DDT COA #000111 **REQUEST FOR QUALIFICATION PLAN**

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Dear Dr. Kirby,

We have completed our review of the letter of intent (LOI) submission for DDT COA #000111 dated January 29, 2019 and received on January 30, 2019.

You have proposed to develop a patient-reported clinical outcome assessment (COA) to evaluate symptom severity, limitations in performance of activities, and psychosocial effects in adult patients with Hidradenitis Suppurativa (HS). 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 patient-reported outcome (PRO) measures in adult patients with HS. The tracking number for this project has been reassigned to DDT COA #000111. Please refer to DDT COA #000111 in all future communications.

Over the course of instrument development, specific details related to the qualification (e.g., concepts of interest, context of use) are likely to evolve. As limited information was provided related to the development history of the Hidradenitis Suppurativa Quality of Life (HiSQOL), we cannot agree to specifics until you have provided detailed materials for review and comment (e.g., qualitative reports from patient and clinician interviews). We recommend that you request a meeting with the qualification review team (QRT) prior to initiating your psychometric evaluation of the HiSQOL to ensure there is agreement on the instrument's content validity.

Our comments regarding the submission can be found below.

QRT Response:

The QRT has the following comments and recommendations.

1. You propose to develop HiSQOL for use as a primary or secondary outcome measure in HS clinical trials to demonstrate an improvement in HS-related quality of life. Note that a greater

body of evidence is generally needed to support a primary outcome measure versus a secondary outcome measure, which may be obtained with further experience of a COA in clinical trials. At this time, we view the target endpoint positioning of the HiSQOL as a supportive/complementary measure to other COAs (e.g., pain NRS and clinician-reported outcome measures of disease severity).

2. Health-related quality of life (HRQoL) is a complex, multi-domain concept that can be challenging to measure as it consists of concepts that might be influenced by factors beyond the treatment and consequently not sensitive to treatment effect. Therefore, we recommend that you consider using a domain score(s) as a trial endpoint (i.e., select and separately analyze the most important patient-reported symptoms and functional impacts that are responsive to treatment) versus a total score.

3. The HiSQOL measures symptom burden (e.g., bother) which can be a challenging concept to measure, as it can vary as a function of disease stage and individual tolerance. For example, patients may report being bothered by a symptom that is not very severe, or alternatively, a patient may become tolerable to a symptom and report less "bother" even though the symptom remains severe. Further, different patients may have different levels of perceived bother with the same level of symptom intensity. Because of these challenges, symptom intensity (e.g., itch numeric rating scale) or frequency might be more sensitive to treatment effect than the concept of bother, but the HiSQOL lacks items related to symptom assessment (e.g., symptom intensity or frequency). We recommend that you consider capturing symptom experience in addition to symptom burden (e.g., supplement HiSQOL with a symptom intensity item(s), such as a Pain NRS or Itch NRS).

4. Since HS clinical trials may include a younger subpopulation (e.g., adolescents), you may want to consider whether it is feasible to administer the HiSQOL to both adolescents and adults and whether the concepts being measured in the HiSQOL are relevant and appropriate for use in both populations. Additional qualitative interviews may be needed to support the content relevance of this instrument for adolescents.

Appendix 1 of this letter outlines the contents to include in the next milestone submission, the Qualification Plan. Please contact the COA Staff at COADDTQualification@fda.hhs.gov should you have any questions. Please refer to DDT COA #000111.

Sincerely,

Elektra J. Papadopoulos -S

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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))

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