DDT 000015 **COMMENTS ON COA DDT SUBMISSION**

March 5, 2018

Stephen Coons, PhD
Executive Director
PRO Consortium
Critical Path Institute
1730 E. River Road
Tucson, AZ 85718

Regarding: DDT #000015 Initial Briefing Package for the PROMIS® Short Form Fatigue 10a for use as a secondary endpoint evaluating fatigue severity among adults, 18 years and older, with a definite diagnosis of rheumatoid arthritis (RA)

Dear Dr. Coons:

Please refer to your August 11, 2017 submission of the initial briefing package for the COA DDT Qualification: PROMIS® Short Form Fatigue 10a, first submitted to the FDA on June 3, 2010 (DDT #000015). We have reviewed your initial briefing package and associated documents.

We thank you for providing the documentation referred to above. After reviewing this submission, the QRT recommend that you submit the documents requested below and address the QRT's comments before proceeding with your plan to conduct further development to support this qualification program.

Our responses to the specific questions posed to the QRT in Section 3 of the initial briefing package (page 24) are provided below:

SUBMITTER QUESTIONS

1. **Does the agency agree that the development and validation of the *PROMIS® Short Form Fatigue 10a* supports its consideration for qualification as a Drug Development Tool for fatigue in Rheumatoid Arthritis?**

   QRT Response:

   It is premature for us to fully comment on the content validity of the PROMIS® Short Form Fatigue 10a. Please submit for following documents for our review:

- The research report "Strand V, Simon LS, Bingham III CO, Hewlett S. Gap analysis on measures used to assess fatigue in adult patients with rheumatoid arthritis. A report prepared for the Critical Path Institute, PRO Consortium, RA Working Group. August 18, 2014."

- If available, the full study report for the study described in "Kaiser K, Shaunfield S, Clayman ML, Ruderman E, Cella D. Content validation of the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale in moderately to highly active rheumatoid arthritis. *Rheumatology (Sunnyvale) 2016;* 6:193".

There is insufficient information regarding psychometric properties for the PROMIS® Short Form Fatigue 10a based on data from the RA patient population. The Johns Hopkins Arthritis Center RA cohort study used computerized adaptive testing (CAT) administration and scoring for the PROMIS® Fatigue, which is related but does not directly inform the measurement properties of the PROMIS® Short Form Fatigue 10a in patient with RA. Likewise, the STAR study which used PROMIS® Short Form v1.0 Fatigue 13a also does not directly inform the measurement properties about PROMIS® Short Form Fatigue 10a. Please submit the following publication and document for our review:

- Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, Fischkoff SA, Chartash EK. Adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *Journal of Rheumatology* 2003; 30(12):2563-2571.

- Your plan for assessing the measurement properties of the PROMIS® Short Form Fatigue 10a in patient with RA including, but not limited to, reliability, construct validity, ability to detect change, and meaningful within-patient score change for score interpretation.

2. Does the agency agree that the *PROMIS® Short Form Fatigue 10a* is appropriate for use as a secondary endpoint measure in Rheumatoid Arthritis registration trials?

ORT Response:

It is premature for us to make this determination. Please see our response to Question 1. Additionally, we note that fatigue would be assessed, along with other measures of RA symptoms and disease activity, at baseline and then repeatedly, but no more often than weekly, while the patient remains in the study. To assist in interpreting these repeated measurements, in addition to reporting the individual responses at various time points, determine a clinically meaningful within-patient change (i.e., the individual patient *PROMIS Short Form Fatigue 10a* score change over a predetermined time-period that should be interpreted as a treatment benefit) of the endpoint. While you have provided a preliminary proposal of a clinically meaningful within-patient change threshold in your briefing package, also consider anchor-based methods and distribution-based methods to support this within-patient change threshold.

We also refer you to the *Guidance for Industry Rheumatoid Arthritis: Develop Drug Products for Treatment* https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm354468.pdf which provides details on the information needed to support additional endpoints in RA, such as the proposed PROMIS® Short Form Fatigue 10a. Please note that such endpoints will not be sufficient, on their own, to support a regulatory approval for products in RA.

3. **What further information would be helpful for reviewing this proposed outcome assessment?**

ORT Response:

Please see our response to Question 1. In addition, please identify when the PROMIS® Short Form Fatigue 10a was finalized in relationship to the initial development and finalization of the PROMIS® Fatigue bank, the Johns Hopkins Arthritis Center RA cohort study, and the STAR study, and the Kaiser et al (2017) qualitative study.

Please describe in detail your plan for scoring the PROMIS® Short Form Fatigue 10a when there is item-level missing data and how missingness will be handled in analyses of PROMIS® Short Form Fatigue 10a.

If you have any questions or would like to set up a teleconference to answer questions, please contact the Clinical Outcome Assessments Staff at COADDTQualification@fda.hhs.gov.

Sincerely,

Elektra J. Papadopoulos -S

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