deviations from the validated method need to be described with clear instructions on how an analyst must proceed in such cases. For example, is re-testing allowed? What are the limits and objective criteria for re-testing? What are the objective

criteria under which a CSF sample might be rejected? Is sample pooling allowed?

2. Regarding your bioassay validation for the ELISA method submitted in Appendix 3:
    a. Clarify whether the kit standard included as part of the commercial kit or the recombinant human PrP standard you generated will be used for the proposed study. Additionally,
        i. Provide data for the source, purity, identity (peptide sequence, tags), and stability of your in-house recombinant human PrP reference standard.
        ii. Justify the representativeness of the in-house recombinant human PrP reference standard to the human PrP found in pre-symptomatic patient CSF.
        iii. We are unclear on what you mean by “A recombinant standard curve was prepared from AAA-quantified recombinant huPrP” in Appendix 3 Supplemental Figure S3. Clarify if the recombinant PrP concentration measurement uses extinction coefficient for the calculations.
        iv. We are concerned that your currently validated range for the standard curve may not capture the range of pre- and post-treated CSF PrP concentrations. In Appendix 3, Supplemental Figure S3B, the linear portion of recombinant human PrP standard curve, measured within the BetaPrion Human ELISA kit’s detection range 1-20 ng/ml, has only 4 points in the linear portion of the curve. The two highest concentrations of recombinant human PrP standard resulted in plateauing of the absorbance units and are not part of the linear standard curve drawn. You should ensure that a sufficient number of data points form the linear standard curve within a range that is clinically meaningful in terms of the anticipated drug response you expect from the ASOs you study. We generally recommend at least 6 non-zero data points in the linear range. Please provide a narrative that justifies your choice of the reference standard and the linear range of the validated reference standard.
        v. Clarify the matrix used to dilute the reference standard and clinical samples.
        vi. In the Appendix 3 paper and the supplementary discussion, you conclude that “kit standards, while technically reproducible, may most usefully inform relative rather than absolute quantification of PrP.” We are unclear on what this statement means. Please clarify and justify your quantitative output given this potential caveat.
    b. Clarify the source and epitope specificity of the antibodies used in the ELISA method.
    c. The critical reagents in the modified ELISA should be evaluated for their stability at the intended storage or in-use temperature.

d. Appendix 3 provides data on dilution range, spiking, plate to plate variation, and within plate variation produced with different CSF samples. We generally recommend the inclusion of quality control samples, such as a positive and negative control CSF sample. Will quality control samples of known concentrations of PrP be included in the validation runs of the assay?
e. According to submitted information, the LLOQ reported is 3-5x the blank signal. We generally recommend ≥ five times the analyte response of the zero calibrator (see Table 1 in FDA Bioanalytical Method Validation Guidance for Industry (2018)). You state that the variation stems from different plate readers; therefore, consider validating the method using a plate reader of choice or predefine the instrument variables that achieves the recommended LLOQ level in relation to the blank and independent of the plate reader choice.
f. As drug development proceeds, you should plan to include inter-laboratory variability testing (reproducibility), in addition to the intra-laboratory variability (intermediate precision) you have tested.

3. Regarding the mass spectrometry (MS) data submitted in Appendix 4.
   a. Targeted MS is used to show that correlation of total protein to measured PrP in ELISA is not due to ELISA measuring off-target proteins. We are unclear if you are proposing to use the targeted MS for additional assay validation and use with clinical samples. Please clarify your proposed plan for use of the MS method.
   b. If you chose to include this method as part of your proposed clinical study, additional data confirming assay validation would be needed.
   c. We note that the targeted MS method appears to provide greater values for PrP concentration than the ELISA method for comparable samples (Figure 3 in Appendix 4). Please provide your explanation for this difference. If differences might be due to protein conformational and peptide sequence differences as detected by the ELISA method, please consider including both the ELISA and MS methods in your proposed study as orthogonal measures of PrP concentration.

Question 2: Have we adequately controlled pre-analytical variability in our handling of CSF for PrP quantification? What, if any, further experiments are needed?

FDA Response to Question 2:

While your overall approach seems reasonable, please provide a detailed SOP that allows a review of the standardized and objective methods you propose to use to control for the pre-analytical variability during the handling of CSF. Also see general comments on SOPs in response to Question 1.

We note that some of the CSF samples tested in the data you submitted were collected almost two years prior to the analysis. In your SOPs, please define limits for storage time and temperature for the samples based on available data on the stability of PrP concentration measured over time.

Question 3: Have we adequately established that the tissue of origin for CSF PrP is brain? Besides the planned preclinical experiments in rats to correlate CSF PrP to brain PrP following ASO treatment (described below), what other experiments would be necessary?

FDA Response to Question 3:

See responses to Questions 6 and 7.

Question 4: Have we adequately established test-retest reliability of CSF PrP in presymptomatic genetic prion disease mutation carriers? Other than continuing to collect a larger cross-sectional cohort and additional longitudinal timepoints, what other data will be necessary?

FDA Response to Question 4:

See responses to Questions 1 and 2.

Question 5: What, if any, further studies in this domain will best help to support this biomarker for use as a surrogate endpoint under the Accelerated Approval program?

FDA Response to Question 5:

See responses to Questions 6 and 7.

Questions Regarding Preclinical Experiments to Support Use of PrP as a Biomarker

Question 6: Pending results from ongoing analytical validation, will any further validation of the cross-species ELISA be required to support its use in preclinical studies related to this project?

FDA Response to Question 6:

See responses to Questions 1 and 2 for comments regarding ELISA methods validation.

There may be there may be additional considerations for a rodent-specific PrP ELISA bioassay that will need to be reviewed. We ask that you submit data supporting analytical validation of the animal PrP assay to allow our assessment, including species specificity of the antibodies and reference standard, assay linearity, matrix effects, limits of quantitation, and variability of the method. When successfully validated, provide your standard operating protocols for specific use in your rodent studies.

Question 7: Will our proposed experiments relating brain PrP knockdown to survival time in prion-infected mice be adequate to establish the minimum reduction in PrP needed to confer a clinical benefit? What other experiments would be required?

FDA Response to Question 7:

Based on the limited discussion provided in the briefing documents and the proposed use of the nonclinical data, we have the following comments on your nonclinical program:

- To more convincingly demonstrate the relationship between brain PrP knockdown, disease progression, and survival time in animals, we recommend you conduct studies in more than one animal model of prion disease. Justification (with supportive data) should be provided for the animal models selected, as well as a discussion as to the clinical relevance of each. These studies should:
    - Test a wide dose range to fully explore dose-response in vivo, using a sufficient number of animals per group to ensure adequate power to detect a meaningful effect.
    - Be conducted using a clinically relevant route of administration and dosing regimen. In the completed proof-of-concept (PoC) studies in the infected mouse, animals were initially administered the ASO prior to infection, which may be less relevant to the human situation.
- The relevance of data on the tissue of origin of csf PrP and relationship between brain and csf levels of PrP in a species (e.g., rat) other than the one(s)

used for animal efficacy studies is uncertain. However, in evaluating the relationship between brain and csf PrP levels, it would be potentially important to assess regional differences in PrP levels in brain as well as total brain levels, prior to and after ASO administration.

- Pivotal nonclinical studies to support the use of csf PrP as a biomarker for humans and to establish a minimum reduction in csf PrP necessary to predict clinical benefit should be conducted in a rigorous manner, with appropriate controls. Study reports should provide a detailed description of the methods used and the results, to include summary and individual animal data.

Question 8: Will our proposed experiments in rats correlating CSF PrP to brain PrP upon administration of a range of ASO doses be adequate to establish that CSF PrP reflects brain PrP knockdown? Are any other studies required?

FDA Response to Question 8:

See response under Questions 6 and 7.

Question 9: What further studies in this domain will best help to support this biomarker for use as a surrogate endpoint under the Accelerated Approval program?

FDA Response to Question 9:

See response under Questions 6 and 7.

3.0 ADDITIONAL INFORMATION

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to [redacted]. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

[redacted]

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

[redacted]