DDT 000018 **COMMENTS ON COA DDT SUBMISSION**

March 22, 2018

Kellee Howard, MA, MSc
Director
ICON Commercialisation & Outcomes
456 Montgomery St., Suite 2200
San Francisco, CA 94104
Phone: 415 856 0840
Email: Kellee.Howard@iconplc.com

Regarding: DDT #000018 Updated psychometric evaluation and SAP for the Community-Acquired Bacterial Pneumonia Daily Symptom Diary (CABP PRO) instrument for the measurement of respiratory and systemic symptoms of community-acquired bacterial pneumonia (CABP).

Dear Ms. Howard:

Please refer to your October 20, 2017 submission to the Clinical Outcome Assessment (COA) Qualification Program for DDT#18: CABP PRO, first submitted to the FDA on April 5, 2013. This letter also reflects the ICON/FNIH teleconference held on February 13, 2018. As discussed during the teleconference, we acknowledge that you will be proceeding with your psychometric study prior to item reduction and agree with the plan to proceed with formal item reduction after an evaluation of the quantitative evidence and convening an expert panel (which will include FDA representatives).

We appreciate your attention to our requests for revision of your psychometric evaluation study protocol and statistical analysis plan (SAP). We have reviewed the revised documents and you have addressed many of our previous concerns. However, we have the following additional comments and suggestions that reflect what will need to be addressed during the qualification review:

CABP PRO and Protocol Comments:

1. CABP PRO Items: While we agree that it is acceptable to proceed with the full 29-item CABP PRO diary in your psychometric evaluation study at this time, note that you will need to submit a copy of your psychometric study report, along with a full data set (including longitudinal item response data from each participant, baseline information, and other measures completed by participants and clinicians) to facilitate qualification review. We

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Silver Spring, MD 20903
www.fda.gov

remind you that we are most interested in core disease-related symptoms and impacts, as outlined in the CABP guidance. Careful attention to content validity and other measurement properties of the instrument and adherence to the agreed upon concept(s) and context of use for the instrument will be needed for successful qualification effort. Retention of items that do not closely adhere to the concept(s) could present a content validity issue.

2. Not Applicable Response Option: You have chosen to retain the "Not Applicable" response option for items 24-29 (see FDA letter of August 17, 2017) and have requested clarification regarding our recommendation.
    a. To clarify, we continue to recommend the removal of the "Not Applicable" options from items 24-29. We do not believe that "Not Applicable" is a meaningful response to these items.
    b. The Rating Scale model and classical test theory scoring you will use in your psychometric analysis assume that items have ordinal response scales. The CABP PRO's first 23 items have a 5-point ordinal response scale (from "Not at all" to "Very Much") but items 24-29 do not have an ordinal response scale due to the inclusion of the "Not Applicable" option. Please explain how your IRT and classical test theory scoring will accommodate item responses of "Not Applicable."
    c. Please provide us with a rationale, supported by the qualitative interview data (patient understanding of this option within the context of each question), to justify the inclusion of the "Not Applicable" option for items 24-29. We continue to have concerns that patients might have difficulty interpreting the meaning of the "Not Applicable" response option for items 24-29.

3. **Item Interpretation for Inpatients vs. Outpatients:** We continue to have concerns regarding the interpretation of items 24 (difficulty sleeping), 25 (difficulty doing usual activities), and 27 (social activities) among inpatients and outpatients (see FDA letter of August 17, 2017). Specifically, we are concerned that inpatients' responses to these items could be limited by hospital protocol/ environment (e.g., level of independence and sleep schedules) whereas outpatients don't have these same constraints. Please explain how your scoring algorithm will account for these differences between the two subpopulations.

4. **Item Skipping:** We understand that the ePRO device used at US sites will be programmed to require participants to respond to every item.
    a. We are concerned that forcing patients to respond to each of the 29 items will add undue patient burden, increase chances for fatigue, and consequently impact the quality of response received over the 14-day period. That is, valid item responses will be discarded if a patient decides not to complete the entire PRO, and other fatigued patients will sometimes give rote responses to hasten completion. Please explain your plan for empirically evaluating the effect of response requirements on the quality, validity and reliability of the CABP PRO data. If evidence in the literature is available to justify this approach with other PRO measures, please provide us with copies of these references for review. In addition, we recommend you consider (i) programming the ePRO devices so that the first 7 item responses measuring core disease-related symptoms are uploaded automatically once a patient completes them; this will ensure that these responses are collected for all patients even if they do not complete the entire PRO, and (ii) administering the full CABP PRO every other day, while only administering the first 7 items on the remaining, alternating days.

5. **Language Translation and Cultural Adaptation:** Per our February 13, 2018 ICON/FNIH teleconference meeting, we acknowledge that plans for translation and cultural adaptation will be discussed later, after final item reduction is complete for the English version of the CABP PRO diary.
6. **Exclusion criteria:** We recommend that you consider exclusion of patients with post-obstructive pneumonia and known bronchial obstruction (e.g., in the setting of pulmonary malignancy) because the symptoms of the pulmonary disease process are likely to be progressive and may not respond to antibacterial drug therapy. Also, this exclusion criterion is consistent with the FDA guidance on CABP.

SAP Comments:

7. Page 17 of your SAP briefly discusses how endpoints will be constructed from longitudinal CABP PRO data.
    a. The SAP details how the reliability and validity of the CABP PRO will be assessed. However, please be aware that the FDA will be qualifying the PRO instrument in the context of the endpoint(s) it will support. In this case, the endpoint should be in alignment with the FDA's CABP Guidance. Please propose an endpoint(s) based on the CABP PRO.
        - The FDA guidance on CABP (p. 8) notes two possible primary efficacy endpoints: (i) improvement in respiratory symptoms (corresponding to CABP PRO items 1, 2, 4, and 6), and (ii) 28-day mortality. If your intention is that the CABP PRO be used to define a primary efficacy endpoint, then the average of CABP PRO scores over 7 days (discussed in the SAP) will not correspond to the guidance recommendation for a suitable primary endpoint for a noninferiority trial. Likewise, defining a primary efficacy endpoint that includes the assessment of non-respiratory symptoms will also not be aligned with guidance recommendations. Please explain whether you aim to define a primary efficacy endpoint and discuss whether it will conform to FDA guidance recommendations.
    b. Any PRO assessing symptoms of serious diseases will sometimes have missing data due to patient incapacity or death. For example, CABP inpatients will be unable to complete the CABP PRO on any days they are ventilated. Endpoints should be defined so that they still have meaningful values in the face of PRO data that are missing due to patient incapacity or death. Please explain how you will do this.
    c. If you define an efficacy endpoint in terms of averaging some number of daily CABP PRO scores, then participant status over the days that are averaged should be stable. Otherwise, for some participants, the endpoint could represent the average of poor and good status at different time points, which would be hard to interpret.
    d. As you plan to recruit CABP and HABP patients together to develop a single instrument that can be used by CABP and HABP patients, you will need to submit a letter explaining your new plan to develop your instrument in both populations and a revised SAP reflecting these changes and how the two populations will be analyzed.

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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Date: 2018.03.26 17:48:37 -04'00'

Elektra Papadopoulos, MD, MPH
Associate Director
Clinical Outcome Assessments Staff
Office of New Drugs
Center for Drug Evaluation and Research

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products (DAIP)
Office of Antimicrobial Products
Center for Drug Evaluation and Research