DRUG DEVELOPMENT TOOL
LETTER OF INTENT DETERMINATION
DDT COA #000127

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 #000127 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, an observer reported outcome (ObsRO), proposed for the assessment of "visual function and functional vision" in pediatric (3-11 years) 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 an ObsRO measure for completion by parents/caregivers of pediatric 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 ObsRO development study

Does the Agency agree that the samples of patients included in the ObsRO development research provide adequate representation of different RP gene mutations (excluding Usher Syndrome), such that the ObsRO instrument could be appropriate for completion with parents/caregivers of pediatric patients (3-11 years) with all RP gene mutations (excluding Usher Syndrome)?

FDA Response: See Introductory Comments.

Question 2 – Regarding the ObsRO 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 ObsRO instrument 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. We cannot yet agree that content validity has been established as your qualitative work is still ongoing and we have also recommended to narrow the context of use to patients with RLBP1 RP genotype. To fully assess the content validity of the FVQ ObsRO, we would need to review the following qualitative information: qualitative protocol, interview guide and qualitative study report (including transcripts).

Question 3 – Regarding concepts assessed in the ObsRO

Does the Agency agree that the concepts included in the ObsRO assess the most important visual function and functional vision concepts relevant for RP, and are appropriate and relevant to pediatric patients 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 ObsRO measure) has been established.

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 ObsRO

Does the Agency agree that the ObsRO is appropriate for use in parents or caregivers of pediatric patients aged 3-11 years with RP?

FDA Response: See Introductory Comments.

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

FDA Response: See Introductory Comments.

Question 6 – Regarding ObsRO instrument wording
Does the Agency agree that the proposed wording used for the ObsRO 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. However, we note that some items of the draft FVQ ObsRO include concepts that may be impacted by factors other than treatment effect (i.e., upset, frustrated). Data from your cognitive interviews will help inform the suitability of the proposed wordings of the ObsRO instrument.

Question 7 – Regarding ObsRO 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 ObsRO 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 (PAP) with adequate time for FDA review prior to database lock. Please consider the following comments when you prepare the protocol and the PAP:

- The proposed sample size of 40 subjects appears to be small to adequately evaluate the psychometric properties of the ObsRO instrument; however, we recognize this is a rare disease and are open to alternative approaches. Please provide a justification for the proposed sample size as part of your Qualification Plan.

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 qualitative study report (including transcripts) for FDA review and comment prior to submitting your Qualification Plan.

The following weblink contains the contents to include in your Qualification Plan submission: 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 #000127).

Sincerely,

Elektra J. Papadopoulos -S

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