DDT 000019 **COMMENTS ON COA DDT SUBMISSION**

November 20, 2017

FNIH BC
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Regarding: DDT #000019 Psychometric Evaluation Protocol and SAP for the Acute Bacterial Skin and Skin Structure Infection Patient Reported Outcome (ABSSSI PRO) for use as a secondary endpoint in phase 3 clinical trials evaluating symptoms and symptom impact of acute bacterial skin and skin structure infection characterized by cellulitis (including erysipelas), abscesses, and wound infections (traumatic or surgical site).

Dear Mr. Hoffmann:

Please refer to your February 23, 2017 submission for COA DDT Qualification: Acute Bacterial Skin and Skin Structure Infection Patient Reported Outcome (ABSSSI PRO), first submitted to the FDA on October 15, 2012 (DDT #000019). We have reviewed your responses and associated documents. We appreciate your attention to our requests (FDA Comments Letter March 23, 2016) for revision of your psychometric evaluation study protocol and SAP (FDA Comments Letter dated March 23, 2016). We have reviewed the revised documents and while you have addressed some of our previous concerns, the QRT believes that further revisions are required prior to study implementation. Most importantly, we recommend that you further reduce items in the draft instrument prior to formal psychometric testing on the final instrument, and provide greater detail on your ePRO implementation plan, instrument administration schedule, and proposed analyses.

Specific recommendation and comments related to your revised psychometric evaluation protocol and SAP submission are provided below:

General Comments:

1. We continue to believe that the current instrument is too long and that it should be further revised to only include items that focus on cardinal symptoms and impacts of the disease and are most relevant to the broader ABSSSI patient population. We are concerned that the current length will increase missing data and limit the assessment's ability to detect change.

We recommend that you incorporate a preliminary item reduction phase (including multiple iterations of expert panel consultation and psychometric analyses), prior to instrument finalization, to reduce item redundancy and remove items measuring concepts that can be attributed to treatment side effects (e.g., headache, nausea) or that are distal to treatment effects (e.g., worried). This item reduction phase should be well-documented in your psychometric validation protocol and SAP – including plans for creating an item reduction table detailing your rationale for retaining and deleting individual items and an item-tracking matrix. We recommend that you conduct item selection based on findings from all qualitative and quantitative data analyses and not just Rasch model fit statistics. You may also want to consider a modular approach, where a specific domain (such as cardinal symptoms) with domain based scoring is consider for qualification.

2. Your protocol still lacks details regarding your study administration. Please revise to include additional information about the following:
    a. Data collection procedures for inpatients and outpatients: Procedures will differ for these subpopulations, especially in instances where a patient's condition worsens to the point of hospitalization over the course of the study, following the initial diagnosis of ABSSSI. In these cases, a patient may be enrolled in the study in the outpatient setting, but complete the study in the inpatient setting. Details regarding how these administrations will differ need to be added to the protocol.

3. Please clarify which study protocol is to be followed when the ABSSSI PRO data collection is conducted within the pharmaceutical company sponsored clinical trials, i.e., pharmaceutical company sponsored clinical trial protocol or the ABSSSI PRO psychometric evaluation protocol. In addition, please address the following issues:
    a. The process to ensure the consistency between the pharmaceutical company sponsored clinical trial data collection and the ABSSSI PRO psychometric evaluation data collection.
    b. The process to resolve the discrepancies between the pharmaceutical company sponsored clinical trial protocol and ABSSSI PRO psychometric evaluation protocol, in particular the discrepancy between the inclusion/exclusion criteria and the study design.
    c. The decision making process to stop data collection in pharmaceutical company sponsored clinical trials and to start the data collection from the ICON clinical sites.
    d. The process to pool the data sets collected from different trials.

4. Information regarding your eCOA system and implementation plan are not included in your protocol. We recommend the following:
    a. Submit Screenshots and training materials (site and patient) for your eCOA implementation for Agency review and comment.
    b. Plan to perform usability testing of eCOA devices and implement a back-up plan (e.g., paper, web-based) in case of any malfunctions with the electronic devices, prior to using the devices in your psychometric evaluation study. Please include details regarding this stage of development and submit protocols and materials related to this usability testing for Agency review and comment.

5. Currently, your protocol indicates that patients will either complete ABSSSI PRO using the eCOA hand held devices or a telephone interview. We recommend that you move forward with only the eCOA mode of administration (with paper backup in case of device malfunction only) as this will be the least complicated and in alignment with development efforts to date. If telephone interviews are also adopted, you will need to provide details on how patients will be selected for the telephone interviews. Likewise, you will need to develop and submit an interviewer administered version of the ABSSSI PRO instrument (including prompts) for review and comment.

6. Please provide further details regarding your quality assurance procedures, including: 1) requirements and methods for site and study staff qualifications and training; 2) data monitoring and 3) data entry quality assurance (for paper backup entry into the electronic system).

7. Please provide details regarding plans for translation and cultural adaptation of the ABSSSI PRO. This instrument will need to be culturally adapted and adequately translated for all intended study populations for use in multinational trials. We refer you to the ISPOR principles for the translation and cultural validation process**.** [1]

We offer the following additional comments and suggestions related to your submission:

ABSSSI PRO Instrument

We are concerned that Item 23 (daily activities like showering, dressing, or eating) and Item 25 (difficulty sleeping) will not be applicable to the inpatient population as performing these daily activities and sleep schedules would likely be influenced by hospital protocol.

Psychometric Evaluation Protocol

1. We recommend that you add further details and procedures (e.g., detailed data monitoring at regular intervals; program daily reminders and/or implement daily reminder phone calls or texts for outpatient participants) in order to minimize missing data.
2. Please specify whether respondents will be allowed to skip answers or whether each response will be a forced choice. We would prefer if respondents are allowed to skip to avoid erroneous answers. We recommend that you add a skip option to each question and program a logic check that will ask respondents to indicate whether they intentionally skipped items. This way, there is a systematic way to account for missing data.
3. P. 9 notes that the days 7 and 10 administrations will be used to assess test-retest reliability among stable patients based on PGI/PGIC and CGI/CGIC. However, only PGI is available for use to determine stable patients between days 7 and 10 which is correctly stated in P. 20. You may also consider using any two consecutive days' ABSSSI PRO scores from participants whose supplemental question 1 (p. 45) response is "About the same" (this

[1] Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P; ISPOR Task Force for Translation and Cultural Adaptation. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005 Mar-Apr;8(2):94-104.

question asks: Overall, how are your skin infection symptoms today compared to yesterday?).

4. P. 12: "Specifying a target number of patient subgroups such as inpatients and outpatients is not required for psychometric evaluation": our concern here is whether any items function differently for inpatients than for outpatients. For example, below we raise the question of whether items 24 and 25 mean something different for inpatients and outpatients. In order to address the general possibility of differential item functioning, there needs to be adequate numbers of both inpatients and outpatients. Such numbers may not be reached if target numbers are not set for your sample.
   P. 14 top: Please clarify the *Known groups validity* section to say that a 150 participants vs. 150 participants comparison is powered to detect an effect size of 0.32, but a 100 participants vs. 100 participants comparison is powered to detect an effect size of 0.18.
   P. 14 top: 0.8 should be 0.08.
   P. 17: Please clarify whether the same clinician complete the CGI on days 1 and 14.
   P. 20: Please ensure that Section 5.2 is consistent with the Statistical Analysis Plan document.

<u>Statistical Analysis Plan</u>

1. Section 4.2 Handling of Missing Data
   a. Item and assessment level missingness needs to be assessed. Consider using multiple imputation to handle the missing responses, or consider conducting weighted data analyses with inverse probability of missingness weights. Single imputation with the mean of the observed item responses does not adequately account for variability due to missingness and should be avoided. Additionally, depending on the missingness MCAR may not be a valid assumption. If the MCAR assumption does not hold, then factor analyses and other psychometric data analyses may yield biased results
   b. Using LOCF to impute item responses post symptom resolution: If, after symptom resolution prior to Day 14, participants do not complete daily diaries, then the post-resolution responses are missing, contrary to the SAP. Instead of handling these responses with LOCF imputation, per the previous two comments there are a number of good reasons why the use of multiple imputation might be appropriate for handling missingness in general, and it could certainly be additionally useful for handling post symptom resolution missingness. In general, LOCF has poor statistical properties, and it is unwarranted to assume that, once rated as resolved, symptoms necessarily stay resolved.
   c. The Guidance for Industry: Patient-Reported Outcome Measures (p. 30) recommends at least two sensitivity analyses if multiple imputation is used to handle missing data.
   d. Implement procedure to limit the extent of missing responses such as programing daily reminder in the eCOA devices or sending out reminder texts or phone calls.
2. Section 4.3 Distributional Considerations
   a. Q-Q plots can also be used to assess normality.
3. Figure 1: The only arrow coming out of "EFA" should go to "Rasch," and the other arrows currently coming out of "EFA" (e.g., going to "Ability to Detect Change" should instead come out of "Rasch." This is because the proposed Rasch analysis could result in dropping

items, and the dropped items would not be included in analyses assessing the ability to detect change.

4. We recommend that you describe the item selection process in detail and that it be based on results from all analyses including both qualitative and quantitative data.
5. We recommend moving up the 5.2.3.1 Item-Level Analysis as the first analysis to be conducted. Specifically, frequency of endorsement, floor and ceiling effect should be examined to inform the factor analysis and Rasch analysis, and whether some items are potential candidates for deletion.
6. Section 5.2.2 EFA
    a. Given your 2015 final conceptual framework decomposition, please provide rationale for conducting EFA rather than confirmatory factor analysis.
7. Section 5.2.3 Rasch Analysis
    a. Please specify the exact Rasch models for polytomous items be used.
    b. If a research category has zero or few responses, it is not feasible to estimate the item parameters. In this case, it may be necessary to use a different day of data for the Rasch model analysis.
    c. Please specify whether separate Rasch/IRT analysis will be conducted for each subscale if results from your factor analysis (Section 5.2.2) reveal multidimensionality.
8. Section 5.2.4 Scoring Algorithm
    a. The SAP describes the scoring algorithm for the "CABP PRO." We assume "ABSSSI PRO" was intended.
    b. Please clarify when an overall ABSSI PRO score will be created in the situation where the ABSSSI PRO is not unidimensional.
    c. Please clarify how you envision the ABSSSI PRO will be used to define efficacy endpoints for ABSSSI clinical trials. Relatedly, it is unclear what is the role of a summary score of longitudinal diary data.
    d. The SAP presupposes that classical test theory (CTT) should be used for scoring; Rasch/IRT analysis is intended to play a subsidiary role in determining item adequacy. Please provide rationale the CTT approach is chosen instead of the Rasch/IRT approach to generate scores.
9. Section 5.2.5.1 Internal Consistency
10. Section 5.2.8 Exploring Responder Definitions

We agree with the idea of using PGI change and PGIC to anchor the establishment of responder definitions. We suggest basing this on the separate empirical CDFs of ABSSSI PRO change scores within each PGI change and PGIC category. The ROC approach is appropriate to examine the sensitive and specificity of a selected responder definition, however, it is not appropriate for determine a responder definition of meaningful change.

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
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