DRUG DEVELOPMENT TOOL
LETTER OF INTENT DETERMINATION
DDT COA #000130

Lupus Foundation of America
Attention: Alyssa Parks
2121 K Street NW, Suite 200
Washington, DC 20037

Dear Ms. Parks,

We have completed our review of the Letter of Intent (LOI) for Drug Development Tool (DDT) COA #000130 received on May 4, 2020, by the CDER Clinical Outcome Assessments (COA) Qualification Program, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act.

The LOI is for the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), a Clinician Reported Outcome (ClinRO) proposed for the presence and severity of signs of cutaneous lupus erythematosus (CLE) in patients with CLE.

FDA has completed its review and has agreed to accept your LOI into the CDER COA Qualification Program.

FDA's response to the questions included in the LOI can be found below.

1. The CLASI-A measures ***CLE activity.*** Does FDA agree that ***CLE activity***, based on clinical examination disease severity findings, is a clinically meaningful outcome that will support drug approval and claims in labeling if measured in a well-defined and reliable manner and adequate and well-controlled studies?

FDA Response:
We agree that CLE activity is an important concept to clinicians and to patients with CLE and a measure of "CLE activity" may be clinically-meaningful, if it is adequately defined. Furthermore, CLE activity outcomes may support labeling claims, if assessed in a well-defined and reliable manner and the definition for success represents a clinical benefit to patients. An important challenge in measurement of CLE activity is related to the fact that there are different types of CLE. Please also see the response to Question 2.

2. Does FDA agree that the item content of the CLASI-A as described in this briefing document is adequate to measure the outcome of ***CLE activity***?

FDA Response:
The item content of the CLASI-A appears relevant to CLE. However, the information on both the content development, rationale and data to support scoring and extent to which

the CLASI-A would adequately measure CLE activity should ultimately be provided for FDA review.

We also have the following comments:

- With regard to scoring, we note that the signs of the CLASI are weighted differently, with erythema carrying the greatest weight. While FDA reviews the components of a multi-component endpoint to understand the effect of the medical product on each, this does not address the concern that a reduction in redness, for example, may drive the overall score without substantive response observed in the other components. In this context, claims of a decrease in CLASI overall could potentially be somewhat misleading in labeling. Therefore, it would be important to understand the rationale for the differential weighting and to consider its implications on regulatory decision-making.

- It is unclear how enrollment based on a CLASI-A score would necessarily define similar subjects for study eligibility, given the item content of the scale. For example, a subject who has only erythema could have the same baseline score as a subject with erythema, alopecia and ulceration; it is not clear that these would necessarily represent like subjects with similar disease severity.

- It is unclear how patient-reported recent hair loss in the past 30 days contributes to the assessment of CLE activity and whether this is a well-defined item.

3. Does FDA agree that the scoring algorithm of the CLASI-A as described in this briefing document is adequate to measure the outcome of ***CLE activity***?

FDA Response:
It is premature to agree to the scoring algorithm of the CLASI-A in the current form. Please see Comments under Question 2.

4. Does FDA agree that the psychometric properties of the CLASI-A including test-retest reliability, construct validity and ability to detect change are adequate for use in studies to support product approval and labeling?

FDA Response:
It is premature to comment on the psychometric properties of the CLASI-A and its adequacy to support product approval and labeling; this is reviewed at the time of the Full Qualification Package. It is important to note that we cannot interpret results from quantitative analyses (i.e., psychometric properties and performance) without first establishing that an instrument has content validity. Please see Comments under Question 1 and Question 2.

5. Does FDA agree that the plans for exploring the interpretability of CLASI-A score, including identification of meaningful within-patient change in CLASI-A score, are adequate to support review of clinical studies to support product approval and labeling?

FDA Response:

It is premature to comment on whether your plans for exploring the interpretability of the CLASI-A score are adequate to support product approval and labeling. We will review your study protocol for psychometric evaluation and provide comments.

In preparing to submit a Qualification Plan (QP), please ensure that the QP submission addresses the scientific issues and the recommendations outlined below in addition to the QP outline provided in the link below.

1. Provide detailed reports of the CLASI qualitative studies with clinicians/clinician input.
2. Provide full description of the targeted patient population.
3. For your planned quantitative study plan, consider scoring CLASI-A excluding the recent hair loss item reported by patients. If you want to include the recent hair loss item in CLASI-A, please provide the rationale for its inclusion and specify the definition of recent hair loss.
4. Provide additional information regarding why reporting a decrease in CLASI is itself clinically meaningful and interpretable. The Agency recommends anchor-based methods for interpretation of clinically meaningful within-patient change in score.
5. Clarify whether CLASI-A will be used in the patient inclusion/exclusion criteria for the future clinical trials. Please discuss and provide information on whether/how the CLASI-A can be relied on to adequately define a study population.
6. There is an implicit weighting of constructs in the proposed summary score (e.g., erythema is weighted the most, followed by scale/hypertrophy, etc.). Please provide a rationale for the weights given to each construct (e.g., erythema, scale/hypertrophy, mucous membrane involvement, etc.).

The next milestone submission you would be working towards is a Qualification Plan (QP). You may submit your **qualitative protocol and results** for FDA review and comment prior to submitting your QP.

The following weblink contains the contents to include in your submission to reach the next milestone (Qualification Plan): www.fda.gov/media/123245/download. Please contact the CDER COA Qualification Program at COADDTQualification@fda.hhs.gov should you have any questions (refer to DDT COA #000130).

Sincerely,

Elektra J. Papadopoulos -S

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