DDT #101 **REQUEST FOR QUALIFICATION PLAN**

March 8, 2018

Dory Kranz
President and CEO
National Alopecia Areata Foundation
65 Mitchell Boulevard
Suite 200B
San Rafael, CA 94903

Dear Ms. Kranz:

We have completed our review of the Letter of Intent (LOI) submission for pDDT 2017-05 dated October 16, 2017 by the Clinical Outcome Assessments Drug Development Tool (COA DDT) Qualification Program.

You have proposed to develop a patient-reported outcome (PRO) instrument to evaluate concepts related to hair loss and regrowth deemed important by adult patients (≥18 years) with alopecia areata. At this time, we agree to enter this LOI into the CDER COA DDT Qualification Program given the unmet medical need and lack of fit-for-purpose patient-reported outcome (PRO) instruments in alopecia areata. The tracking number for this project is DDT# 101. Please refer to DDT# 101 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 concepts of interest and context of use, we cannot agree to specifics until you have provided detailed materials for review and comment.

We strongly encourage you to request a meeting with the QRT following completion of your literature review, concept elicitation qualitative interviews with patients, and expert input prior to proceeding forward with the cognitive interview study. Please submit the following for review and comment prior to the meeting:

- Draft copy of your PRO measure including the corresponding conceptual framework.
- Qualitative summary report describing literature review, concept elicitation research, and expert input. Please include study protocols, the patient interview guide, interview transcripts, and analysis plans along with study results.

The QRT has the following comments and recommendations:

- In your development process, consider the inclusion of concepts that are clinically relevant, meaningful to patients, and modifiable because of a treatment (e.g., drug, biologic) in the context of a clinical trial. Note that importance and meaningfulness of disease-related impacts (e.g. psychological and social functioning) may vary depending on target patient population in terms of age groups (e.g. adolescents, young adults) and sex; however, ultimately, patient input should help guide the development process.

- In addition to seeking input from patients with ≥25% hair loss, we recommend you also evaluate patients in separate cohorts according to clinical severity levels (e.g., hair loss: <25%, 25%-50%, >50% scalp but less than 100%, alopecia totalis and alopecia universalis). A well-represented patient population in terms of sample size and clinical characteristics (e.g., extent and severity of disease) and demographic characteristics should be enrolled for both qualitative and quantitative research portions of your development work. We encourage you to recruit patients whose alopecia areata diagnosis is confirmed and clinically verified in your qualitative work. We encourage you minimize enrolment of patients with confounding skin diseases (e.g., androgenetic alopecia, telogen effluvium, drug induced alopecia and other causes of non-scarring alopecia) if possible. Patients' comorbid conditions and concomitant medications should be documented.
- While your target population is adults (≥18 years) with alopecia areata who are generally healthy, we agree with your proposal to incorporate input from a representative sample of adolescents (12-17 years).

We recommend that you engage with the Critical Path Institute (C-Path) as you prepare your Qualification Plan. 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, we believe there is benefit to working with them to refine your project's goals and define the necessary components to support a future qualification effort.

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.

If you have any questions, please contact the COA Staff via email at COADDTQualification@fda.hhs.gov. Please refer to DDT # 101.

Sincerely,

Elektra J. Papadopoulos -S

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Elektra Papadopoulos, MD, MPH
Associate Director
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Kendall Marcus, MD
Director
Division of Dermatology and Dental Products
Office of New Drugs
Center for Drug Evaluation and Research

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.

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)
- Provide a hypothesized conceptual framework for the outcome assessment(s)

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.

1.4 Critical details of the measure to the degree known

- COA type
- Item content or description of the measure
- Mode of administration (e.g., self-administration, interview)
-Data collection method (e.g., paper-based, computer-assisted, and telephone-based)

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: Qualitative Evidence

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

2.2 Literature review

2.3 Concept elicitation

2.4 Item generation- including rationale for choice of recall period, item stems, and response scales, as applicable

2.5 Cognitive interviews- including evidence of respondent understanding of recall period, item stems and response scales and qualitative evidence of clinical meaningfulness of response scale based on respondent input, as applicable.

2.6 Draft Conceptual Framework-including plans for potential item reduction, as applicable

3.0: Proposed Quantitative Analysis Plan

3.1 Cross-sectional evaluation of measurement properties

3.1 Item Level Description

3.1.1 Item descriptive statistics including frequency distribution of both item response and overall scores, floor and ceiling effect, and percentage of missing response

3.1.2 Inter-item relationships and dimensionality analysis (e.g., factor analysis or principal component analysis and evaluation of conceptual framework)

3.1.3 Item inclusion and reduction decision, identification of subscales (if any), and modification to conceptual framework

3.2 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.

3.3 Reliability

3.3.1 Test-retest (e.g., intra-class correlation coefficient)

3.3.2 Internal consistency (e.g. Cronbach's alpha)

3.3.3 Inter-rater (e.g. kappa coefficient)

3.4 Construct validity

3.4.1 Convergent and discriminant validity (e.g., association with other instruments assessing similar concepts)

3.4.2 Known groups validity (e.g., difference in scores between subgroups of subjects with known status)

3.5 Score reliability in the presence of missing item-level and if applicable scale-level data

3.6 Copy of instrument, conceptual framework, provisional scoring algorithm

3.7 User manual and plans for further revision and refinement

3.7.1 Administration procedures

3.7.2 Training administration

4.0 Longitudinal evaluation of measurement properties (If Known)

4.1 Ability to detect change

4.2 Evaluation of individual patient change

5.0 Language translation and cultural adaptation (If Applicable)

5.1 Process for simultaneous development of versions in multiple languages or cultures

5.2 Process of translation/adaptation of original version

5.3 Evidence that content validity is similar for versions in multiple languages

6.0 Questions to CDER- consider moving up to section 1

7.0 Appendices

- References and copies of the most important references that the submitter feels CDER reviewers may want to review
- Study documents (e.g., protocols, analysis plan, interview guide, data collection form(s))