DRUG DEVELOPMENT TOOL
QUALIFICATION PLAN DETERMINATION
DDT COA #000125

Debora D. Merrill, MBA
Vice President, COPD Biomarkers Qualification Consortium
COPD Foundation
3300 Ponce de Leon Boulevard
Miami, FL 33134

Dear Ms Merrill:

We have completed our review of the Qualification Plan (QP) for Drug Development Tool (DDT) COA #000125 received on March 25, 2020 by the CDER Clinical Outcome Assessments (COA) Qualification Program, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act.

The QP is for the Endurance Shuttle Walking Test (ESWT), a performance outcome (PerfO) assessment, proposed for the assessment of walking endurance in patients with a diagnosis of COPD.

We have completed our review of your QP and have determined that we are unable to accept your QP at this time. However, we want to work with you to ensure the necessary elements are included in a revised QP submission. The following additional information would help us to do so.

1. Provide rationale and a plan for how the measure of endurance time (ET) can be interpreted and how much a change is important in COPD patients in your proposed context of use.
2. Provide us specific trials and sufficient details that will be used in your proposed measurement property evaluation analyses. We recommend that you provide a table of studies that will be used for each analysis and list all COAs available in those studies and copies of the COAs, and describe the important study design elements, including study population and timepoints of assessments. Please also see previous Reviewability Memo sent to you on January 30, 2020 where specific information and comments were requested for inclusion in a QP submission in red font in the QP outline's section. The table should include only existing COPD trials where study populations are consistent with the proposed context of use and include the following information:
    - Key inclusion/exclusion criteria of study population

- Names of COAs and relevant assessments (links to copies)
- Timing/schedule of assessments for each of the assessment above
- Number of patients enrolled in each trial and number of patients eligible for measurement property evaluation

Additional comments:

1. You proposed to conduct psychometric analyses using an integrated database that consists of previously collected data from prospective interventional studies in patients with COPD. Please conduct your psychometric analyses using data from existing COPD trials where study populations are consistent with the proposed context of use.

2. You proposed that for pre-/post-intervention analyses, only subjects with non-missing ET during ESWT at baseline and at end-treatment would be included in the dataset. However, it is important to assess the impact of missing data and propose ways to handle missing data as part of your qualification package. Please include a plan for how you will assess the impact of missing data as part of your QP.

3. For your proposed test-retest reliability assessments, specify the study population, timepoints of assessments, and evidence showing that patients' COPD is stable between the assessment timepoints (e.g., based on relative stability of other clinical parameters). In addition, provide justification for your selections.

4. We acknowledge that inter-rater reliability assessment is not applicable in this context, as the ESWT is not a rated assessment. However, we recommend you address whether it is feasible to assess inter-operator/administrator reliability using existing data, because the operator/administrator could introduce variability into the measurement. Doing so could also provide opportunity to identify potential modification that needs to be made to the training manuals.

5. We acknowledge your plans to use FEV1 in known groups validity analyses. Please provide a rationale that FEV1 is a useful parameter for these analyses. If you choose to conduct known groups validity assessments, we recommend including reports of functioning by patient-reported outcome (PRO) measures, if feasible.

6. Specify construct validity analyses and anticipated relationships with measures of concepts of interest, e.g., total and specific components of SGRQ scores.

7. We do not agree with the statement in the submission that it is not applicable to use anchor scales to evaluate the responsiveness of ESWT. We recommend that you evaluate ESWT's ability to detect small but meaningful within-patient

changes using data that compare change in ET to change in other similar measures that indicate that the patient's state has changed with respect to the concept of interest. For example, ETs are longer among patients who have demonstrated improved functional status as classified by a PRO measure (as the external anchor).

3. Clarify your proposed responder analyses and responder definition. It is important to understand what is meaningful change in ET that is reflective of improvement in patients' daily lives. Therefore, the use of FEV1, a biomarker, has limited utility as an anchor because FEV1 does not assess how patients function in daily life. Anchor-based methods are the primary methods we use to interpret meaningful within-patient score changes in COA endpoints. Anchor-based methods should be supplemented with anchor-based empirical cumulative distribution function and probability density function curves. For anchor-based method, you need to pre-specify and justify clinical meaningful threshold of change in your proposed anchor scales. Additionally, proposed threshold of 0.3 for correlation coefficient which will be used in anchor-based method in defining a responder of ESWT needs to be justified. Note that external anchors should have the following properties and we recommend submitting exact copies of the anchor scales for Agency review and comment:
    - Selected anchor scales should be associated with the target COA endpoint in a way that addresses the question of clinical meaningfulness of the target COA endpoint. For example, for an endpoint measuring a specific aspect of the disease, an anchor scale measuring the global status of the disease may not be helpful.
    - The anchor scale should be easier to interpret than the COA endpoint itself and meaningful to patients. The anchor scale's response categories should be distinct and non-overlapping and should represent meaningful differences among adjacent response categories. For example, an anchor scale that uses a 0-10 numeric rating scale would not be easy to interpret and would not be an appropriate anchor scale in most contexts. An example of a commonly used response scale for rating severity is none, mild, moderate, or severe.
    - The anchor scale's recall period should be consistent with the assessment time period of the prespecified endpoint to the extent possible.
    - The anchor scale should be plainly understood by respondents in the context of use.

    Other methods may be explored to complement the anchor-based methods or when anchor-based methods are not feasible (i.e., when no adequate anchor measure(s) are available, small sample size). For example, patients can be queried via cognitive interviews to help inform the improvement threshold.

8. At this time, we do not envision that ESWT can be used as a primary or co-primary endpoint in confirmatory trials meant as primary support for efficacy or in

pivotal dose-ranging trials. We recommend revising the context of use to be used as a secondary endpoint to support labeling and inform healthcare providers.

9. We recommend inclusion of a stopping rule for SpO2 <=80% when accompanied by symptoms and signs of severe hypoxemia during the ESWT test for subject safety.

10. You may refer to the 2009 FDA Guidance for Industry entitled, "Patient Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatory information/guidances/ucm193282.pdf) and our website for the FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making (https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical) for information regarding the psychometric analysis plan. The information includes sections on evidence of construct validity and the assessment of reliability, validity, and ability to detect change.

Please contact the CDER COA Qualification Program at COADDTQualification@fda.hhs.gov should you have any questions (refer to DDT COA #000125).

Sincerely,

Elektra J. Papadopoulos -S

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