Development of a working core outcome set for cutaneous lupus erythematosus: a practical approach to an urgent unmet need

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To cite: Guo LN, Perez-Chada LM, Borucki R, et al. Development of a working core outcome set for cutaneous lupus erythematosus: a practical approach to an urgent unmet need. *Lupus Science & Medicine* 2021;8:e000529. doi:10.1136/lupus-2021-000529

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/lupus-2021-000529>).

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Received 28 June 2021
Accepted 5 November 2021

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ABSTRACT

Objective The lack of standardised outcomes and outcome measures for cutaneous lupus erythematosus (CLE) represents a substantial barrier to clinical trial design, comparative analysis and approval of novel investigative treatments. We aimed to develop a working core outcome set (COS) for CLE randomised controlled trials and longitudinal observational studies.

Methods We conducted a multistage literature review of CLE and SLE studies to generate candidate domains and outcome measures. Domains were narrowed to a working core domain set. Outcome measures for core domains were identified and examined.

Results Proposed core domains include skin-specific disease activity and damage, investigator global assessment (IGA) of disease activity, symptoms (encompassing itch, pain and photosensitivity), health-related quality of life (HRQoL) and patient global assessment (PtGA) of disease activity. Recommended physician-reported outcome measures include the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) and Cutaneous Lupus Activity IGA (CLA-IGA). For the domains of symptoms, HRQoL and PtGA of disease activity, we were unable to recommend one clearly superior instrument.

Conclusion This work represents a starting point for further refinement pending formal consensus activities and more rigorous evaluations of outcome measure quality. In the interim, the proposed working COS can serve as a much-needed guide for upcoming CLE clinical trials.

INTRODUCTION

Cutaneous lupus erythematosus (CLE) is a potentially disfiguring skin disease that substantially impacts quality of life (QoL).^{1,2} CLE can occur independently or as a manifestation of SLE.³ While some treatments are effective for CLE, many patients remain refractory or cannot tolerate current therapies, thus there is a need for new, safe and effective treatments.^{4–7} Unfortunately, no medications have been approved for CLE in over 50 years.^{8,9} A major driver of this has been

Key messages

What is already known about this subject?

- There is a lack of consensus on outcome measures for cutaneous lupus erythematosus (CLE) clinical trials, hindering drug approval and clinical trial design.

What does this study add?

- A working core outcome set (COS) consisting of outcomes to be measured in CLE randomised controlled trials and longitudinal observational studies was developed.
- Instruments to measure core outcomes were reviewed, with areas for future work identified.

How might this impact on clinical practice or future developments?

- This working COS can serve as an interim guide for upcoming CLE trials and inform the agenda for future efforts to standardise outcomes and outcome measurements in CLE clinical research.

the lack of validated CLE outcome measures and a focus on SLE for new drug development.¹⁰ The lupus research communities have worked for years to reach a consensus on how to measure lupus disease severity outcomes,¹⁰ and a valid, reliable and clinically meaningful disease severity measure for CLE trials now exists—the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), which has been implemented in most recent lupus trials.¹¹

However, clinical and outcomes research in CLE remains challenging. First, other measures of CLE disease severity have been used in CLE trials, leading to significant heterogeneity in outcome reporting. Furthermore, other aspects of CLE beyond clinician-reported disease severity may be important to investigators and patients, which have also been variably included in trials, further obfuscating interpretation of findings and

comparisons of efficacy across CLE studies. More broadly, clinical trial design and regulatory approval of new therapeutics is difficult without clear guidelines regarding which outcomes are important and appropriate to measure. This has already held up and is actively holding up the development of products. Consequently, there is a need for consensus regarding the relevant outcomes and corresponding instruments to implement in CLE clinical research. These same issues have been raised and addressed in other disease states through the development of core outcome sets (COS), which consist of a minimum set of outcomes to be measured and reported in all clinical trials for a given disease.¹² They encompass both the outcomes (*core domain set*) and instruments to measure those outcomes or domains.¹³

Ideally, as recommended by the COMET (Core Outcome Measures in Effectiveness Trials) Initiative, COS development would involve extensive systematic literature reviews, solicitation of input from patients and other relevant stakeholders, and finally time, resource and labour-intensive consensus exercises.¹² These formal consensus efforts are valuable and important but can take years to complete. There are already upcoming clinical trials and new therapeutics being developed in the pipeline that would greatly benefit from additional guidance in trial design and outcome and measurement instrument selection, and it is not practical to delay such efforts until formal consensus exercises can take place. Conversely, proceeding without agreement or consensus further perpetuates the issues and challenges facing CLE clinical research and may continue to hamper the development and approval of desperately needed new therapies for patients.

Considering the need for timely guidance, we developed a preliminary, working core outcome set (COS) for CLE randomised controlled trials (RCTs) and longitudinal observational studies (LOS). Recognising that ideally this will be further refined through consensus activities in the future, we hope this practical and evidence-based approach will provide interim recommendations for upcoming trials. This working COS is intended to guide RCTs and LOS of adult patients with CLE of any subtype (including acute CLE, subacute CLE, and the various forms of chronic CLE), regardless of concomitant SLE.

METHODS

To identify existing knowledge about CLE outcomes, we systematically reviewed outcomes in CLE and SLE trials and identified outcomes important to patients. Based on these findings, we established a *core domain set* (ie, minimum set of relevant domains and subdomains to be measured in every clinical trial for a given disease state).¹³ Next, we systematically reviewed measurement instruments in CLE and SLE trials and searched for available studies on their measurement properties. An ad hoc steering committee of clinicians and investigators (LMP-C, VEN, VPW, JFM)

with expertise in CLE and outcome measurement was established to lead and inform the process.

CLE outcomes

To identify potential outcomes/domains of interest for CLE, we organised a four-stage literature search. First, we searched MEDLINE (Ovid) and EMBASE for RCTs in adult patients with CLE from inception to January 2021 (search strategies in online supplemental appendix 1). RCTs of CLE patients with and without SLE were eligible; however, RCTs of SLE patients without diagnosed CLE were excluded. Case reports, reviews or commentaries, and uncontrolled, observational, paediatric or non-English studies were also excluded. Two independent reviewers screened titles and abstracts followed by full-text review of eligible studies. Second, we searched ClinicalTrials.gov for Phase II, III or IV CLE RCTs to identify ongoing or unpublished studies. These trials were cross-referenced with MEDLINE/EMBASE results to remove duplicates. Study outcomes and measurement instruments were extracted from each study. Third, we searched ClinicalTrials.gov for Phase III and IV SLE RCTs to explore CLE outcomes measured in SLE RCTs. Finally, we conducted a scoping review of qualitative studies of CLE patients to identify domains important to patients.

The output was then synthesised and categorised by the steering committee as 'core', 'important but optional', and 'research agenda' domains to propose a working *core domain set* following the OMERACT Filter 2.1 Onion framework.¹³

CLE measurement instruments

We then turned to identifying measurement instruments used in CLE. From all studies retrieved in the above literature searches, we extracted outcome measures. We also searched PubMed for systematic reviews of CLE outcome measures.¹⁴ We preliminarily paired outcome measures to each core domain.

Working COS

To refine outcome measures to be included in the COS, we systematically searched PubMed and EMBASE for studies evaluating measurement properties of identified instruments in CLE from inception to February 2021 (search strategies in online supplemental appendix 2). Number of validation studies and measurement properties assessed were extracted as a broad gauge of each instrument's validation. Formal appraisal of instrument quality by applying the COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) methodology is ongoing and will be published separately.^{15 16} Based on available validation data and face validity for each instrument (degree to which an instrument reflects the measured construct),¹⁷ the steering committee preliminarily recommended candidate instruments for each core domain.

RESULTS

Identification of candidate domains

MEDLINE and EMBASE searches for CLE RCTs with adult patients retrieved 325 unique articles. After screening

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart for CLE/SLE RCTs. CLE, cutaneous lupus erythematosus; RCT, randomised controlled trial; SLE, systemic lupus erythematosus.

and full-text review, we found 22 eligible CLE RCTs (online supplemental appendix 3, table I). ClinicalTrials.gov yielded 29 CLE protocols of which 15 were eligible for inclusion (online supplemental appendix 3, table II). After removal of 4 overlapping references, 33 total RCTs were included in the qualitative synthesis (figure 1).

We retrieved 153 Phase III and IV lupus erythematosus RCTs in ClinicalTrials.gov. Of these, 123 RCTs were eligible (online supplemental appendix 3, table III); 26 studies that were not RCTs and 4 studies already identified from the CLE systematic review were excluded (figure 1).

The scoping review of qualitative studies of patients with CLE identified two studies. Ogunsanya *et al* explored CLE's impact on QoL,¹⁸ while McGarry *et al* focused on impact of photosensitivity and photoprotective practices.¹⁹

In all, 20, 21 and 9 domains were extracted from CLE trials, SLE trials and qualitative studies, respectively

(box 1). Common domains included skin-specific disease activity, skin-specific disease damage, flares/relapses, investigator global assessments (IGAs), patient global assessments (PtGAs), health-related quality of life (HRQoL), mental health, fatigue, physical function and side effects/toxicity. CLE studies further captured skin symptoms, mucous membrane involvement and alopecia. Other outcomes of interest among SLE studies included SLE disease activity/damage, SLE flares/relapses and other systemic manifestations (joint, cardiovascular, renal involvement). Distinct domains from qualitative studies included treatment satisfaction and impact on body image and social functioning.

Informed by the steering committee's clinical and research experience, as well as domains prioritised by patients in qualitative studies, we modelled the *core domain set* (figure 2, inner circle). Physician-reported

Box 1 List of all domains relevant to CLE identified

Domains assessed in CLE RCTs

1. Skin-specific disease activity.
2. Skin-specific disease damage.
3. Lesion-specific disease activity.
4. Extent of disease/area of involvement.
5. Disease flares/relapse.
6. Mucous membrane involvement.
7. Alopecia.
8. SLE disease activity.
9. Other systemic symptoms (joint pain).
10. Investigator global assessment of:
 - CLE disease activity.
 - Skin disease activity.
 - Improvement.
 - Efficacy.
 - Skin health.
 - Lesion severity.
11. Patient global assessment of
 - Disease activity.
 - Improvement.
 - Skin health.
12. Health-related quality of life.
13. Pain.
14. Itch.
15. Fatigue.
16. Physical function.
17. Corticosteroid use.
18. Pharmacokinetics and pharmacodynamics.
19. Safety, adverse events, side effects, tolerability.
20. Immunologic labs/other labs.

Relevant domains assessed in SLE RCTs

1. Skin-specific disease activity.
2. Skin-specific disease damage.
3. SLE disease activity.
4. SLE disease damage.
5. Disease flares/relapses.
6. Investigator global assessment of
 - SLE disease activity.
 - SLE severity.
7. Depression, suicidality.
8. Physical function.
9. Pain.
10. Other systemic disease manifestations (joints, cardiovascular, renal disease, etc).
11. Patient global assessment of:
 - Well-being.
 - Disease activity.
 - Impression of change.
12. Health-related quality of life.
13. Biomarker, serologies, immunologic and other lab values.
14. Bone mineral density.
15. Fatigue.
16. Nail involvement.
17. Pharmacokinetics and pharmacodynamics.
18. Safety and adverse events.
19. Health economics and cost-effectiveness.
20. Non-adherence.
21. Corticosteroid use.

Continued

Box 1 Continued

Relevant domains identified from qualitative studies

1. Acute manifestations (pain, itch, swelling, burning, photosensitivity).
 2. Chronic manifestations (scarring, hair loss, dyspigmentation).
 3. Disease flares/relapses.
 4. Mental effects (depression, insomnia, anxiety, sleep disturbance, suicidality).
 5. Physical function.
 6. Medication effects (toxicity).
 7. Treatment satisfaction.
 8. Social stigma/anxiety (impact on relationships).
 9. Body image issues.
- CLE, cutaneous lupus erythematosus; RCT, randomised controlled trial, SLE; systemic lupus erythematosus.

core domains included skin-specific disease activity, skin-specific disease damage and IGA of disease activity. IGA was included as a stand-alone domain given the recent push from regulatory agencies to include global measures in clinical trials. Patient-reported domains included symptoms, HRQoL and PtGA of disease activity. The most relevant symptoms based on qualitative studies and expert opinion included itch, pain and photosensitivity. Other domains were deemed important but optional (figure 2, middle circle) or research agenda domains that merit further clarification or investigation (figure 2, outer circle).

Identification of candidate measurement instruments

We identified an extensive list of physician-reported and patient-reported outcome measurements (online supplemental appendix 4, table I). These were preliminarily matched to each core domain (online supplemental appendix 4, table II).

Working COS

The systematic literature review of studies evaluating measurement properties of outcome measurement instruments in CLE yielded 14 studies (online supplemental appendix 5, figure 1 and table I). For the domains of skin-specific disease activity and damage, we identified CLASI as the most appropriate instrument (table 1). The CLASI is extensively validated^{11 20–27} and assesses

Figure 2 Onion model of working core domains for cutaneous lupus erythematosus (CLE).

Table 1 Working core outcome measurement set

Core domain	Outcome measurements		
	CLE-specific	Dermatologic	Generic
Skin-Specific Disease Activity	CLASI-A	–	–
Investigator Global Assessment of Disease Activity	CLA-IGA*		
Skin-Specific Disease Damage	CLASI-D	–	–
Symptoms (pruritus, pain and photosensitivity)	CLEQoL (includes Skindex-29 +3)	DLQI Skindex-29+3 12-Item Pruritus Severity Scale	Itch VAS/NRS Pain VAS/NRS
Health-related Quality of Life	CLEQoL (includes Skindex-29 +3) LEQoL	Skindex-29+3 DLQI	SF-36 EQ-5D
Patient Global Assessment of Disease Activity	–	–	–

*May be considered as a secondary or exploratory endpoint, complementary to CLASI, pending ongoing validation.
 CLA-IGA, Cutaneous Lupus Activity Investigator's Global Assessment; CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity; CLASI-D, Cutaneous Lupus Erythematosus Disease Area and Severity Index-Damage; CLEQoL, Cutaneous Lupus Erythematosus Quality of Life; DLQI, Dermatology Life Quality Index; LEQoL, Lupus Erythematosus Quality of Life Questionnaire; NRS, Numeric Rating Scale; SF-36, Short Form Health Survey; VAS, Visual Analogue Scale.

disease activity (CLASI-A) and damage (CLASI-D) separately. Of note, use of CLASI-D longitudinally should be carefully considered with clearly defined endpoints because damage is not expected to significantly improve with treatment but prevention of damage accrual may be a meaningful outcome. CLASI, lesion-specific or other modified versions of CLASI were used in 54.5% (n=18) of CLE RCTs reviewed (figure 3) and 66.7% of studies published in PubMed or ClinicalTrials.gov since the CLASI was developed and validated (online supplemental appendix 6), demonstrating its acceptability and feasibility for use in clinical trials. In contrast, RCLASI (a revised version of the CLASI with more granular assessments of alopecia and mucous membrane involvement)²⁸ was less commonly used (6.1% of reviewed RCTs, n=2).

Figure 3 Frequency (%) of use of outcome measures in CLE RCTs (n=33). CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; CLE, cutaneous lupus erythematosus; DLQI, Dermatology Life Quality Index; NRS, Numeric Rating Scale; RCT, randomised controlled trial; SF-36, Short Form Health Survey; VAS, Visual Analogue Scale.

Score of Activity and Damage in Discoid Lupus Erythematosus (SADDLE) was also identified but is specific for discoid lupus and thus not applicable to all patients with CLE.²⁹ IGA instruments in CLE studies were poorly defined and highly heterogeneous, and we did not find any validation studies for CLE. However, the steering committee recommended the Cutaneous Lupus Activity IGA (CLA-IGA), which was recently developed by experts in CLE and is currently undergoing validation as an exploratory or secondary endpoint in several CLE development programmes (online supplemental appendix 7).
 For HRQoL, we found two CLE-specific instruments: Cutaneous Lupus Erythematosus Quality of Life (CLEQoL)³⁰ and Lupus Erythematosus Quality of Life Questionnaire (LEQoL),³¹ each supported by a validation study. Skin-specific instruments for HRQoL with high face validity based on steering committee discussion included Skindex-29³² with three additional questions related to photosensitivity and alopecia (Skindex-29 +3)² and the Dermatology Life Quality Index (DLQI).³³ Of these, we only found one validation study for the Brazilian version of the DLQI.³⁴ Of note, CLEQoL encompasses Skindex-29 +3 with additional questions. Relevant generic QoL indices identified included the EQ-5D and Short Form Health Survey (SF-36),^{35 36} neither of which have been validated in CLE.
 For symptoms (itch, pain and photosensitivity), no CLE-specific measures were found. The 12-Item Pruritus Severity Scale (12-PSS) was not originally developed with patients with CLE, but severity bands were later defined for CLE.³⁷ Therefore, we included it in the working COS. The pain and pruritus Visual Analogue Scales (VAS) and Numeric Rating Scales (NRS), for which no formal validation data in CLE was available, presented acceptable face validity for the relevant symptoms and were also included. Because Skindex-29 +3 and CLEQoL include questions

about CLE symptoms, they were also preliminarily recommended for symptom measurement.

Finally, for PtGA of disease activity, instruments cited in studies were poorly defined, and we did not find any validated PtGA of disease activity in CLE.

DISCUSSION

Novel and efficacious treatments are needed to improve CLE management. However, the development of potential pharmaceutical trials has been hindered by slow adoption of validated approaches to measuring CLE and lack of consensus around the most appropriate outcome measures to use. Informed by a multistage literature review of CLE and SLE studies as well as expert input from the steering committee, we proposed a working COS for CLE RCTs and LOS to preliminarily standardise outcomes and outcome measurements in CLE clinical research.

The final proposed *core domain set* includes skin-specific disease activity and damage, IGA of disease activity, symptoms (including itch, pain and photosensitivity), HRQoL and PtGA of disease activity. In determining core domains, there was much discussion by the steering committee regarding skin disease flares. In qualitative studies, patients report flares having a large impact on QoL,³⁸ and disease flares are a commonly measured endpoint in SLE trials.^{39 40} A recent study measuring flares in CLE established a cut-off for flare-based endpoints.⁴¹ However, assessing frequency or occurrence of flares may not be applicable to all trials, depending on study period length. Thus, the domain was deemed important but optional. Similarly, SLE disease activity and flares were also categorised as important but optional. This was informed by an FDA industry guidance document for developing medical products for SLE treatment, which recommended assessing overall disease activity in organ-specific trials as a secondary endpoint.⁴² Thus, clinical trials for CLE, especially if patients who meet criteria for SLE are enrolled, should strongly consider including SLE disease activity (and potentially SLE disease flares, if applicable) in study outcomes.

Mucous membrane involvement and alopecia are also two important clinical manifestations of CLE and components of disease activity. However, because not all patients have mucous membrane involvement and/or alopecia and not all therapies are targeted at these manifestations, these outcomes were not included as core domains. Instead, the steering committee deemed these as important but optional domains (figure 1, middle circle) that should be measured when present. Regarding their measurement, CLASI captures alopecia and mucous membrane involvement in a categorical fashion (presence or absence).

For outcome measures, COSMIN guidelines recommend selecting one instrument for each core domain.⁴³ For physician-reported domains, we selected the CLASI-A (*skin-specific disease activity*), CLASI-D (*skin-specific disease damage*) and the CLA-IGA (*IGA of disease activity*).

Although CLASI-A is an ideal primary endpoint to assess skin-specific disease activity, inclusion of an IGA as a secondary or exploratory endpoint after validation studies provides complementary insights. Specifically, IGAs are highly feasible measures that consider morphology and lesion quality and are particularly relevant for studies including patients with low BSA and/or for assessing target lesions. However, anchoring IGA scales is difficult given multiple morphologies and characteristics of CLE lesions, making assignment of features such as specific level of erythema challenging. Furthermore, it may be difficult to capture meaningful change, as IGAs do not consider varying lesion attributes in different body parts, and more subtle change can be lost with cut-offs such as at least 2-point change. Nevertheless, such global measures are supported by regulatory bodies. Parallels can be drawn to psoriasis, in which the Psoriasis Area and Severity Index (PASI) (similar to CLASI) and an IGA of disease activity often serve as co-primary outcomes and are recommended by the FDA for use in trials. IGAs used in the reviewed studies were very diverse, often not well-defined, and none were currently validated in patients with CLE. Thus, we recommend the CLE-specific CLA-IGA, currently undergoing validation as an exploratory or secondary endpoint for CLE.

For patient-reported domains, we were unable to recommend one clearly superior instrument due to lack of validation data and the vast number of instruments identified. Suitable instruments include the CLEQoL, LEQoL, Skindex 29+3, DLQI, SF-36 and EQ-5D (*HRQoL*), and 12-PSS, CLEQoL, Skindex 29+3, DLQI, itch VAS/NRS and pain VAS/NRS (*symptoms*). For PtGA of disease activity, no specific outcome measure could be recommended given that instruments retrieved were both poorly defined and not validated in CLE. Notably, most were skin-specific but not necessarily CLE-specific.

Next steps

The main limitation of this work is that the proposed COS was not agreed on by consensus among relevant stakeholders as suggested by groups such as COSMIN, COMET and OMERACT^{12 13 43} but rather reflects expert opinion informed by exhaustive review of the available literature. Considering the urgent need to establish outcomes to be measured in upcoming CLE clinical studies, time and resource-intensive large-scale, consensus-based efforts were not practical, and expedited interim guidelines were needed. Should consensus exercises be conducted in the future, the domains and outcome measurements generated from the literature review and the resulting working COS can provide a useful foundation and inform discussion.

Likewise, outside of the CLASI, there is a lack of validation studies in CLE, particularly in patient-reported outcomes. Thus, the proposed patient-reported outcome measurement set is based on face validity of available instruments and minimally informed by extent of validation, and we were unable to recommend a single best

instrument for each domain. In order to move towards a final set of outcome measures, an exhaustive validation of candidate instruments will likely be needed. We are currently evaluating the quality of candidate measures to provide strength of recommendation for existing instruments, and validation of the CLA-IGA is also underway. On formal appraisal of instrument quality by applying the COSMIN checklist,¹⁵ we hope to further refine the COS. In addition to validating existing instruments, further work may be needed to develop and validate novel outcome measures, including a PtGA for CLE. These needs revealed by our work can also help direct the agenda for future efforts.

In conclusion, there is vast heterogeneity in the core outcomes assessed and measurement instruments used in CLE clinical trials, and many of the available measurement instruments are not well-validated in patients with CLE. We have proposed this working COS to serve as a much-needed, interim guide to advance clinical trial design and drug development until further evidence on outcome measure quality becomes available and a formal process to achieve consensus can be executed. Developed based on extensive literature review and expert opinion, this COS should not be viewed as restrictive or unchangeable but rather as a timely starting point that will likely continue to be refined. Importantly, the establishment and uptake of a CLE COS will enable improved design of CLE clinical studies and better synthesis of trial data.

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Contributors LMP-C, VPW and JFM conceptualised and designed the study. LNG, LMP-C and RB performed the data collection, literature review and drafted the manuscript. All authors contributed to data analysis and interpretation, provided input to the manuscript and approved the final version. VPW and JFM are responsible for the overall content as guarantors.

Funding This project is supported by the Department of Veterans Affairs Veterans Health Administration, Office of Research and Development, Biomedical Laboratory Research and Development and National Institutes of Health (National Institute of Arthritis and Musculoskeletal and Skin Diseases) R01AR071653 (VPW).

Competing interests LNG, LMP-C, RB and VEN have no competing interests. VPW has received honoraria from Biogen, Celgene, Eli Lilly, GlaxoSmithKline, Resolve, Abbvie, AstraZeneca, Kyowa Kirin, Cugene and Medimmune and has received grants from Biogen, Celgene and Vela. In addition, she holds patents for the Cutaneous Lupus Erythematosus Disease Area and Severity Index (owned by the University of Pennsylvania). JFM is a consultant and/or investigator for Biogen, Amgen, Bristol-Myers Squibb, Abbvie, Dermavant, Eli Lilly, Novartis, Janssen, UCB, Sanofi, Regeneron, Sun Pharma, Pfizer and Leo Pharma. Both VPW and JFM were involved in the development of the Cutaneous Lupus Activity Investigator's Global Assessment (CLA-IGA).

Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Additional data available in supplementary materials.

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