DRUG DEVELOPMENT TOOL
LETTER OF INTENT DETERMINATION
DDT COA #000126

Attention: Orin Tempkin
Executive Director, Regulatory Affairs
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

Dear Dr. Tempkin:

We have completed our review of the Letter of Intent (LOI) for Drug Development Tool (DDT) COA #000126 received on January 22, 2020 by the CDER Clinical Outcome Assessments (COA) Qualification Program, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act.

The LOI is for the Functional Vision Questionnaire, a patient reported outcome (PRO), proposed for the assessment of "visual function and functional vision" in adolescent (12-17 years) and adult (18 years or older) patients with a clinical and genetic confirmed diagnosis of retinitis pigmentosa (RP).

FDA has completed its review and has agreed to accept your LOI into the CDER/CBER COA Qualification Program provided the context of use is narrowed to specify a more homogeneous patient population (i.e., patients with clinical and genetic confirmed diagnosis of RLBP1 RP) for the reasons described below.

Introductory Comments:
We acknowledge your plan to develop a PRO measure for use in patients with different RP gene mutations. However, given the heterogenous nature of RP, especially regarding variability among RP subtypes in the rate and extent of progression of loss of vision, the age of onset of symptoms and the features of visual impairment, we ask that you limit the context of use to patients with a clinical and genetic confirmed diagnosis of RLBP1 RP. As such, patients with RLBP1 RP genotype should be well-represented in your concept elicitation and cognitive interviews, as well as instrument validation.

Following agreement on the patient population for purposes of qualification, we can provide more targeted comments on instrument development to-date, including content validity, as well as your plans for future validation of the instrument. It is premature to comment on content validity of the instrument at the time.

FDA's response to the questions included in the LOI can be found below.

Question 1 – Regarding the population included in the PRO development study
Does the Agency agree that the samples of patients included in the PRO development research provide adequate representation of different RP gene mutations (excluding Usher Syndrome), such that the instruments could be appropriate for completion with patients with all RP gene mutations (excluding Usher Syndrome)?

FDA Response: See Introductory Comments.

Question 2 – Regarding the PRO concept elicitation and cognitive debriefing research
Does the Agency agree that the qualitative evidence generated to-date and the concept elicitation and cognitive debriefing methods being used in the current qualitative research, are adequate and appropriate for the instruments in question, and will be sufficient to demonstrate content validity of the specific FVQ PRO instruments within the proposed context of use (RP population)?

FDA Response:
The described methodology for your qualitative research appears to be a reasonable approach to establish content validity. However, we cannot yet agree that content validity has been established as your qualitative work is still ongoing. Additionally, given our request to narrow the context of use to patients with the RLBP1 genotype, we will need to review the data for patients with the RLBP1 RP genotype. To fully assess the content validity of the FVQ PRO, we would need to review the following qualitative information: qualitative protocol, interview guide and qualitative study report (including transcripts); the latter should focus on the genotype of interest for purpose of this qualification project. You may submit this information for FDA review and comment as a stand-alone submission prior to submission of your Qualification Plan.

Currently, we note redundancies across the items which may increase patient burden. Carefully consider the length of the FVQ PRO. Consider identifying the optimum number of items to measure the concept(s) of interest and avoid duplication, where feasible, to reduce respondent burden and maximize the quality and completeness of PRO data.

Question 3 – Regarding concepts assessed in the PRO
Does the Agency agree that the concepts included in the PRO assess the most important visual function and functional vision concepts relevant for RP, and are appropriate for use with adults and adolescents with RP?

FDA Response: As discussed in the Introductory comments and in our response to Question 2 above, we cannot yet agree that content validity (including the concepts incorporated in the PRO measure) has been established. However, we note that some items of the draft FVQ PRO include activities that may be less applicable to adolescents less than 16 years of age (i.e., driving, cooking, etc.).

We also recommend that you adopt a more descriptive term when referring to the concept of interest (e.g., vision-dependent daily life activities). We are concerned that terms such as “functional vision” may not clearly describe what is being measured and will not be clear to a broad set of stakeholders.

Question 4 – Regarding appropriate use of the PRO
Does the Agency agree that the PRO is appropriate for use in adolescents aged 12-17 years and adults aged 18 years or more with RP of all severity levels?

FDA Response: See Introductory Comments.

Question 5 – Regarding specification of lighting conditions and familiarity of environment in PRO items
Does the Agency agree with the proposed structure of items in the FVQ PRO to assess the impact of different lighting conditions and familiarity of environments, to facilitate patient understanding and to assess different severities of functional vision?

FDA Response: See Introductory Comments.

Question 6 – Regarding administration format of PRO
Does the Agency agree that the FVQ PRO should be self-administered or interviewer-administered depending on the patient’s visual ability and whether they can read the questions and complete the instrument without help?

FDA Response: Yes, this approach appears reasonable. However, training materials should be developed to ensure that the interviewers do not lead the patients in their responses and that they administer the instrument free of bias and in a standardized manner.

Question 7 – Regarding PRO instrument wording
Does the Agency agree that the proposed wording used for the PRO instructions, questions and response options is appropriate and consistent with the evidence generated so far from this study and the previous research conducted?

FDA Response: We cannot agree as your qualitative study is still ongoing. Data from your cognitive interviews will help inform the suitability of the proposed wording of the PRO instrument.

Question 8 – Regarding PRO conceptual framework and plan for psychometric analysis and validation
Does the Agency agree with the proposed plan to: confirm the appropriateness of the conceptual framework, establish scoring and evaluate reliability and validity in the RP population for the specified PRO instrument?

FDA Response: There is insufficient information for review and comment. Plan to submit the protocol for the observational, non-interventional study and psychometric analysis plan with adequate time for FDA review prior to database lock.

The next milestone submission you would be working towards is a Qualification Plan. However, we encourage you to submit your qualitative protocol, interview guide and study results (including interview transcripts) for FDA review and comment prior to submitting your Qualification Plan.

The following weblink contains the contents to include in your Qualification Plan: www.fda.gov/media/123245/download. Please contact the CDER COA Qualification Program at COADDTQualification@fda.hhs.gov should you have any questions (refer to DDT COA #000126).

Sincerely,

Elektra J. Papadopoulos -S

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