<u>Appendix 1:</u> Identification of Cutaneous Lupus Erythematosus (CLE) and Systemic Lupus Erythematosus (SLE) Randomized Controlled Trials (RCTs)

Search Strategy MEDLINE (Ovid)

- From inception to January 28, 2021
- RCT search filters used: Cochrane RCT terms as identified in Cochrane Handbook 5.1

1 randomized controlled trial.pt. (521766)
2 controlled clinical trial.pt. (94043)
3 randomi#ed.ab. [modified to pick up 's' and 'z' variants] (610182)
4 placebo.ab. (215459)
5 clinical trials as topic.sh. (194466)
6 randomly.ab. (351188)
7 trial.ti. (235051)
8 or/1-7 (1385623)
9 exp animals/ not humans.sh. (4781739)
10 8 not 9 [Cochrane RCT Filter: sensitivity- and precision-maximizing version (2008 revision)] (1278027)
11 exp Lupus Erythematosus, Cutaneous/ (5114)
12 cutaneous lupus.mp. (2045)
13 exp Lupus Erythematosus, Discoid/ (3200)
14 discoid lupus.mp. (1781)
15 exp Chilblains/ (443)
16 chilblain lupus.mp. (158)
17 exp Panniculitis, Lupus Erythematosus/ (276)
18 panniculitis, lupus erythematosus.mp. (277)
19 lupus erythematosus profundus.mp. (144)
20 lupus tumidus.mp. (33)
21 or/11-20 (6640)
22 10 and 21 (136)

Search Strategy for EMBASE:

- From inception to January 28, 2021
- RCT search filters used: Cochrane RCT Filter: sensitivity- and precision-maximizing version (2008 revision)

'skin lupus erythematosus'/exp OR 'skin lupus erythematosus':ti,ab,kw OR 'cutaneous and lupus':ti,ab,kw OR 'discoid lupus erythematosus' OR 'discoid lupus':ti,ab,kw OR 'chilblain' OR 'chilblain':ti,ab,kw OR 'lupus panniculitis' OR 'lupus panniculitis':ti,ab,kw OR 'lupus profundus' OR 'lupus profundus':ti,ab,kw OR 'lupus tumidus' OR 'lupus tumidus':ti,ab,kw) AND ((random$:ti,ab,kw OR factorial$:ti,ab,kw OR crossover$:ti,ab,kw OR placebo$:ti,ab,kw OR assign$:ti,ab,kw OR allocat$:ti,ab,kw OR volunteer$:ti,ab,kw OR 'crossover procedure' OR 'double blind procedure' OR 'randomized controlled trial' OR 'single blind procedure' OR (singl* NEAR/3 blind*):ti,ab,kw OR (doubl* NEAR/3 blind*):ti,ab,kw) NOT ('animal'/exp NOT 'human'/exp))

Search Strategy for *ClinicalTrials.gov:*

CLE:

Filter for phase 2, 3 and 4 clinical trials

Search terms:

“cutaneous lupus erythematosus”

“cutaneous lupus”

“lupus cutaneous”

“lupus discoid”

“lupus erythematosus, discoid”

“lupus erythematosus, cutaneous”

SLE:

Filter for phase 3 and 4 clinical trials

Search terms:

“lupus erythematosus”

Appendix 2: Identification of Studies Evaluating the Measurement Properties of Outcome Measures in CLE Patients

Search Strategy for PubMed

- From inception to February 2, 2021
- Validation studies filters used: Terwee CB, Jansma EP, Riphagen II, de Vet HC. Development of a methodological PubMed search filter for finding studies on measurement properties of measurement instruments. Qual Life Res. 2009 Oct;18(8):1115-23. doi: 10.1007/s11136-009-9528-5.

((Disease Area and Severity Index[tiab] OR CLASI[tiab] OR Score of Activity and Damage[tiab] OR SADDLE[tiab] OR Global Assessment[tiab] OR PGA[tiab] OR IGA[tiab] OR Life quality[tiab] OR Quality of life[tiab] OR DLQI[tiab] OR Skindex[tiab] OR SF-36[tiab] OR SF36[tiab] OR short form 36[tiab] OR EuroQoL[tiab] OR EQ5D[tiab] OR EQ-5D[tiab] OR EQ5D OR CLEQoL[tiab] OR LupusPRO[tiab] OR SLEQOL[tiab] OR LupusQoL[tiab] OR L-QoL[tiab] OR Visual Analogue Scale[tiab] OR VAS[tiab] OR Numeric Rating Scale[tiab] OR NRS[tiab] OR Worst Pain[tiab] OR Promis[tiab] OR McGill Pain[tiab] OR Brief Pain Inventory[tiab] OR BPI[tiab] OR Global Skin Health[tiab] OR Global Improvement[tiab] OR Patient Global[tiab]) AND ("Lupus Erythematosus, Cutaneous"[Mesh] OR "Lupus Erythematosus, Discoid"[Mesh] OR Cutaneous lupus[tiab] or Discoid lupus[tiab] or Lupus erythematosus profundus[tiab] or Chilblain lupus[tiab] or Lupus tumidus[tiab])) AND ((instrumentation[sh] OR methods[sh] OR Validation Studies[pt] OR Comparative Study[pt] OR "psychometrics"[MeSH] OR psychometr*[tiab] OR clinimetr*[tw] OR clinometr*[tw] OR "outcome assessment (health care)"[MeSH] OR outcome assessment[tiab] OR outcome measure*[tw] OR "observer variation"[MeSH] OR observer variation[tiab] OR "Health Status Indicators"[Mesh] OR "reproducibility of results"[MeSH] OR reproducib*[tiab] OR "discriminant analysis"[MeSH] OR reliab*[tiab] OR unreliab*[tiab] OR valid*[tiab] OR coefficient[tiab] OR homogeneity[tiab] OR homogeneous[tiab] OR "internal consistency"[tiab] OR (cronbach*[tiab] AND (alpha[tiab] OR alphas[tiab])) OR (item[tiab] AND (correlation*[tiab] OR selection*[tiab] OR reduction*[tiab])) OR agreement[tiab] OR precision[tiab] OR imprecision[tiab] OR "precise values"[tiab] OR test–retest[tiab] OR (test[tiab] AND retest[tiab]) OR (reliab*[tiab] AND (test[tiab] OR retest[tiab])) OR stability[tiab] OR interrater[tiab] OR inter-rater[tiab] OR intrarater[tiab] OR intra-rater[tiab] OR intertester[tiab] OR inter-tester[tiab] OR intratester[tiab] OR intra-tester[tiab] OR interobserver[tiab] OR inter-observer[tiab] OR intraobserver[tiab] OR intraobserver[tiab] OR intertechnician[tiab] OR inter-technician[tiab] OR intratechnician[tiab] OR intra-technician[tiab] OR interexaminer[tiab] OR inter-examiner[tiab] OR intraexaminer[tiab] OR intra-examiner[tiab] OR interassay[tiab] OR inter-assay[tiab] OR intraassay[tiab] OR intra-assay[tiab] OR interindividual[tiab] OR inter-individual[tiab] OR

intraindividual[tiab] OR intra-individual[tiab] OR interparticipant[tiab] OR inter-participant[tiab] OR intraparticipant[tiab] OR intra-participant[tiab] OR kappa[tiab] OR kappa's[tiab] OR kappas[tiab] OR repeatab*[tiab] OR ((replicab*[tiab] OR repeated[tiab]) AND (measure[tiab] OR measures[tiab] OR findings[tiab] OR result[tiab] OR results[tiab] OR test[tiab] OR tests[tiab])) OR generaliza*[tiab] OR generalisa*[tiab] OR concordance[tiab] OR (intraclass[tiab] AND correlation*[tiab]) OR discriminative[tiab] OR "known group"[tiab] OR factor analysis[tiab] OR factor analyses[tiab] OR dimension*[tiab] OR subscale*[tiab] OR (multitrait[tiab] AND scaling[tiab] AND (analysis[tiab] OR analyses[tiab])) OR item discriminant[tiab] OR interscale correlation*[tiab] OR error[tiab] OR errors[tiab] OR "individual variability"[tiab] OR (variability[tiab] AND (analysis[tiab] OR values[tiab])) OR (uncertainty[tiab] AND (measurement[tiab] OR measuring[tiab])) OR "standard error of measurement"[tiab] OR sensitiv*[tiab] OR responsive*[tiab] OR ((minimal[tiab] OR minimally[tiab] OR clinical[tiab] OR clinically[tiab]) AND (important[tiab] OR significant[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR (small*[tiab] AND (real[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR meaningful change[tiab] OR "ceiling effect"[tiab] OR "floor effect"[tiab] OR "Item response model"[tiab] OR IRT[tiab] OR Rasch[tiab] OR "Differential item functioning"[tiab] OR DIF[tiab] OR "computer adaptive testing"[tiab] OR "item bank"[tiab] OR "cross-cultural equivalence"[tiab])) NOT ("addresses"[Publication Type] OR "biography"[Publication Type] OR "case reports"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "practice guideline"[Publication Type]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]))

Search strategy for EMBASE

- From inception to February 2, 2021
- Validation studies filters used: *Translation from* Terwee CB, Jansma EP, Riphagen II, de Vet HC. Development of a methodological PubMed search filter for finding studies on measurement properties of measurement instruments. Qual Life Res. 2009 Oct;18(8):1115-23. doi: 10.1007/s11136-009-9528-5.

(('intermethod comparison'/exp OR 'intermethod comparison' OR 'data collection method'/exp OR 'data collection method' OR 'validation study'/exp OR 'validation study' OR 'feasibility study'/exp OR 'feasibility study' OR 'pilot study'/exp OR 'pilot study' OR 'psychometry'/exp OR 'psychometry' OR 'reproducibility'/exp OR 'reproducibility' OR reproducib*:ab,ti OR 'audit':ab,ti OR psychometr*:ab,ti OR clinimetr*:ab,ti OR clinometr*:ab,ti OR 'observer variation'/exp OR 'observer variation' OR 'observer

variation':ab,ti OR 'discriminant analysis'/exp OR 'discriminant analysis' OR 'validity'/exp OR 'validity' OR reliab*:ab,ti OR valid*:ab,ti OR 'coefficient':ab,ti OR 'internal consistency':ab,ti OR (cronbach*:ab,ti AND ('alpha':ab,ti OR 'alphas':ab,ti)) OR 'item correlation':ab,ti OR 'item correlations':ab,ti OR 'item selection':ab,ti OR 'item selections':ab,ti OR 'item reduction':ab,ti OR 'item reductions':ab,ti OR 'agreement':ab,ti OR 'precision':ab,ti OR 'imprecision':ab,ti OR 'precise values':ab,ti OR 'test-retest':ab,ti OR ('test':ab,ti AND 'retest':ab,ti) OR (reliab*:ab,ti AND ('test':ab,ti OR 'retest':ab,ti)) OR 'stability':ab,ti OR 'interrater':ab,ti OR 'inter-rater':ab,ti OR 'intrarater':ab,ti OR 'intra-rater':ab,ti OR 'intertester':ab,ti OR 'inter-tester':ab,ti OR 'intratester':ab,ti OR 'intra-tester':ab,ti OR 'interobeserver':ab,ti OR 'inter-observer':ab,ti OR 'intraobserver':ab,ti OR 'intra-observer':ab,ti OR 'intertechnician':ab,ti OR 'inter-technician':ab,ti OR 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score'/exp OR 'physician global assessment score' OR 'physician global assessment of disease activity'/exp OR 'physician global assessment of disease activity' OR 'investigator global assessment'/exp OR 'investigator global assessment' OR 'investigator global assessment scale'/exp OR 'investigator global assessment scale' OR 'investigator global assessment score'/exp OR 'investigator global assessment score' OR iga:ab,ti,kw OR pga:ab,ti,kw OR 'dermatology life quality index'/exp OR 'dermatology life quality index' OR 'skindex'/exp OR 'skindex' OR 'skindex 29 score'/exp OR 'skindex 29 score' OR 'skindex 29 questionnaire'/exp OR 'skindex 29 questionnaire' OR 'skindex 29'/exp OR 'skindex 29' OR 'skindex 16'/exp OR 'skindex 16' OR 'skindex 17'/exp OR 'skindex 17' OR skindex:ab,ti,kw OR 'life quality':ab,ti,kw OR 'quality of life':ab,ti,kw OR dlqi:ab,ti,kw OR 'short form 36'/exp OR 'short form 36' OR 'short form':ab,ti,kw OR 'sf 36':ab,ti,kw OR sf36:ab,ti,kw OR 'european quality of life 5 dimensions questionnaire'/exp OR 'european quality of life 5 dimensions questionnaire' OR eq) AND 5d:ab,ti,kw OR 'eq 5d':ab,ti,kw OR eq5d:ab,ti,kw OR 'eqol 5d':ab,ti,kw OR euroqol:ab,ti,kw OR 'euroquol 5 dimension*':ab,ti,kw OR 'euroquol 5d':ab,ti,kw OR cleqol:ab,ti,kw OR sleqol:ab,ti,kw OR lupusqol:ab,ti,kw OR 'l qol':ab,ti,kw OR 'pain numeric rating scale'/exp OR 'pain numeric rating scale' OR 'pain numerical rating scale'/exp OR 'pain numerical rating scale' OR 'visual analogue scale'/exp OR 'visual analogue scale' OR 'numeric rating scale'/exp OR 'numeric rating scale' OR 'verbal rating

scale'/exp OR 'verbal rating scale' OR 'numeric rating score' OR 'itch numeric rating scale'/exp OR 'itch numeric rating scale' OR 'itch severity scale'/exp OR 'itch severity scale' OR 'mcgill pain questionnaire'/exp OR 'mcgill pain questionnaire' OR 'brief pain inventory'/exp OR 'brief pain inventory' OR 'brief pain inventory short form'/exp OR 'brief pain inventory short form' OR 'visual analogue scale':ab,ti,kw OR 'numeric rating scale':ab,ti,kw OR 'numerical rating scale':ab,ti,kw OR 'vas':ab,ti,kw OR 'nrs':ab,ti,kw OR 'itch scale':ab,ti,kw OR 'promis itch':ab,ti,kw OR 'mcgill pain':ab,ti,kw OR 'brief pain inventory':ab,ti,kw OR 'patient global assessment'/exp OR 'patient global assessment' OR 'patient global assessment of disease activity'/exp OR 'patient global assessment of disease activity' OR 'patient global assessment score'/exp OR 'patient global assessment score' OR 'patient global impression of change'/exp OR 'patient global impression of change' OR 'patient global impression of change scale'/exp OR 'patient global impression of change scale' OR 'patient global impression of improvement'/exp OR 'patient global impression of improvement' OR 'patient global impression of improvement questionnaire'/exp OR 'patient global impression of improvement questionnaire' OR 'patient global impression of improvement score'/exp OR 'patient global impression of improvement score' OR 'patient global impression of improvement scale'/exp OR 'patient global impression of improvement scale' OR 'global skin health':ab,ti,kw OR 'global improvement':ab,ti,kw OR 'global assessment':ab,ti,kw OR 'global impression':ab,ti,kw) AND ('skin lupus erythematosus'/exp OR 'skin lupus erythematosus':ti,ab,kw OR 'cutaneous and lupus':ti,ab,kw OR 'discoid lupus erythematosus' OR 'discoid lupus':ti,ab,kw OR 'chilblain' OR 'chilblain':ti,ab,kw OR 'lupus panniculitis' OR 'lupus panniculitis':ti,ab,kw OR 'lupus profundus' OR 'lupus profundus':ti,ab,kw OR 'lupus tumidus' OR 'lupus tumidus':ti,ab,kw)

Appendix 3: Results of CLE and SLE RCTs

Table I. Characteristics of CLE Randomized Controlled Trials From MEDLINE/EMBASE

Study	Study Phase	Study Population	Intervention	Comparison	Study Outcomes	Measurement Instrument(s) Used	Domains
Tzung 2007	NA	Facial CLE +/- SLE	Tacrolimus 0.1% ointment	Clobetasol propionate 0.05% ointment	Severity of lesions based on clinical signs of erythema, desquamation, induration, and telangiectasias using a 7-point scale (0: none, 1: mild, 2: moderate, 3: severe, at 0.5 increments), side effects	-	Skin-specific disease activity, side effects
Jemec 2009	Phase 2	DLE	R-salbutamol 0.5% cream	Placebo	Lesion-specific CLASI after 8 weeks, pain and itch, general improvement scored by investigator, global improvement of lesions by patient, size of lesion, plasma concentration of R-salbutamol, adverse events	Lesion-specific CLASI, IGA for general improvement (-1 to 3), PtGA of lesion global improvement (-1 to 3), VAS pain and itch (0: no pain/no itching to 10: worse possible pain/worse imaginable itching)	Skin-specific disease activity, pain and itch, IGA, PtGA of lesion global improvement, safety and adverse events, pharmacokinetics
Wang 2015	NA	Labial DLE, without SLE	Tacrolimus 0.03% ointment	Triamcinolone acetonide 0.1% cream	Surface areas of erosion, erythema and reticulation, pain NRS, safety	Physically measured surface areas of erosion, erythema and reticulation, NRS (0-10) for pain	Skin-specific disease activity, pain, safety
Rerknimitr 2019 / NCT03178188	Phase 2 Phase 3	DLE	Vbeam 595 nm pulsed-dye laser	Sham treatment with cryogen spray	Antera 3D to evaluate erythema and texture/irregularity of DLE lesions, lesion-specific CLASI scores (activity and damage), IGA of lesion improvement	Antera 3D (erythema and texture index), lesion-specific CLASI, IGA of improvement of lesions (-4: worsen 76–100%, -3: worsen 51–75%, -2: worsen 26–50%, -1: worsen 1–25%, 0: no difference, +1: improved 1-25%, +2: improved 26-50%, +3: improved 51–75%, +4: improved 76–100%)	Skin-specific disease activity and damage, IGA of improvement
Presto 2018 / NCT01597050	Phase 2	DLE	Topical R333 ointment	Placebo ointment	≥50% decrease in erythema and scaling for lesions based on CLASI, change from baseline in activity score of target lesions, change in baseline erythema score and scaling, change from baseline in IGA and PtGA of disease activity of lesions	Lesion-specific degree of erythema (0-3), scaling/hypertrophy (0-2) adapted from CLASI; horizontal VAS for IGA and PtGA of disease activity of lesions	Skin-specific disease activity, IGA of activity, PtGA of activity
Kuhn 2011 / NCT00317681	Phase 2	CLE	Tacrolimus 0.1%	Vehicle control	Difference between baseline and last visit in clinical evaluation scores of skin lesions	Digital photography and clinical evaluation	Skin-specific disease activity
Morita 2016 / NCT01551069	Phase 3	CLE +/- SLE	Hydroxychloroquine	Placebo	Pharmacokinetics	-	Pharmacokinetics
Kraak 1965	NA	DLE	Hydroxychloroquine	Placebo	Clinical change on a scale of -1: deterioration after cure, 0: unchanged also continuing of cure, +1: improved and cured after improvement in earlier periods, +2: cured without improvement or deterioration in earlier periods, +3: cured after deterioration in earlier periods	-	Skin-specific disease activity
Levy 2001	NA	SLE or DLE, pregnant women	Hydroxychloroquine	Placebo	SLEDAI scores for disease activity (0-3: no activity, 4-11: moderate activity, >12: severe activity), Apgar scores, ophthalmologic exam, pediatrician examination of children 1.5-3 years later	SLEDAI	Skin-specific disease activity, side effects

Barikbin 2009	Pilot study	Facial DLE without SLE	Pimecrolimus 1% cream	Betamethasone 17-valerate 0.1% cream	Clinical severity score - rate erythema, infiltration and presence of scale (0: normal, 1: slight, 2: moderate, 3: severe), added together to get 0-9 score. Mild: 1-3, moderate: 4-6, severe: 7-9	-	Skin-specific disease activity
Yokogawa 2017 / NCT01551069	Phase 3	CLE +/- SLE	Hydroxychloroquine	Placebo	Change in CLASI activity score (response rate defined as 4 point or 20% decrease in CLASI-A score), IGA (7-point scale based on central photo evaluation which is a 5-point scale, PtGA on a 7-point scale and Skindex-29), for SLE patients: pain and fatigue VAS, PtGA of SLE, RAPID3, IGA of SLE (7-point) and BILAG, anti-ds DNA, complement levels, steroid dose, safety endpoints (adverse event, serious events, lab test values, vital signs, ophthalmologic examinations), population pharmacokinetics	IGA, PtGA for CLE, CLASI, Skindex-29, BILAG, PtGA for SLE (0-10 VAS), pain and fatigue VAS, RAPID3	Skin-specific disease activity, PtGA, quality of life, pharmacokinetics, corticosteroid use, safety, lab values, pain, fatigue
Ruzicka 1992	NA	DLE or SCLE without SLE, LE profundus	Acitretin	Hydroxychloroquine	Erythema, infiltration and scaling/hyperkeratosis score (0: absent, 1: moderate, 2: severe), clearance (1: improvement and 2: no change or deterioration), area of skin affected, clinical and lab findings, adverse events, LE specific lab tests, blood count, UA, overall investigator assessment of efficacy (complete clearing with or without central atrophy 90-100% improvement, marked improvement 50-89%, slight improvement 25-49%, no change <25%, deterioration < 0% improvement)	IGA of efficacy	Skin-specific disease activity, safety, lab values, IGA of efficacy
Bjornberg 1976	NA	DLE	Betamethasone-17,21-dipropionate 0.05% ointment	Betamethasone-17-valerate 0.1% ointment	Rate side was better, equal or worse	-	Skin-specific disease activity
Kuhn 2011	NA	DLE, LE tumidus, SCLE, without SLE	Sunscreen	Vehicle	Positive photoprovocation test, histologic analysis, adverse events	-	Skin-specific disease activity, safety
Pothinamthong 2012	NA	DLE	Tacrolimus 0.1% ointment	Clobetasol propionate 0.05% ointment	CLASI (excluding scalp, mucous membrane and alopecia score), PtGA (patient evaluated each side for 0 to 4 level of improvement score compared with before study using the scale 0: not improved, 1: mild improved 1-25%, 2: moderate improved 26-50%, 3: marked improved 51-75%, and 4: excellent improved 75-100%)	Modified CLASI-A and D excluding scalp, mucous membranes and alopecia, PtGA for improvement	Skin-specific disease activity, skin-specific disease damage, PtGA of improvement of skin/lesions
Furie 2019	Phase 1	SLE patients with ACLE, SCLE, and/or CCLE	BIIB059	Placebo	CLASI-A, SLEDAI, safety endpoints (adverse events, vital signs, EKG, labs), immunologic labs, serum antibodies to BIIB059, pharmacokinetics, histology	CLASI-A, SLEDAI	Safety, tolerability, immunogenicity, pharmacokinetics, SLE disease activity, skin-specific disease activity
Medeiros Bezerra 2005	NA	SLE patients with active typical malar rash and/or discoid lesions and/or SCLE	Clofazimine	Chloroquine disphosphate	Lab values, immunologic labs, change from baseline in the Mexican version of the SLEDAI, rating of cutaneous lupus lesions (6: total response, 5: good response, improvement of >50% of the lesion, 4: partial response, improvement of <50% of the lesions, 3: no response, no improvement of	Mex-SLEDAI	Immunologic tests, lab values, skin-specific disease activity, SLE disease activity

					lesions, 2: worsening, deterioration of existing lesions, 1: new lesions)		
Masek-Hammerman 2016	Phase 1	SCLE or DLE, +/- SLE	PD-0360324	Placebo	Pharmacokinetics, pharmacodynamics, CD14+ CD16 + monocyte fluorescence activated cell sorter assay, tissue immunohistochemistry, routine lab safety tests, absolute change from baseline in CLASI activity and damage scores, SLEDAI-2K scores, IGA (100 mm VS), adverse events	CLASI-A, CLASI-D, SLEDAI-2K, IGA (100 mm VAS)	Pharmacokinetics, pharmacodynamics, immunologic labs, adverse events, safety, skin-specific disease activity and damage, SLE disease activity, IGA
Werth 2017	Phase 1	DLE	AMG 811	Placebo	Changes related to IFN gamma in serum and skin, CXCL10 protein concentrations in serum, adverse events, changes in CLASI-A and CLASI-D, IGA of skin disease, PtGA of skin disease, SLEDAI-2K, pharmacodynamics	CLASI-A, CLASI-D, IGA, PtGA of skin disease, SLEDAI-2K	Pharmacodynamics, safety, skin-specific disease activity and damage, SLE disease activity, PtGA of skin disease, IGA of skin disease
Walker 2020	Phase 1	CCLE, SCLE	GSK2646264	Placebo	Safety (adverse events, labs, vital signs, EKG, physical assessments), pharmacokinetic parameters, change from baseline in R-CLASI-A, mRNA expression in skin related to IFN, skin tolerability test (dermal response from 0: no evidence of irritation to 7: strong reaction spreading beyond test site)	R-CLASI-A	Safety, tolerability, pharmacokinetics, skin-specific disease activity, immunologic labs
Szepietowski 2013	Phase 1	CLE (including SCLE, DLE and LE tumidus)	Sirukumab	Placebo	Safety (adverse events, vital signs, EKG, safety-related labs), pharmacokinetics, antibodies to sirukumab, immunologic labs, CLASI change from baseline, SF-36, DLQI	CLASI, SF-36, DLQI	Safety, pharmacokinetics, immunologic labs, skin-specific disease activity and damage, quality of life
Bjornberg 1966	NA	DLE	Betamethasone-17-valerate 0.1% ointment	Fluocinolone acetonide 0.025% ointment	Change from baseline in redness, scaling, infiltration, and distribution of lesions	-	Skin-specific disease activity

DLE, discoid lupus erythematosus; CLASI(-A and -D), Cutaneous Lupus Erythematosus Disease Area and Severity Index(-Activity and -Damage); IGA, investigator global assessment; PtGA, patient global assessment; VAS, visual analogue scale; NRS, numeric rating scale; SLEDAI, SLE Disease Activity Index; RAPID3, Routine Assessment of Patient Index Data; BILAG, British Isles Lupus Assessment Group; SCLE, subacute CLE; ACLE, acute CLE; SLEDAI-2K, SLE Disease Activity Index-2000; IFN, interferon; R-CLASI-A, Revised-CLASI-Activity; SF-36, Short Form Health Survey; DLQI, Dermatology Life Quality Index

Table II: CLE RCT Eligible Protocols Identified in Clinicaltrials.gov

Study	Study Phase	Study Population	Intervention	Comparison	Study Outcomes	Measurement Instrument(s) Used	Domains
NCT00470912	Phase 3	Chronic CLE without SLE	Sunscreen RV 2547C	Not specified	Not specified	-	-
NCT03122431	Phase 4	CLE (other subarms with SLE, juvenile SLE)	Thalidomide (hydroxychloroquine for other subarms)	Not specified	Improvement in CLASI, disease flares evaluated using SLEDAI-2K, disease flares evaluated using SLEDAI (no further details), drug serum levels	CLASI, SLEDAI-2K, SLEDAI	Skin-specific disease activity and damage, SLE disease flares
NCT03134222	Phase 2	CLE (SCLE, CCLE)	Lanraplenib, Filgotinib	Placebo	Change in CLASI-A score from baseline, decrease in CLASI-A by ≥5 points from baseline, no worsening in CLASI-A score	CLASI-A	Skin-specific disease activity
NCT00523588	Phase 2	CLE	Laser treatment (Candela Vbeam Perfecta[tm])	Untreated lesion	CLASI and modified CLASI, pain and itch relief compared to baseline (not further specified), reduction or increase in CLASI and modified CLASI scores	CLASI, modified CLASI	Skin-specific disease activity and damage, pain, itch
NCT01300208	Phase 2	DLE or SCLE	CC-11050	Placebo	Lab values for safety concerns, pharmacokinetics, response rate based on CLASI	CLASI	Safety, pharmacokinetics, skin-specific disease activity and damage
NCT02847598	Phase 2	SLE with skin and joint involvement, CLE	BIIB059	Placebo	Change from baseline in 28-joint assessment and CLASI-A, CLASI-50 response, % change in CLASI-A score from baseline, ≥4 point CLASI-A reduction from baseline, composite SRI response (≥4 points in SLEDAI-2K, no new BILAG-2004 A and no more than one new B, <0.3 point increase in IGA VAS, no protocol-prohibited medication or treatment, concomitant corticosteroid dosage <=10 mg/day, concomitant corticosteroid dosage <=Day 1 corticosteroid dosage, and no increase in corticosteroid dose), change in SLEDAI-2K score, no new BILAG-2004 A and no more than one new BILAG-2004 B, change from baseline in IGA VAS	CLASI-A, SRI, SLEDAI-2K, BILAG, IGA VAS, 28-joint assessment	Skin-specific disease activity, SLE disease activity, joint symptoms, IGA
NCT01294774	Phase 2	SCLE	KRP203	Placebo	Efficacy in reduction of severity of symptoms as measured by CLASI, safety and tolerability, blood concentration of drug, patient and investigator VAS for global skin health, SLEDAI	CLASI, SLEDAI, IGA and PtGA VAS for global skin health	Skin-specific disease activity and damage, safety and tolerability, pharmacokinetics, IGA for global skin health, PtGA for global skin health, SLE disease activity
NCT01498406	Phase 2	CLE without SLE	High dose vitamin D	Low dose vitamin D	Severity as measured by CLASI, quality of life measured by Skindex-29, serum vitamin D level	CLASI, Skindex-29	Skin-specific disease activity and damage, quality of life
NCT01466725	Phase 2	DLE without SLE	CC-930	Placebo	Adverse events, pharmacokinetics	-	Safety, pharmacokinetics

NCT03958955	Phase 2	DLE	Delgocitinib cream	Delgocitinib cream vehicle	Lesion-specific IGA severity score of 0 (clear) or 1 (almost clear), adverse events, ≥2 point reduction in IGA score, ≥2 point reduction in erythema score for lesion using CLASI, total disease activity score based on CLASI and R-CLASI	IGA of lesion severity (0: clear, 4: severe), CLASI, R-CLASI (lesion-specific and overall)	Skin-specific and lesion-specific disease activity, IGA of lesion severity, safety, global disease severity
NCT00625521	Phase 2	DLE or SLE	ASF 1096 0.5% cream	Cream vehicle	Safety profile, CLASI score, IGA, PtGA	CLASI, IGA, PtGA	Skin-specific disease activity, IGA, PtGA

Note: Clinical trials NCT00317681, NCT01551069, NCT01597050, and NCT03178188 overlapped with published studies from MEDLINE/EMBASE (see Table 1) and were thus omitted.

CLASI(-A), Cutaneous Lupus Erythematosus Disease Area and Severity Index(-Activity); SLEDAI, SLE Disease Activity Index; SLEDAI-2K, SLE Disease Activity Index-2000; SCLE, subacute CLE; CCLE, chronic CLE; SRI, SLE Responder Index; BILAG, British Isles Lupus Assessment Group; IGA, investigator global assessment; VAS, visual analogue scale; PtGA, patient global assessment; R-CLASI, Revised CLASI; DLE, discoid lupus erythematosus

Table III: SLE RCT Protocols Identified in Clinicaltrials.gov

NCT Number	Phase	Intervention	Comparison	Measurement Instrument(s) Used	Domains
NCT02794285	Phase 3	Anifrolumab	Placebo	-	Safety, adverse events
NCT02446899	Phase 3	Anifrolumab	Placebo	BICLA, CLASI-A, Joint Counts	SLE disease activity, steroid use, skin-specific disease activity, disease flare, adverse events, vitals and lab value changes
NCT02446912	Phase 3	Anifrolumab	Placebo	SRI4, SLE Responder Index, CLASI-A, BICLA, SELENA-SLEDAI Flare Index, Columbia Suicide Severity Rating Scale, PHQ-8	SLE disease activity, steroid use, safety, adverse events, skin-specific disease activity, vital signs/physical exam/ECG/lab abnormality, disease flares, suicide ideation, depression
NCT04294667	Phase 3	DZP	Placebo	BICLA, LLDAS, BILAG, SLEDAI-2K, IGA of SLE signs and symptoms and functional capacity of the study participant, SRI-4	SLE disease activity, disease flares, adverse events, IGA of SLE disease activity and function
NCT03312907	Phase 3	Belimumab + rituximab then standard of therapy; belimumab + standard	Belimumab + placebo then standard of therapy	Modified SLE flare index, SLEDAI-2K, IGA of disease activity (VAS), SLICC damage index, LLDAS, PtGA of current disease activity (rate severity of SLE between 0: very well and 10: very poor), LupusQoL, FACIT-Fatigue	SLE disease activity, SLE disease remission, disease flare, SLE disease damage, adverse events, PtGA of disease severity/activity, quality of life, fatigue, IGA of disease activity
NCT03843125	Phase 3	Baricitinib high dose	Baricitinib lose dose	SRI-4, LLDAS, SELENA-SLEDAI flare rate, CLASI-A, Tender and Swollen Joint Count, SLICC Damage index, Worst Pain NRS	Adverse events, SLE disease activity, steroid use, disease flares, skin-specific disease activity, joint pain, SLE disease damage, pain
NCT03616964	Phase 3	Baricitinib high and low dose	Placebo	SRI-4, LLDAS, Worst pain NRS, FACIT-Fatigue, CLASI-A, Tender and Swollen Joint Count	SLE disease activity, disease flare, steroid use, pain, fatigue, skin-specific disease activity, joint pain, pharmacokinetics
NCT03616912	Phase 3	Baricitinib high and low dose	Placebo	SRI-4, LLDAS, Worst Pain NRS, FACIT-Fatigue, CLASI-A, Tender and Swollen Joint Count	SLE disease activity, disease flare, steroid use, pain, fatigue, skin-specific disease activity, joint pain, pharmacokinetics
NCT04082416	Phase 3	RC18	Placebo	SRI-4, SELENA-SLEDAI score, IGA of disease activity (VAS 0-100 mm)	SLE disease activity, steroid use, lab values, disease flare, IGA of disease activity
NCT04060888	Phase 3	Ustekinumab	Placebo	SRI-4, number of joints with pain and signs of inflammation, CLASI-A	SLE disease activity, disease flare, joint pain, steroid use, skin-specific disease activity,
NCT00413361	Phase 4	Hydoxychloroquine	Placebo	SELENA-SLEDAI flare index, SF-36, SELENA-SLEDAI, analogical visual scale (not further specified)	Disease flare, steroid use, quality of life, treatment tolerance/side effects
NCT03517722	Phase 3	Ustekinumab	Placebo	SRI-4, number of joints with pain and signs of inflammation, CLASI-A	SLE disease activity, disease flare, joint pain, steroid use, skin-specific disease activity
NCT02953821	Phase 4	Acthar gel	Placebo gel	IGA of disease activity (100 mm VAS), BILAG, SLEDAI-2K, SELENA flare index, CLASI-A, 28-Joint Count	IGA of disease activity, SLE disease activity, disease flare, skin-specific disease activity, joint pain, steroid use
NCT00470522	Phase 3	Methotrexate and folic acid	Placebo	SLAM, SLICC Damage Index, SF-36, SLEDAI	SLE disease activity and damage, quality of life

NCT01632241	Phase 4	Belimumab + standard therapy	Placebo + standard therapy	SRI, SLE Flare Index, Division of Microbiology and Infectious Diseases Adult Toxicity Adverse Event Severity Grading	SLE disease activity, renal disease, adverse events, toxicity, disease flare, steroid use
NCT01484496	Phase 3	Belimumab + standard therapy	Placebo + standard therapy	SRI, SLE Flare Index	SLE disease activity, disease flare, steroid use
NCT01345253	Phase 3	Belimumab	Placebo	SRI-4, SRI-7, SELENA-SLEDAI, SLE Flare Index	SLE disease activity, steroid use, disease flare
NCT02504645	Phase 3	IPP-201101	Placebo	SRI	SLE disease activity
NCT01395745	Phase 3	Blisibimod	Placebo	SRI, number of tender or swollen joints	SLE disease activity, steroid use, disease flare, joint pain, renal disease, mucocutaneous disease, safety, immunologic labs
NCT01597492	Phase 4	Belimumab + early vaccination	Belimumab plus late vaccination	-	Antibody response to vaccination
NCT01408576	Phase 3	Epratuzumab 600 mg per week	Epratuzumab 1200 mg every other week	BILAG, SLEDAI, IGA of disease	Adverse events, SLE disease activity, IGA of disease
NCT01322308	Phase 4	Pioglitazone	Placebo	-	Cardiovascular disease markers
NCT01262365	Phase 3	Epratuzumab, 600 mg per week or 1200 mg every other week	Placebo	BILAG, SLEDAI-2K, IGA of disease activity	SLE disease activity, steroid use, IGA of disease activity
NCT00410384	Phase 3	Belimumab 1 mg/kg, 10 mg/kg	Placebo	SRI, SELENA-SLEDAI, IGA of disease activity (from 0 to 3, 1: mild, 3: severe), SF-36	SLE disease activity, quality of life, steroid use, IGA of disease activity
NCT01261793	Phase 3	Epratuzumab, 600 mg per week or 1200 mg every other week	Placebo	BILAG, SLEDAI-2K, IGA of disease activity	SLE disease activity, steroid use, IGA of disease activity
NCT00424476	Phase 3	Belimumab 1 mg/kg or 10 mg/kg	Placebo	SRI, SELENA-SLEDAI, IGA of disease activity (from 0 to 3, 1: mild, 3: severe), SF-36	SLE disease activity, quality of life, steroid use, IGA of disease activity
NCT02514967	Phase 3	Blisibimod	Placebo	SRI-6	SLE disease activity, SLE flare, skin-specific disease activity, joint pain, steroid use, renal disease, adverse events, immunologic labs
NCT00739050	Phase 4	Simvastatin	Placebo	-	Vascular function, cardiovascular labs
NCT00082511	Phase 3	Prasterone (GL701)	Placebo	-	Bone density
NCT00504244	Phase 3	Switch to Myfortic	Continuation of azathioprine	SLEDAI, BILAG, SF-36	SLE disease activity, renal disease, steroid use, quality of life
NCT00383214	Phase 3	Epratuzumab	Placebo	BILAG, IGA, PtGA	Renal disease, SLE disease activity, PtGA, IGA, steroid use, pharmacokinetics, quality of life
NCT01753401	Phase 4	Acthar	Placebo	SELENA-SLEDAI, IGA of disease severity (100 mm VAS from none to severe), BILAG, Tender or Swollen Joints, CLASI-A, Krupp Fatigue Severity Score, SF-36	SLE disease activity, IGA of disease severity, joint pain, fatigue, quality of life, skin-specific disease activity

NCT02074020	Phase 3	Blisibimod	Placebo	SRI-8	SLE disease activity, disease flare, joint pain, skin disease activity, renal disease, steroid use, immunology labs, adverse events
NCT00539838	Phase 3	Ocrelizumab	Placebo	BILAG, SLEDAI-2K, SF-36, FACIT-Fatigue, Brief Pain Inventory, EQ-5D	Renal disease, SLE disease activity, disease flare, quality of life, fatigue, pain, health economics, adverse events
NCT00111306	Phase 3	Epratuzumab	Placebo	BILAG, IGA, PtGA	SLE disease activity, PtGA, IGA, steroid use, quality of life
NCT00668330	Phase 4	Ibandronate + alfacalcidol + calcium	Placebo	-	Bone density, fractures
NCT00336414	Phase 3	Prednisone + oral cyclophosphamide	High dose IV cyclophosphamide, intermediate dose IV cyclophosphamide + azathioprine	IGA of disease activity on a 10 cm VAS, European Consensus Lupus Activity Measure, Parent's/Patient's Global Assessment of Overall Well-being	SLE disease activity, quality of life, PtGA of well-being, steroid use, renal disease, IGA of disease activity, drop-out
NCT02741960	Phase 4	Metformin	Placebo	-	Disease flares, steroid use, BMI changes, adverse events
NCT02779153	Phase 4	Acthar low dose	Acthar high dose	SLEDAI, BILAG, IGA of disease activity (10 cm VAS), SELENA Flare Index, SLICC damage index, SF-36, FACIT-Fatigue, PtGA for SLE disease activity (100 mm VAS)	SLE disease activity, disease flares, SLE disease damage, quality of life, fatigue, IGA of disease activity, PtGA of disease activity
NCT01705977	Phase 4	Belimumab + standard therapy	Placebo + standard therapy	-	Mortality, adverse events, steroid use
NCT00392093	Phase 4	Conjugated equine estrogens 0.625 mg/d + MPA 5 mg/d/10d	Placebo	SLEDAI	SLE disease activity, disease flare, bone density, mammographic changes, cardiovascular labs
NCT02477150	Phase 4	Zostavax	Placebo	-	Immune response to vaccination
NCT00004662	Phase 3	Dehydroepiandrosterone	Placebo	-	-
NCT00724867	Phase 3	Belimumab 1mg/kg	Belimumab 10 mg/kg	SLICC Damage Index, SF-36, FACIT-Fatigue	Adverse events, immunologic labs, lab changes, vitals, renal function, steroid use, SLE disease damage, quality of life, fatigue
NCT02041091	Phase 3	Tabalumab auto-injector	Tabalumab prefilled syringe	SQAAQ	Pharmacokinetics, patient drug administration ability
NCT00626197	Phase 3	Ocrelizumab 400 mg + standard of care, ocrelizumab 1000 mg + standard of care	Placebo + standard of care	SLEDAI-2K, SF-36, FACIT-Fatigue, Modified Brief Pain Inventory Short Form	Renal disease, SLE disease activity, renal flare, quality of life, fatigue, healthcare utilization, steroid use, immunologic labs
NCT00188188	Phase 4	Quinipril	Placebo	-	-
NCT03042260	Phase 4	Trimethoprim-Sulfamethoxazole	Placebo	-	Adverse events, mortality
NCT00000420	Phase 3	Ortho-Novum 777	Placebo	-	-
NCT00000419	Phase 3	Premarin and Provera	Placebo	-	-
NCT01488708	Phase 3	LY2127399	Placebo	SRI, SLEDAI, LupusQoL	Adverse events, SLE disease activity, steroid use, disease flare, quality of life, immunologic labs
NCT00065806	Phase 3	Atorvastatin	Placebo	-	Cardiovascular labs, vascular function

NCT04515719	Phase 4	Belimumab	Placebo	SELENA-SLEDAI Flare Index, SELENA-SLEDAI, BILAG	Disease flares, steroid use, SLE disease activity, adverse events
NCT01205438	Phase 3	LY2127399	Placebo	SRI, SLEDAI-2K, SLE Flare Index, IGA of disease activity (100 mm VAS with benchmarks of 0, 1, 2, and 3 corresponding to no, mild, moderate, and severe SLE disease activity), LupusQoL, Brief Fatigue Inventory, BILAG, SELENA-SLEDAI	SLE disease activity, steroid use, immunologic labs, disease flare, quality of life, fatigue, IGA of disease activity
NCT01196091	Phase 3	LY2127399	Placebo	SRI, SLEDAI-2K, SELENA-SLEDAI, SLE Flare Index, IGA of disease activity (100 mm VAS with benchmarks of 0, 1, 2, and 3 corresponding to no, mild, moderate, and severe SLE disease activity), Brief Fatigue Inventory, LupusQoL, BILAG	SLE disease activity, steroid use, immunologic labs, fatigue, quality of life, IGA of disease activity
NCT02558517	Phase 3	Prednisone discontinuation	Prednisone maintenance	SLE Flare Index	Disease flare
NCT00866229	Phase 4	Rosuvastatin	Simvastatin	-	Cardiovascular labs
NCT00371501	Phase 4	Rosuvastatin, aspirin	Placebo	-	Cardiovascular markers, thrombotic events, adverse events
NCT01101802	Phase 4	Mycophenolate mofetil	Placebo	BILAG, SLEDAI	Vascular function, SLE disease activity
NCT04275193	Phase 2 Phase 3	Zishenqing	Placebo	SF-36, LupusQoL, SLEDAI	Quality of life, SLE disease activity
NCT03979976	Phase 2 Phase 3	Ramipril	No intervention	-	Vascular function
NCT03543839	Phase 4	Belimumab	Placebo	SRI, LLDAS, DORIS, SELENA-SLEDAI	Immunologic labs, disease flare, SLE disease activity, adverse events and safety, cardiovascular disease, disease remission
NCT03098823	Phase 4	RAYOS	Prednisone	FACIT-Fatigue	Fatigue
NCT04127747	Phase 4	Standard dose of rituximab	Individualized dose of rituximab	-	SLE disease activity
NCT00005778	Phase 3	High-dose immunoablative therapy	Monthly IV cyclophosphamide	RIFLE	Renal disease
NCT01112215	Phase 4	Azathioprine	Enteric-Coated mycophenolate sodium	SLEDAI, BILAG	SLE disease activity, disease remission, disease flares
NCT00828178	Phase 4	Omega-3	Corn starch	-	Vascular blood flow, SLE disease activity, inflammatory markers
NCT00089804	Phase 3	Abetimus sodium	Placebo	-	Renal flare, disease flare, renal disease
NCT00611663	Phase 2 Phase 3	Prevnar + Pneumo23	Placebo	SLEDAI	SLE disease activity, immune response to vaccination
NCT00624338	Phase 2 Phase 3	Atacicept	Placebo	BILAG	Disease flare, steroid use
NCT00137969	Phase 2 Phase 3	Rituximab + prednisone	Placebo + prednisone	BILAG, SF-36	Renal disease, SLE disease activity, disease flare

NCT01773616	Phase 3	Rituximab	Oral prednisolone	BILAG	Renal disease, adverse events, steroid use, SLE disease activity, renal flare, immunologic labs
NCT00120887	Phase 4	Atorvastatin	Placebo	-	Cardiovascular function, vascular measures, bone mineral density
NCT00432354	Phase 2 Phase 3	Atorvastatin	Placebo	SLEDAI, Raynaud's Condition Score	SLE disease activity, microcirculation
NCT00189124	Phase 2 Phase 3	Dehydroepiandrosterone	Placebo	SLEDAI	Cardiovascular markers, immunologic labs, SLE disease activity
NCT00004795	Phase 2 Phase 3	Dehydroepiandrosterone	Dehydroepiandrosterone different dose	-	-
NCT00430677	Phase 2 Phase 3	Abatacept + corticosteroids + mycophenolate mofetil	Placebo + corticosteroids + mycophenolate mofetil	SLICC Damage Index, SF-36, fatigue VAS, Krupp Fatigue Severity Scale	Renal disease, SLE disease damage, quality of life, fatigue, adverse events, labs, vital signs, immunologic measures
NCT01014260	Phase 4	Doxycycline	Placebo	-	Inflammatory labs
NCT00368264	Phase 2 Phase 3	Infliximab	Placebo	SIS, SLEDAI, SF-36, Fatigue Severity Scale	Renal disease, SLE disease activity, quality of life, fatigue
NCT00053560	Phase 3	Prasterone (GL701)	Placebo	-	-
NCT00035308	Phase 3	Abetimus sodium	Placebo	-	-
NCT01359826	Phase 4	Milnacipran	Placebo	Fatigue Severity Scale, Short Form McGill Pain Questionnaire, Fatigue VAS, Pain VAS, SF-36, Patient Global Impression of Change	Fatigue, pain, quality of life, PtGA of change
NCT04424602	Phase 4	Cyclophosphamide	Mycophenolate	-	Renal disease, immunologic labs, labs
NCT04221477	Phase 3	Obinutuzuma	Placebo	SLEDAI-2K, FACIT-Fatigue	Renal disease, immunologic labs, SLE disease activity, fatigue, adverse events, pharmacokinetics
NCT04181762	Phase 3	Secukinumab	Placebo	FACIT-Fatigue, SF-36, LupusQoL	Renal disease, steroid use, fatigue, quality of life, adverse events
NCT04146220	Phase 4	Prednisolone low dose	Prednisolone high dose	-	Renal disease remission
NCT04145687	Phase 4	Metformin	Placebo	SLEDAI	SLE disease activity, renal disease, steroid use
NCT03920059	Phase 4	Mycophenolate mofetil dosed based on blood level	Mycophenolate mofetil fixed dose	-	Adverse events, pharmacokinetics, immunologic labs, renal disease
NCT03859570	Phase 4	Pentoxifylline	Placebo	SLEDAI, PtGA of disease activity (0-10 with 10 being the worst), IGA of disease activity (0-10 with 10 being the worst)	Renal disease, SLE disease activity, PtGA of disease activity, steroid use, IGA of disease activity
NCT03684564	Phase 2 Phase 3	Rivaroxaban	Warfarin	EQ-5D-5L	Neuroradiologic changes, vascular events, death, cardiovascular events, safety, health economics
NCT03597464	Phase 3	Voclosporin	Placebo	SELENA-SLEDAI, SF-36	Adverse events, renal disease, renal flare, SLE disease activity, immunologic labs, quality of life, health resource utilization
NCT03214731	Phase 4	Artesunate	Placebo	-	Disease remission
NCT03021499	Phase 3	Voclosporin	Placebo	SELENA-SLEDAI	Renal disease, immunology labs, SLE disease activity, quality of life

NCT02645565	Phase 4	Low dose Cyclophosphamide + Azathioprine + Methylprednisolone	High dose Cyclophosphamide + Azathioprine + Methylprednisolone	-	Renal disease, renal and non-renal disease flares, adverse events
NCT02630628	Phase 4	Tacrolimus	Mycophenolate mofetil	-	Renal disease
NCT02457221	Phase 3	Tacrolimus capsules + steroid	Cyclophosphamide injection + steroid	-	Renal disease, immunologic labs
NCT02444728	Phase 3	Hydroxychloroquine	Cyclophosphamide	-	Renal disease
NCT02256150	Phase 3	Mizoribine	Cyclophosphamide	-	Renal disease, immunology labs
NCT02226341	Phase 4	Mycophenolate mofetil + Acthar gel BIW	Mycophenolate mofetil + Achtar gel QOD	-	Renal Disease, disease flares, side effects
NCT02081183	Phase 3	Mycophenolate mofetil + prednisone	Cyclophosphamide + prednisone	-	Renal disease
NCT01926054	Phase 4	Acthar gel BIW	Acthar gel TIW	SLEDAI	Adverse events, labs, renal disease
NCT01765842	Phase 3	Rituximab 2 cycles	Rituximab 1 cycle	-	Renal disease, safety
NCT01714817	Phase 3	BMS-188667 + mycophenolate mofetil + prednisone	Placebo + mycophenolate mofetil + prednisone	BILAG	Renal disease, SLE disease activity, adverse events, pharmacokinetics, vitals, labs
NCT01673295	Phase 3	RTX infusions	Standard of care	-	Renal disease
NCT01646736	Phase 2 Phase 3	Tripterygium wilfordii Hook F + steroid	Steroid + cyclophosphamide	-	Renal disease, immunologic labs
NCT01639339	Phase 3	Belimumab	Placebo	-	Renal disease, death
NCT01342016	Phase 3	Tacrolimus + leflunomide placebo	Tacrolimus placebo + leflunomide	-	Renal disease
NCT01299922	Phase 3	Cyclosporine + mycophenolic acid + prednisone	Mycophenolic acid + prednisone	-	Renal disease, adverse events
NCT01257802	Phase 3	Depot leuprolide acetate	Placebo	-	Fertility labs
NCT01015456	Phase 3	Mycophenolate sodium	Cyclophosphamide	-	Renal disease
NCT00615173	Phase 3	Tacrolimus	Cyclophosphamide or azathioprine	-	Renal disease
NCT00573157	Phase 2 Phase 3	Atacicept + mycophenolate mofetil + steroids	Placebo + mycophenolate mofetil + steroids	-	Renal disease, disease flares
NCT00539799	Phase 3	Prednisolone	Placebo	-	Renal and non-renal disease relapse, quality of life, adverse events, renal disease
NCT00429377	Phase 3	Tacrolimus	-	-	Renal disease, immunologic labs
NCT00425438	Phase 3	Mycophenolate mofetil	Cyclophosphamide/azathioprine	-	Renal disease
NCT00404794	Phase 3	Prednisolone + mycophenolate mofetill	Prednisolone + tacrolimus		Renal disease, adverse events
NCT00377637	Phase 3	Mycophenolate mofetil + steroids for induction; mycophenolate + placebo to azathioprine + steroid for maintenance	Cyclophosphamide + steroids for induction; azathioprine + placebo to mycophenolate mofetil + steroid for maintenance	BILAG, SF-36	SLE disease activity, quality of life, adverse events, deaths, disease flare

NCT00371319	Phase 4	Tacrolimus	Mycophenolate mofetil	-	Renal disease, mortality
NCT00282347	Phase 3	Rituximab	Placebo	BILAG, SF-36	Renal response/disease, SLE disease activity, immunologic labs
NCT00277251	Phase 2 Phase 3	Alendronate	Standard of care	-	Bone density, growth, fractures
NCT00204022	Phase 3	Mycophenolate mofetil	Azathioprine	-	Renal flares, toxicity, steroid use, renal disease
NCT00508898	Phase 4	Calcitriol	Multivitamin	SLEDAI	Renal disease, disease flare, SLE disease activity, immunologic labs
NCT04702256	Phase 3	Obinutuzumab + Mycophenolate mofetil	Corticosteroids + mycophenolate mofetil	SELENA-SLEDAI, SLICC damage index, EQ-5D, MASRI	Renal disease, SLE disease activity, safety, adverse events, SLE disease damage, non-adherence, cost effectiveness

Note: Clinical trials NCT01551069, NCT03178188, NCT00470912, NCT03122431 overlapped with CLE RCTs identified from Clinicialtrials.gov and were thus omitted.

BICLA, BILAG-Based Combined Lupus Assessment; BILAG, British Isles Lupus Assessment Group; CLASI(-A), Cutaneous Lupus Erythematosus Disease Area and Severity Index(-Activity); SRI, SLE Responder Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus: National Assessment - SLE Disease Activity Index; PHQ-8, Patient Health Questionnaire; LLDAS, Lupus Low Disease Activity State; SLEDAI-2K, SLE Disease Activity Index-2000; IGA, investigator global assessment; VAS, visual analogue scale; SLICC, Systemic Lupus Erythematosus International Collaborating Clinics; PtGA, patient global assessment; LupusQoL, Lupus Quality of Life; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy Fatigue; NRS, numeric rating scale; SF-36, Short Form Health Survey; SLAM, Systemic Lupus Activity Measure; SLEDAI, SLE Disease Activity Index; SQAAQ, Subcutaneous Administration Assessment Questionnaire; DORIS, Definition of Remission in SLE; SIS, SLE Index Score; MASRI, Medication Adherence Self-Report Inventory

Appendix 4: Outcome Measurement Instruments Identified

Table I. Physician and Patient-Reported Outcome Measurement Instruments Identified in CLE and SLE Studies

	CLE RCTs	SLE RCTs	CLE Outcome Measures SLR	SLR of Validated CLE Measures
Physician-Reported	CLASI* R-CLASI* SLEDAI/SELENA-SLEDAI/SLEDAI-2K SRI BILAG IGA (unspecified, general improvement, lesion improvement, efficacy, skin disease, skin health, lesion severity, disease activity) 28 Joint Count/Assessment	CLASI-A* SLEDAI/SELENA-SLEDAI/SLEDAI-2K SRI BILAG IGA (unspecified, of disease activity, disease activity and patient function, disease severity) 28 Joint Count/Assessment SLAM SIS SELENA Flare Index BICLA LLDAS SLICC Damage Index DORIS RIFLE Classification Criteria Division of Microbiology and Infectious Diseases Adult Toxicity Adverse Event Severity Grading Raynaud's Condition Score ECLAM	N/A	CLASI* R-CLASI* SADDLE*
Patient-Reported	PtGA (unspecified, global improvement of lesions, improvement, lesion disease activity, skin disease, global skin health) Fatigue VAS Pain NRS Pain VAS Pruritus VAS Skindex-29 RAPID3 DLQI SF-36	PtGA (unspecified, of disease activity, global impression change) Fatigue VAS Worst Pain NRS Pain VAS Patient Global Impression of Change LupusQoL Parent's/Patient's Global Assessment of Overall Well-being Short Form McGill Pain Questionnaire Brief Pain Inventory Short Form	Pain VAS Pruritis VAS Skindex-29 Skindex-29+3 DLQI SF-36	Brazilian-Portuguese DLQI CLEQoL* LEQoL* 12-PSS

		EQ-5D SF-36 FACIT-Fatigue Score Brief Fatigue Inventory Krupp Fatigue Severity Score PHQ-8 Columbia Suicide Severity Rating Scale SQAAQ MASRI		

SLR, systematic literature review; CLASI(-A), Cutaneous Lupus Erythematosus Disease Area and Severity Index(-Activity); R-CLASI, Revised-CLASI; SLEDAI, SLE Disease Activity Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus: National Assessment - SLE Disease Activity Index; SLEDAI-2K, SLE Disease Activity Index-2000; SRI, SLE Responder Index; BILAG, British Isles Lupus Assessment Group; IGA, investigator global assessment; SLAM, Systemic Lupus Activity Measure; SIS, SLE Index Score; BICLA, BILAG-Based Combined Lupus Assessment; LLDAS, Lupus Low Disease Activity State; SLICC, Systemic Lupus Erythematosus International Collaborating Clinics; DORIS, Definition of Remission in SLE; ECLAM, European Consensus Lupus Activity Measure; SADDLE, Score of Activity and Damage in DLE; PtGA, patient global assessment; VAS, visual analogue scale; NRS, numeric rating scale; RAPID3, Routine Assessment of Patient Index Data; DLQI, Dermatology Life Quality Index; SF-36, Short Form Health Survey; LupusQoL, Lupus Quality of Life; FACIT-Fatigue Score, Functional Assessment of Chronic Illness Therapy Fatigue Score; PHQ-8, Patient Health Questionnaire; SQAAQ, Subcutaneous Administration Assessment Questionnaire; MASRI, Medication Adherence Self-Report Inventory; CLEQoL, Cutaneous Lupus Erythematosus Quality of Life; LEQoL, Lupus Erythematosus Quality of Life Questionnaire; 12-PSS; 12-Item Pruritus Severity Scale

*CLE-specific

Table II. Preliminary Pairing of Identified Outcome Measures to Core Domains

	Dermatologic	Generic	CLE-Specific	SLE-Specific
Skin-specific Disease Activity	N/A	N/A	CLASI R-CLASI SADDLE	N/A
IGA of Disease Activity	5-point IGA of lesion severity: 0 (clear) to 4 (severe) 7-point IGA: remarkably aggravated, aggravated, slightly aggravated, not changed, slightly improved, improved, remarkably improved IGA of efficacy: complete clearing with or without central atrophy (90-100% improvement), marked (50-89% improvement), slight (25-49% improvement), no change (<25% improvement), deterioration (<0% improvement) 9-point IGA of lesion improvement: -4: worsen 76-100%, -3: worsen 51–75%, -2: worsen 26–50%, -1: worsen 1-25%, 0: no difference, +1: improved 1-25%, +2: improved 26–50%, +3: improved 51–75%, +4: improved 76–100% IGA VAS of global skin health IGA of skin disease IGA VAS of disease activity of skin lesions	IGA (unspecified) IGA VAS 5-point IGA of general improvement: -1 to 3	N/A	N/A

Skin-specific Disease Damage	N/A	N/A	CLASI R-CLASI SADDLE	N/A
Health-related Quality of Life	DLQI Skindex-29 Skindex-29+3	SF-36 EQ-5D	CLEQoL LEQoL	LupusPRO SLEQOL L-QoL LupusQoL LEQoL
Symptoms	DLQI Skindex-29+3	Pain VAS/NRS Itch VAS Short Form McGill Pain Questionnaire Brief Pain Inventory Short Form		
PtGA of Disease Activity	PtGA of Global Improvement of Lesions: -1 to 3 PtGA VAS of Lesion Disease Activity 5-point PtGA of Lesion Improvement: 0: not improved, 1: mildly improved 1-25%, 2: moderately improved 26-50%, 3: markedly improved 51-75%, 4: excellent, improved 75-100% PtGA of Skin Disease PtGA VAS of Global Skin Health	7-point PtGA PtGA (unspecified) PtGA Overall Well-being Patient Global Impression of Change	PtGA VAS of Disease Activity	PtGA of SLE on a 1-10 VAS PtGA of Disease Activity: 0: very well, 10: very poor; 100 mm VAS; 0-10 with 10 being the worst

CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; R-CLASI, Revised-CLASI; SADDLE, Score of Activity and Damage in DLE; IGA, investigator global assessment; VAS, visual analogue scale; DLQI, Dermatology Life Quality Index; SF-36, Short Form Health Survey; CLEQoL, Cutaneous Lupus Erythematosus Quality of Life; LEQoL, Lupus Erythematosus Quality of Life Questionnaire; LupusPRO, Lupus Patient Reported Outcome; SLEQOL, SLE Quality of Life; L-QoL, SLE Quality of Life; LupusQoL, Lupus Quality of Life; NRS, numeric rating scale; PtGA, patient global assessment

Appendix 5: Studies Evaluating the Measurement Properties of Outcome Measurement Instruments in CLE

Figure 1. PRISMA Flow Chart for Validation Studies of Outcome Measures in CLE

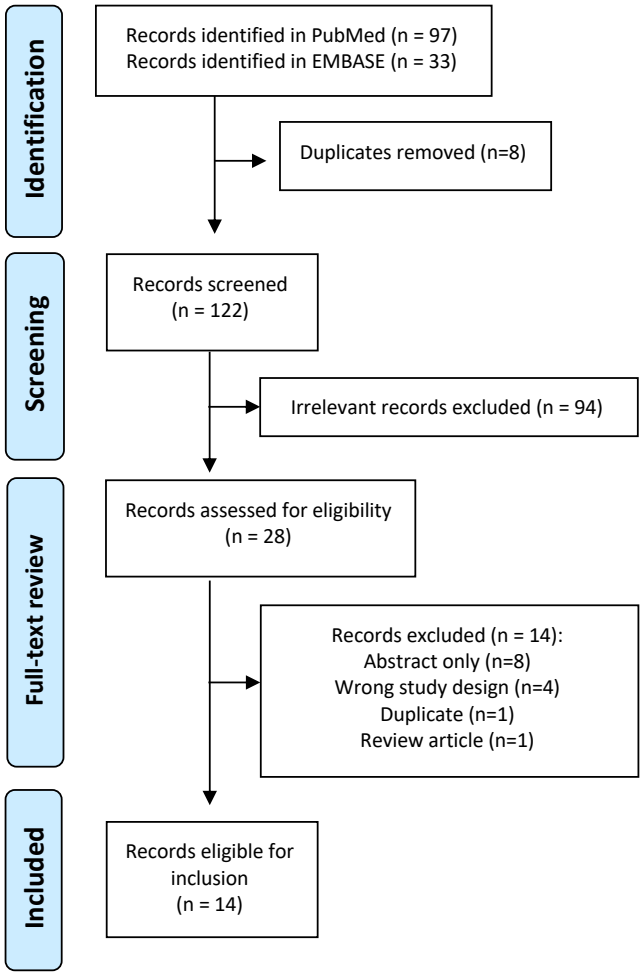
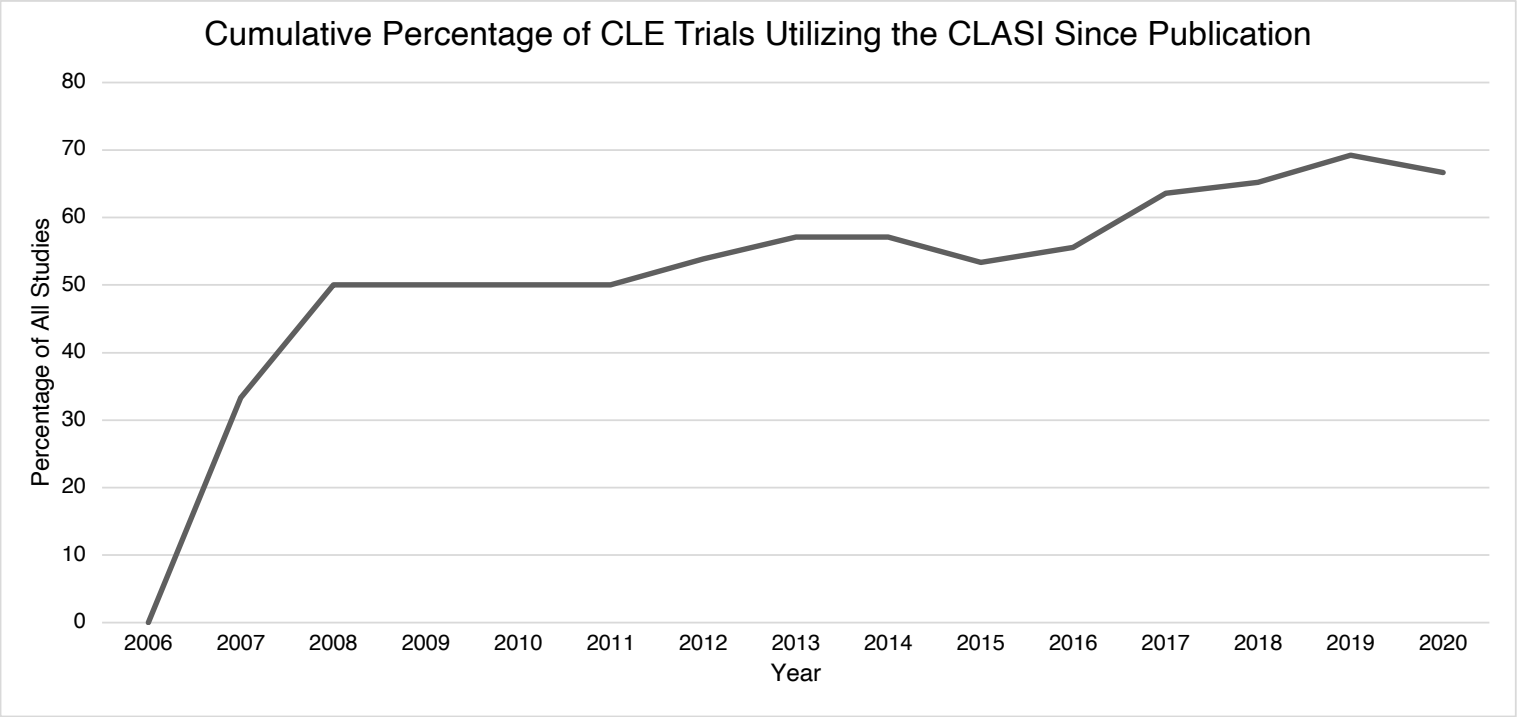


Table I. Validation Studies Identified

Validation Study	Measurement Properties Assessed
CLASI	
1. Albrecht 2005	Content validity Inter-rater reliability Intra-rater reliability Feasibility (time to complete the assessment)
2. Bonilla-Martinez 2008	Responsiveness Known-groups validity
3. Krathen 2008	Inter-rater reliability Intra-rater reliability
4. Bein 2011	Known-groups validity
5. Klein 2011	Construct validity Known groups validity Interpretability: Cut-off scores for severity groups Interpretability: Cut-off scores for clinical improvement
6. Jolly 2013	Construct validity
7. Verma 2016	Construct validity Known-groups validity
8. Chakka 2020	Interpretability: minimal clinically significant improvement in disease activity
RCLASI	
1. Kuhn 2010	Content validity Inter-rater reliability Intra-rater reliability Feasibility (time to complete the assessment)
SADDLE	
1. Wahie 2009	Content validity Inter-rater reliability Intra-rater reliability Known-groups validity
DLQI	
1. Ferraz 2006	Cross-cultural validity (Brazilian version) Construct validity Inter-rater reliability
LeQoL	

1. Castellano-Rioja 2020	Content validity Structural validity Internal consistency
CLEQoL	
1. Ogunsanya 2019	Structural validity Internal consistency Construct validity
12-Item Pruritus Severity Scale	
1. Stepien 2020	Interpretability: definition of severity bands

Appendix 6: Usage of CLASI in CLE RCTs Since Development



CLASI was published in 2005. Year reflects study publication date in PubMed or first posting date on ClinicalTrials.gov.

Appendix 7: Cutaneous Lupus Activity Investigator's Global Assessment (CLA-IGA)

Cutaneous Lupus Activity Investigator's Global Assessment (CLA-IGA)	
0- Clear	**Erythema** - none **Scale** - none **Edema/infiltration** - none **Follicular involvement:** *follicular plugging / follicular hyperkeratosis – absent* **Secondary Change:** no vesicles, erosion, crusting
1- Almost clear	**Erythema** – faint **Scale** - minimal **Edema/infiltration** - minimal (barely palpable) **Follicular involvement:** *follicular plugging / follicular hyperkeratosis – minimal and diffuse* **Secondary Change:** no vesicles, erosion, crusting
2- Mild	**Erythema** – pink/mild **Scale** – thin, patchy **Edema/infiltration** – mild, palpable, barely visible **Follicular involvement:** *follicular plugging / follicular hyperkeratosis* (recent) in one quadrant of scalp **Secondary Change:** mild superficial erosion, crusting present; no vesicles
3- Moderate	**Erythema** - red erythema **Scale** – thick, patchy **Edema/infiltration** – moderately raised, palpable, visible **Follicular involvement:** *follicular plugging / follicular hyperkeratosis* in more than one quadrant of scalp **Secondary Change:** moderate, superficial erosion, crusting; no vesicles
4- Severe	**Erythema** – violaceous/bright red erythema **Scale** – thick, confluent **Edema/infiltration** – thick, raised, easily palpable, easily visible **Follicular involvement:** *follicular plugging / hyperkeratosis* in more than two quadrants of scalp **Secondary Change:** Marked erosion, crusting and/or vesicular change present

CLA-PGA Version 004, June 15, 2021

Instructions:

Severity is determined by a combination of 3 plaque characteristics (erythema, scale, elevation) based on descriptions of each characteristic. Scalp involvement includes an assessment of peri-follicular keratosis as noted. Scarring alopecia / areas of permanent scarring on the scalp are NOT counted.

Erythema is the PRIMARY characteristic that should influence the rating, with plaque elevation, scaling and other secondary characteristics considered *secondarily.* Telangiectatic change should NOT be considered.

Assessment does NOT require all four characteristics to be present.

Severity of the morphologic features **are AVERAGED over the burden of lesions**.

Other Notes:
Anchored to photographic teaching / investigator education teaching set.