DDT 000071 **COMMENTS ON COA DDT SUBMISSION**

December 1, 2017

ICON
Attention: Kellee Howard, MA, MSc
Senior Principal, Clinical Outcomes Assessments
456 Montgomery St. Suite 2200
San Francisco, CA 94104
Phone: (226) 647-0629
Fax: (415) 856-0840
Email: kellee.howard@iconplc.com

Regarding: DDT COA 071 Initial Briefing Package (May 3, 2017) for Hospital-acquired Bacterial Pneumonia Daily Symptom Diary (HABP PRO) for the measurement of respiratory and systemic symptoms of Hospital-acquired Bacterial Pneumonia (HABP).

Dear Ms. Howard:

Please refer to your May 3, 2017 submission for COA DDT Qualification: HABP PRO (DDT #000071). As communicated in our response to your submission for COA DDT Qualification: CABP PRO (DDT #000071), we acknowledge that you will be proceeding with your psychometric study for the HABP PRO prior to item reduction. However, as with the CABP PRO, it is possible that administering the draft instrument items prior to item reduction phase can impact the sensitivity of the instrument and its ability to accurately assess core concepts of HABP. In the absence of a formal item reduction phase prior to psychometric testing, we recommend that you engage in multiple iterations of item reduction using qualitative (i.e., expert consensus panel review with subject matter experts, including FDA representatives; exit interviews with patients) and quantitative methods to ensure that the most relevant items are included in the final instrument. Note that another clinical study may be needed to confirm the psychometric properties of the reduced instrument. As you have stated in your submission, you intend to administer one common instrument in both CABP and HABP patient populations in a combined CABP/HABP study. While we are open to considering this approach, we would need to evaluate the results of the planned psychometric evaluation to determine whether this approach is appropriate.

Our responses to the specific questions posed to the QRT in Section 1 of the IBP (PAGE 1) are provided below:

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

1) Does the CDER committee agree that the methodology used to develop the HABP PRO measure, as described in this IBP, was appropriate?

   ORT Response: Yes, we agree.

2) Based on the completed and ongoing development procedures and findings detailed in this IBP, does the CDER committee agree there is good content validity of the draft HABP PRO measure?

   ORT Response: Additional information, including patient demographic and clinical characteristics will need to be submitted for review (see requested information in Agency previous response to the initial IBP). While not a regulatory requirement, additional interviews could also be considered to help determine whether patients can distinguish between concepts (e.g., weakness, low energy, and tiredness; shortness of breath and difficulty breathing). Note that we acknowledge the potential challenges associated with recruiting HABP patients for an additional qualitative study. Therefore, we recommend that you consider generating any additional qualitative evidence through exit interviews that can be conducted after the primary psychometric evaluation study.

   - **While not a regulatory requirement, in addition to evaluating patients' ability to distinguish between concepts, you should consider using the exit interviews to cognitively debrief patients about:**
     - **Their thoughts on what they believe constitutes a meaningful improvement from baseline in their symptoms in terms of each item.**
     - **What they consider to be a meaningful improvement in terms of PGIS category changes (e.g., 1-category change, 2-category change, etc.), as well as in PGIC categories (e.g., reporting "a little better," "a lot better").**
   - **If you choose to conduct exit interviews, we recommend that you submit an exit interview protocol and interviewer guide to the Agency for review and comment. The interviews should be conducted after the patients complete the main portion of the study to avoid any potential compromise to trial integrity.**

3) The qualitative data support the use of items from the CABP PRO instrument in HABP patients. This finding suggests the use of a unified PRO instrument for both types of pneumonia. Does the CDER committee agree?

   ORT Response: While we are open to considering this approach, it is premature for us to agree with this proposal. It is appropriate to proceed with combining both CABP and HABP patients in your planned psychometric evaluation study. However, we would need to review the evidence generated from this study to determine whether this approach is appropriate or whether it is best to create two separate instruments.

We offer the following additional comments and suggestions for your consideration.

General Comments:

1. In your next submission, you should include additional information about data collection procedures for inpatients and outpatients. Note that procedures will differ for these subpopulations, especially in instances where a patient's condition worsens to the point of hospitalization with ventilation over the course of the study, following the initial diagnosis of HABP. A patient may be enrolled in the study in the inpatient setting, but complete the study in the outpatient setting. Details regarding how these administrations will differ when the setting changes need to be added to the protocol.
    a. It is important to note that patients who are ventilated at study start can't complete the PRO in the ventilated state; they can only complete the PRO as they improve. Likewise, those patients who are not ventilated at study start but become ventilated during the study can complete the PRO at the beginning but won't be able to complete the PRO at the end. In both cases, it will be difficult to evaluate change over time.

2. Please clarify which domains/scores are being proposed/the most appropriate for qualification.

HABP PRO Instrument:

1. As with the CABP PRO, we recommend that that you focus on items 1-7 which constitute core symptoms of HABP. Any deviation from these cardinal symptoms has potential to alter the assay sensitivity and therefore create difficulty for the use of a noninferiority trial to establish efficacy of a new antibacterial drug for treatment of HABP. The remaining items may be considered for use as part of supportive endpoints.
    a. Please consider previous advice included our response to your CABP PRO submission (letter dated August 17, 2017). We believe that you should strongly consider reducing items prior to study implementation to reduce patient burden. HABP patients are concurrently experiencing or have recently experienced another medical condition serious enough to require hospitalization. Therefore, we are concerned that administering a 29-item questionnaire could have an adverse impact on data quality and interpretability.
        i. Burden associated with multiple items can lead to missing or spurious item responses.
        ii. Responses to items 8-29 can be confounded by experiences related to other medical conditions. Therefore, it would be hard to determine which changes in HABP PRO scores over time (or the lack thereof) are attributed to HABP status alone.
    b. For items 24-29, we recommend removing the "Not Applicable" response option. We don't believe that "Not Applicable" is a meaningful response option for these items (e.g., Item 24 – "Did you have difficulty sleeping?") and it is unclear how these options would be scored. Additionally, we are concerned that Item 24 (difficulty sleeping), Item 25 (difficulty doing your usual activities), and Item 27

(social activities) will not be applicable to the inpatient population as level of independence (doing usual activities, social interaction) and sleep schedules would likely be influenced by hospital protocol.

2. Psychometric testing of the proposed HABP PRO should be consistent with its intended use for defining efficacy endpoints. The IBP states that participation in the psychometric study will involve completing the HABP PRO for 14 consecutive days. Please distinguish between the burden associated with administering the HABP PRO more frequently during the psychometric study administration (every day for 14 days) compared to an actual clinical trial context. Current qualitative evidence was generated among patients not requiring mechanical ventilation. Please provide evidence to demonstrate how the transition from non-ventilated to ventilated status will impact the scoring of the instrument.

Endpoint Positioning:

1. We do not agree with the proposed use of the HABP PRO as a co-primary endpoint. Instead, we would be open to considering this instrument as a secondary in a subgroup of patients who can self-report.
    a. When defining the endpoint "assessment of resolution of signs and symptoms of HABP at a relevant time point after the completion of antibacterial drug treatment"
        - Please recommend relevant time points when the assessment should occur.
        - Please clarify how "resolution of signs and symptoms of HABP" will be operationalized (e.g., will it be based on attaining a score of zero on the HABP PRO, or on a cutpoint that will be established during the psychometric study?)

2. Please specify the number of days after treatment initiation at which it would be meaningful to assess improvement.

3. In figure 1 in the IBP and in the accompanying discussion you suggest ways in which the HABP PRO can be used to define efficacy endpoints. We recommend that you also consider the impact of ventilation on the ability to generate a score change. For example, for the hypothetical exploratory endpoint "degree of improvement in HABP symptoms between start of treatment and n days after the start of treatment," change scores cannot be computed for patients that were ventilated at the start of treatment and/or at n days during the study as a ventilated patient is unlikely to be able to meaningfully complete the HABP PRO. In this instance, you will need to determine whether the endpoint will then be undefined for these patients.

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

Digitally signed by Elektra J. Papadopoulos-S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300170743, cn=Elektra J. Papadopoulos -S
Date: 2017.12.11 13:04:32 -05'00'

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

Sumathi Nambiar -S

Digitally signed by Sumathi Nambiar -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300145731, cn=Sumathi Nambiar -S
Date: 2017.12.11 13:00:52 -05'00'

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