Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000130: Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)

Administrative Structure:

Description of the submitter including, but not limited to, principal investigator(s), working group member(s), institutions, and contact information not contained within the cover letter.

The submitter is the CLASI Working Group. This group is composed of:

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Drug developers (Biogen, Bristol-Myers Squibb, and Celgene), and regulatory advisors (Hyman, Phelps & McNamara)

Concept(s) of Interest (COI) for Meaningful Treatment Benefit:

A description of the meaningful aspect of patient experience that will represent the intended benefit of treatment (e.g., presence/severity of symptoms, limitations in performance of daily activities).

The CLASI, a clinician reported outcome measure, developed to be a labeling-enabling endpoint assessment for use in clinical trials in SLE patients who may also have cutaneous involvement, generates 2 separate scores that are not intended to be combined into a total score. The CLASI-A score represents "CLE activity," i.e., the overall severity of CLE dermatologic involvement as observed during patient examination at a clinic visit. The CLASI-D score represents "CLE damage," i.e., the overall extent of scaring, pigmentary change, and alopecia, observed by the clinician.

The CLASI does not measure the impact of CLE activity and damage on other aspects of life, e.g., psychological stress, occupational disability, or lowered health-related quality of life (HRQL), even though it is well documented that CLE may have a major impact in these areas.

Provide a conceptual framework for the COA(s)

The CLASI, a clinician reported outcome measure, developed to be a labeling-

enabling endpoint assessment for use in CLE clinical trials, is comprised of two domains: Activity (CLASI-A) and Damage (CLASI-D). The advantage of including CLASI-D in the assessment is it forces investigators to assign skin changes as either activity or damage.

There is only one published version of the CLASI, which includes CLASI-A (left side of instrument) and CLASI-D (right side of instrument). Changes to optimize the instrument content occurred prior to CLASI publication and psychometric testing.

The CLASI-A generates a score that summarizes the activity of CLE. The CLASI-D generates a score that summarizes the visible damage caused by CLE activity. The severity of both activity and damage have an impact on how patients feel and function in their daily lives. However, a summary score is not available and would actually misrepresent severity and change as a result of treatment because CLE damage is an impact of CLE activity and damage normally becomes apparent as activity subsides. The CLASI instrument manual includes a recommendation that 3 single-item patient-reported outcome (PRO) measures be administered during the same visit as the CLASI for itch, pain, and fatigue, however, the actual PRO items are not included in either the CLASI instrument or the total score.

The CLASI-A score is generated by clinician rating of erythema and scale/hypertrophy for each of 13 defined body areas--scalp ears, nose/malar area, rest of face, V-area neck (frontal), posterior neck and shoulders, chest, abdomen, back/buttocks, arms, hands, legs, and feet plus a rating for non-scarring alopecia. Scores represent the worst affected lesion within each area for each CLE-associated sign. In addition, the clinician solicits a yes/no response from the patient concerning hair loss in the past 30 days and current oral/nasal mucous membrane involvement followed by examination if patient confirms involvement. The scores are calculated by simple addition based on the extent of each CLE-associated sign in specific anatomic areas.

The CLASI-D score is generated by clinician rating of dyspigmentation and scarring/atrophy/damage due to resolved panniculitis for the same 13 body areas plus a score for scarring alopecia. The dyspigmentation score of 1 is doubled if the patient indicates the dyspigmentation usually lasts at least 12 months.

The CLASI instrument appears on a single page designed as a table where the rows denote anatomical areas, while the columns represent the score for each CLE-associated sign. Not included in the CLASI instrument are patient-reported symptoms and global summary scores given by either the clinician or the patient although they are recommended to accompany CLASI administration to aid the interpretation of score change. Paper and electronic CRF versions are acceptable and capture data accurately

The CLASI was developed to be different from other dermatology instruments that rely on skin area assessment (e.g., SCORAD) or lesion counting (e.g., acne assessments) because those assessments have limited reliability and validity. Instead, the CLASI defines body areas in a way that reflects the greater importance of visible skin

involvement than covered skin involvement to patient psychological morbidity. For example, the relatively exaggerated weight of the head with 4 body areas (scalp, ears, nose and rest of face) contributes to the clinical relevance of the CLASI-A score and the clinical meaningfulness of CLASI-A score change over time.

Context of Use for COA Qualification:

Targeted study population including a definition of the disease and selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, comorbidities, language/culture groups).

The targeted population is system lupus erythematosus (SLE) patients who may also have cutaneous involvement enrolled in clinical trials of treatments for SLE (1). It was developed because previously available instruments were determined to be inadequate at measuring cutaneous involvement in lupus. Important considerations for design of the CLASI were ease of administration, sensitivity to change, and non-reliance on invasive tests to determine disease severity and outcome. CLASI-A can be administered alone.

In most epidemiological studies, skin involvement has been found to be the second most common manifestation and second most frequent presenting manifestation of systemic lupus erythematosus (SLE) (2)**,** and in some analyses it has been found to be the most prevalent clinical manifestation of SLE (3). Other individuals express typical CLE in the absence of systemic manifestations (4, 5).

In general, CLE most often appears between the ages of 20 and 50 years. It affects women more than men, but children, the elderly, and males may be affected. Of the multiple lesion types, only discoid lesions cause permanent scarring, while others do not. Some types of CLE lesions can occur in individuals who develop only minor manifestations of SLE or never develop any degree of SLE at all. It has been estimated that individuals having isolated CLE is as common as individuals having SLE (6, 7). Thus, in addition to being an integral component of SLE, CLE also impacts the lives of many other individuals suffering from CLE only.

CLE can be categorized into acute, subacute and chronic subtypes. **Acute LE** is frequently seen in patients with active systemic disease. Flat red patches on the cheeks and nose called a butterfly rash that spares the nasolabial fold characterize the most common form of ACLE. Individuals may also present with generalized flat red patches on arms, legs and trunk. These lesions are sensitive to the sun (photosensitive to both sun rays and tanning rays) and therefore commonly appear on sun-exposed areas. While these lesions do not often result in scarring, they may leave dark or light pigment changes. **Subacute cutaneous LE (SCLE)** is often characterized by two lesion types including papulosquamous lesions and annular lesions. Papulosquamous lesions often appear as red scaly patches that look psoriasiform. Annular lesions are ring-shaped with a small amount of scale on the edge of the lesions. These lesions often appear on the chest as well as the upper back, neck, and extensor arms, and less frequently on the face. SCLE is not often

associated with significant systemic disease or associated joint disease. SCLE patients tend to be slightly older, Caucasian, with high titer anti-SSA/SSB, and onset can be medication-related. **CCLE includes localized and generalized DLE, hypertrophic LE, chilblain LE, tumid LE, and LE profundus. DLE lesions**, named for their coin-like shape, are red scaly patches that often appear on the cheeks, nose, ears, and scalp. These lesions may also generalize to areas below the neck, often affecting the V-neck area, upper back, arms, and dorsum of hands. They can be painful or itchy. Once the lesions resolve, they may leave dark or light pigmentation as well as atrophy (thinning of the skin). If lesions are in the scalp or involve the hair follicles, areas of hair loss may develop which could be permanent if the hair follicle is completely destroyed. DLE occurs in all age groups and in all skin colors, however CLE severity is generally worse in African Americans. Variants of DLE include hypertrophic LE, which has a thickened epidermis, and may look wart-like and very thick as well as palmoplantar LE (occurring on palms and soles). CCLE may also affect the fat, resulting in firm deep nodules called lupus profundus or lupus panniculitis. Once, these lesions resolve they may leave indented scars called lipodystrophy due to destruction of the fat cells. Tumid LE occurs often on photodistributed skin, typically without scale. All CLE subtypes are characterized by fluctuations in clinical severity. There are frequently more than one subtype in the same patient, and all subtypes seem to respond to the same therapies.

The disease to be studied includes all forms of CLE, with the exception of lupus panniculitis, where the changes are below the skin and thus difficult to evaluate.

Patients selected for clinical trials should have moderate to severe CLE with or without SLE. They can be of any age, although early studies may target adults rather than children. All language and culture groups may be considered for trials.

***Targeted study design and statistical analysis plan (includes the role of the planned COA in future drug development clinical trials, including the planned set of primary and secondary endpoints with hierarchy, if appropriate*).**

See Attachment A that provides a listing of planned, ongoing and closed studies that include CLASI as an efficacy endpoint.

Clinical trials may be designed to assess treatment efficacy for SLE with or without accompanying CLE diagnoses and include the following general designs that also assess treatment efficacy for CLE in patients who may have such manifestations:

A. Clinical trials to demonstrate an improvement in SLE disease severity
    a. Trial duration: 3-12 months
    b. Endpoint to support labeling claim: CLASI-A change from baseline (change in CLE severity)
    c. Supportive endpoints: Time to improvement in CLASI-A, patient symptoms/HRQL, need for retreatment, use of corticosteroids
    d. Analysis: Proportions of responders defined by a clinically meaningful within-patient change in CLASI-A OR mean change

from baseline to endpoint

e. Patient population enrolled: Moderate to severe CLE severity; all CLE subtypes

B. Clinical trials to demonstrate efficacy as a maintenance therapy for CLE
   a. Trial duration: 6-12 months
   b. Primary endpoint: Durability of CLASI-A response (CLE severity)
   c. Secondary endpoints: patient symptoms/HRQL, need for retreatment, use of corticosteroids
   d. Analysis: Proportions of responders with no meaningful decrement in CLASI-A (CLE severity)
   e. Patient population enrolled: Patients with any CLE subtype who have previous treatment with response and clear or almost clear disease activity at baseline.

Applicable study settings for future clinical trials

- ***Geographic location with language/culture groups***
  All language/culture groups can be included in clinical trials with CLASI-A.

- ***Other study setting specifics (e.g., inpatient versus outpatient)***
  Most trials will be outpatient, but the CLASI-A can be used in either inpatient or outpatient assessments.

<u>COA Type:</u> Clinician-Reported Outcome (ClinRo)