DDT COA #0000118 **LOI Determination**

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Dear Dr. Kirby:

We have completed our review of the Letter of Intent (LOI) submission for pDDT COA #2019-03 dated March 18, 2019 and received on March 18, 2019 by CDER's Clinical Outcome Assessments (COA) Qualification Program.

The submission included an LOI for the HIDRADENITIS SUPPURATIVA AREA AND SEVERITY INDEX (HASI), a clinician reported outcome instrument, proposed for the assessment of disease severity and extent of active (inflamed) hidradenitis suppurativa (HS) in adults with HS, who are participating in a clinical trial.

At this time, we agree to enter this LOI into the COA Qualification Program given the unmet medical need and lack of fit-for-purpose clinician-reported outcome (ClinRO) measures in adult patients with HS. The tracking number for this project has been reassigned to DDT COA #000118. Please refer to DDT COA #000118 in all future communications.

As limited information was provided related to the development history of the HASI, we cannot agree to specifics until you have provided detailed materials for review and comment (e.g., qualitative reports from clinician focus groups). We recommend that you request a meeting with the qualification review team (QRT) to discuss some deficiencies identified in the HASI that may hinder the utility and interpretability of the current version of the instrument in HS clinical trials. We would like to work closely with you to help improve measurement of HS activity with this instrument for successful use in future HS drug development programs.

The QRT has following comments and recommendations.

1. We acknowledge that this is a challenging condition in which to assess clinical benefit. However, the HASI in its current form may be too complex and burdensome for clinicians for operationalization in a clinical trial. Specifically, the layout of the scale may be confusing and susceptible to user errors.

2. While inflammatory color change, inflammatory induration, open skin surface, and tunneling reflect clinically important signs of HS, there is concern whether the remnants of former HS lesions will impact assessment of active HS lesions (i.e., will clinicians be able to distinguish residual scarring from previously active HS from signs of currently active HS?).

3. The scoring algorithm and interpretation for the HASI is unclear. Specifically, we have the following concerns regarding the proposed scoring algorithm of the HASI:

    a. Clinicians are required to estimate BSA to the tenth of a percentage point. We are concerned that clinicians may not be able to reliably estimate BSA to this level of granularity. Refer to comment 3 above regarding the concerns of using BSA.
    b. Insufficient evidence to support how you selected the numerical cutoffs for BSA percentages to be converted to an ordinal scale (i.e., HASI BSA score). Refer to comment 3 above regarding the concerns of using BSA.
    c. The specified maximum BSA for each region may differ across patients. It is unclear what to do in scenarios in which the calculated BSA exceeds the maximum BSA.
    d. If BSA is incorporated in the measurement of disease activity for HS, we recommend providing clinicians with pre-defined options to estimate BSA involvement for each body site, e.g., 10%, 25%, 50%, 75%, etc., as this may be more intuitive for scoring and interpretation.
    e. Insufficient evidence to justify that the four components/domains (inflammatory color change, inflammatory induration, open skin surface, and tunneling) have equal clinical impact, as well as whether each body site involved by HS should have equal weighting. We are concerned that some affected body sites may be more bothersome to patients than others (e.g., patients with HS might consider disease activity in the pubis & genitalis region more significantly bothersome compared to disease activity on the thigh) and may warrant a greater contribution (i.e., weighting) to the HASI domain/total score.
    f. The HASI uses a calculated total score, (arithmetic sum of the product of HS severity and percentage of affected skin for each HS involvement site), which may make scores difficult to interpret and describe clinical benefit (i.e., translate into meaningful labeling). Currently, it is unknown what is a meaningful improvement in the HASI total score (range 0-720).

4. We recommend performing qualitative interviews in patients with HS to understand what components of the disease is of most importance to them, as well as what affected body sites are most bothersome to help inform scoring algorithm for HASI (i.e., is there a need for any weighting of body sites in the scoring?). Additionally, it may be helpful to query patients on what they perceive a meaningful improvement in their disease activity.

5. We recommend performing qualitative interviews with clinicians to evaluate the readability, comphrensibility, relevance, and comprehensiveness of the HASI, including whether clinicians can reliably estimate BSA (if this metric is incorporated in the scale).

6. Consider exploring a component/domain score approach, as a component/domain score may be more feasible as a trial endpoint. Regardless of a domain or total score approach, meaningful interpretability of scores in this instrument will be important (e.g., what does a score represent and how will it be translated for labeling), as well as what constitutes a meaningful improvement in scores (whether domain or total score).

7. Once the content of the HASI is final, consider an electronic mode of administration with built in score calculation (i.e., program scoring algorithm in electronic platform), as this may reduce the perceived complexity of the scale and improve operationalization in a clinical trial.

8. We recommend that you engage with the Critical Path Institute (C-Path) as you prepare your next submission to the FDA. Through a grant provided by FDA, C-Path has agreed to provide DDT development advice for projects referred by FDA. Given C-Path's past and present DDT development efforts and its familiarity with the qualification process, you may benefit from working with them to refine your project's goals and define the necessary components to support a future qualification effort.

   As you engage with C-Path regarding the development of your DDT, there may be a need at times for you to meet with FDA regarding the development of your next regulatory submission. At your discretion and with your permission, C-Path can attend and participate in meetings between you and FDA regarding your DDT qualification program. FDA does not engage with C-Path independent of or outside of such meetings without you.

   Note that C-Path is acting in a purely advisory capacity and is not an agent of FDA. As part of this voluntary process, C-Path will not be responsible for creating or submitting regulatory submissions on your behalf. C-Path makes no guarantee of a specific outcome or result by FDA, nor does C-Path guarantee approval by FDA for your future submission.

   If you wish to contact C-Path with questions or to initiate the external advice process, please email QualificationAdvice@c-path.org.

Appendix 1 of this letter outlines the contents to include in the next milestone submission, Qualification Plan. Please contact the COA Staff at COADDTQualification@fda.hhs.gov should you have any questions. Please refer to DDT COA #000118.

Sincerely,

Elektra J. Papadopoulos -S

Digitally signed by Elektra J. Papadopoulos -S
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Elektra Papadopoulos, MD, MPH
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Kendall A. Marcus, MD
Division Director
Division of Dermatology and Dental Products (DDDP)
Office of New Drugs
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Appendix 1: COA QUALIFICATION PLAN

The COA Qualification Plan should be accompanied by a cover letter and should include the following completed sections. This plan should contain the results of completed qualitative research and the proposed quantitative research plan. If literature is cited, please cite using the number assigned to the source in a numbered reference list.

Note: Sections 1 and 2 will be posted publicly under Section 507 as well as any appendices or attachments referred to in those sections. Section 507 refers to section 507 of the Federal Food, Drug, and Cosmetic Act [FD&C Act] which was created by Section 3011 of the 21st Century Cures Act.

Section 1: Proposed Plan for COA Qualification

1.1 Introduction and overview

- This should include a concise description of the disease and the clinical trial setting in which the COA would be used, the limitations of existing assessments, a brief description of the existing or planned COA, and the rationale for use in drug development.

1.2 Concept of Interest for meaningful treatment benefit

- Describe the meaningful aspect of patient experience that will represent the intended benefit of treatment (e.g., the specific symptom and/or sign presence or severity or limitations in performance or daily activities relevant in the targeted context of use).

1.3 Context of Use

- Identify the targeted study population, including a definition of the disease and selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, language/culture groups).
- Identify the targeted study design. Most commonly the COA will be used to assess the change (compared to a control) induced by a medical treatment.
- Identify the targeted study objectives and endpoint positioning (i.e., planned set of primary and secondary endpoints with hierarchy). Usually, the COA will serve as a primary or secondary study endpoint measure.

1.4 Critical details of the measure to the degree known

- Reporter, if applicable
- Item content or description of the measure (for existing instruments, the specific version of the instrument and copy of the tool from which quantitative evidence has been or will be derived)
- Mode of administration (i.e., self-administered, interview-administered)
- Data collection method

1.5 Description of the involvement of external expertise, including scientific communities or other international regulatory agencies, if applicable (i.e., working group, consortia).

Section 2: Executive Summary

- High-level summary of what is included in the Qualification Plan and results to be described in the sections below

Section 3: Qualitative Evidence and Conceptual Framework

- Evidence of content validity (i.e., documentation that the COA measures the concept of interest in the context of use)

3.1 Literature review
3.2 Expert input
3.3 Reporter input (e.g., for PRO measures, concept elicitation, focus groups, or in-depth qualitative interviews to generate items, select response options, recall period, and finalize item content; for PerfO measures, evidence to support that the tasks being performed are representative of the meaningful health aspect of the concept of interest and are relevant to ability to function in day-to-day life)
3.4 Concept elicitation
3.5 Item generation
3.6 Cognitive interviews
3.7 Draft Conceptual Framework (for existing instruments, the final version conceptual framework)

Sections 4, 5, and 6: Proposed Quantitative Analysis Plan

Section 4: Cross-sectional evaluation of measurement properties

4.1 Item Level Description

- 4.1.1 Item descriptive statistics including frequency distribution of both item response and overall scores, floor and ceiling effect, and percentage of missing response
- 4.1.2 Inter-item relationships and dimensionality analysis (e.g., factor analysis or principal component analysis and evaluation of conceptual framework)
- 4.1.3 Item inclusion and reduction decision, identification of subscales (if any), and modification to conceptual framework

4.2 Preliminary scoring algorithm (e.g., include information about evaluation of measurement model assumptions, applicable goodness-of-fit statistics). The scoring algorithm should also include how missing data will be handled.

4.3 Reliability

- 4.3.1 Test-retest (e.g., intraclass correlation coefficient)
- 4.3.2 Internal consistency (e.g., Cronbach's alpha)
- 4.3.3 Inter-rater (e.g., kappa coefficient)

4.4 Construct validity

- 4.4.1 Convergent and discriminant validity (e.g., association with other instruments assessing similar concepts)
- 4.4.2 Known groups validity (e.g., difference in scores between subgroups of subjects with known status)

4.5 Score reliability in the presence of missing item-level and if applicable scale-level data
4.6 Copy of instrument
4.7 User manual and plans for further revision and refinement

- 4.7.1 Administration procedures
- 4.7.2 Training administration
- 4.7.3 Scoring and interpretation procedures

Section 5: Longitudinal evaluation of measurement properties (If Known)

5.1 Ability to detect change

Section 6: Interpretation of Score (If Known)

6.1 Evaluation and definition of meaningful within person change (improvement and worsening)

Section 7: Language translation and cultural adaptation (If Applicable)

7.1 Process for simultaneous development of versions in multiple languages or cultures
7.2 Process of translation/adaptation of original version
7.3 Evidence that content validity is similar for versions in multiple languages

Section 8: Questions to CDER

Section 9: References

- References and copies of the most important references that the submitter feels CDER reviewers may want to review.

Section 10: Appendices and Attachments

- Study documents (e.g., protocols, analysis plan, interview guide, data collection form(s))