STATISTICAL ANALYSIS PLAN

Protocol title:	**A randomized, double-blind, placebo controlled, proof of concept study assessing the efficacy and safety of the RIPK1-inhibitor SAR443122 in patients with moderate to severe subacute or discoid/chronic cutaneous lupus erythematosus**
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Compound number (INN/Trademark):	**SAR443122**
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VERSION HISTORY

This statistical analysis plan (SAP) for study ACT16404 is based on the Amended Clinical Trial protocol 02 dated 22-Nov-2022. This section summarizes the major changes to the statistical analysis features in the SAP.

The first participant was randomized on 16-Jun-2021. Version 1.0 of this SAP is approved before code release for the interim analysis is performed.

Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	Current	Changed analysis method for binary secondary endpoints from logistic regression to Cochran-Mantel-Haenszel (CMH)	To accommodate anticipated participant distribution across stratums

1 INTRODUCTION

1.1 STUDY DESIGN

This study is a Phase 2a multinational, multi-center, randomized, double-blind parallel group 12-week treatment study to evaluate efficacy and safety of the RIPK1-inhibitor SAR443122 dosed at 300 mg twice a day (BID) compared to matching placebo in patients with moderate to severe subacute cutaneous lupus erythematosus (SCLE) or discoid lupus erythematosus (DLE).

Participants are randomized to receive SAR443122 or placebo in a 1:1 ratio. The randomization is stratified by subtype of CLE (DLE or SCLE), baseline use of chloroquine or hydroxychloroquine (yes/no) and by region (Asia Pacific, Eurasia, Europe, Latin America, North America).

Up to 88 participants are expected to be randomly assigned to the investigational medicinal product (IMP), expecting a total of approximately 80 evaluable participants with approximately 40 evaluable participants per study intervention group.

1.2 OBJECTIVE AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• Assess the efficacy of SAR443122 in CLE	• Percent change from baseline in Cutaneous Erythematosus Disease Area and Severity Index activity (CLASI-A) sub-score at Week 12
Secondary	
• Assess the effect of SAR443122 on the physician's global assessment of disease activity (PhysGA – disease activity)	• Proportion of patients with PhysGA – disease activity of 0 or 1 (disease free or almost disease free) at Week 12
• Assess the effect of SAR443122 on CLE induced itch and overall pain	• Change from baseline in patients reported daily worst itch using Peak Pruritus Numerical Rating Scale (itch-NRS) at Week 12 • Change from baseline in patients reported daily worst pain using Peak Pain Numerical Rating Scale (Pain-NRS) at Week 12
• Assess the effect of SAR443122 on the proportion of disease activity responders compared to placebo	• Proportion of CLASI-A50 and CLASI-A75 responders at Week 12
• Assess the effect of SAR443122 on the CLASI components' score	• Change from baseline in CLASI components' score over time
• Assess the effect of SAR443122 on the Investigator's global assessment for CLE (IGA-CLE)	• Proportion of patients with IGA-CLE score of 0 or 1 (clear or almost clear) at Week 12

Objectives	Endpoints
• Assess oral cavities for patients with oral lesions	• Change from baseline to Week 12 in the Oral Health Impact Profile (OHIP-14) for patients with oral lesions at baseline
• Assess the disease specific quality of life (QoL)	• Change from baseline in SKINDEX-29+3 total score at Week 12
• Assess the safety and tolerability of SAR443122 in patients with CLE	• Total number and percent of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs) • Percent of potentially clinically significant abnormalities (PCSAs) in laboratory tests, electrocardiogram (ECG) or vital signs through end of study (EOS)
• Assess the pharmacokinetics (PK) exposure of SAR443122 in patients with CLE	• Sar443122 plasma concentration • Pharmacokinetic parameters (maximum concentration [C_{max}], time to C_{max} [t_{max}], area under the curve over the dosing interval [$AUC_{0\text{-}tau}$], and elimination half-life [$t_{1/2z}$])
Exploratory	
• Assess the effect of SAR443122 on physicians' and patients' overall impression of change of the disease activity and of the severity, and specific domains of health related QoL	• Change from baseline at Week 12 in each of the sub-scores of the SKINDEX-29+3 • Change from baseline at Week 12 in the patient's global impression of disease severity (PGIS) • Evaluation of patient's global impression of change (PGIC) in overall disease at Week 12 • Evaluation of physician's global assessment of change in disease activity (PhysGAC disease activity) at Week 12
• Assess the effect of SAR443122 on CLE related joint inflammation	• Change from baseline in active joint count assessment (28 joint assessment) at Week 12
• Assess the effect of SAR443122 on reducing systemic lupus erythematosus activity	• Change from baseline in Safety of Estrogens in Lupus Erythematosus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) over time
• Assess the effect of SAR443122 on RNA expression levels from skin biopsy and from blood as an indicator of response/disease progression	• Change from baseline in transcriptomic biomarkers from mRNA derived from skin biopsy and from blood
• Assess the effect of SAR443122 on biomarkers in blood plasma (eg, cytokine and chemokine levels) as an indicator of response/disease progression	• Change from baseline of blood plasma biomarkers (eg, cytokine and chemokine levels) over time
• Assess target engagement of SAR443122 as a function of RIPK1 kinase activity/inhibition achieved by SAR443122 in peripheral blood mononuclear cells (PBMCs) of patients with CLE in a subset of qualified sites	• Demonstrate inhibition of pS-166-RIPK1 in PBMC lysates with SAR443122 treatment compared to placebo in a subset of patients at Week 12

Objectives	Endpoints
• Assess the genital area for female participants with genital lesions	• Change from baseline to Week 12 in Genital Erosive Lichen Planus (GELP) total score for female patients with genital lesions at baseline
• Assess the effect of SAR443122 on skin lesion by photographic assessment of index lesions, oral lesions if present	• Photographic assessment of index lesions (Central imaging acquisition tool), oral lesions if present
• Exploration of histologic changes in skin biopsies	• Histologic changes in skin biopsies (Central pathologist)
• Assess the effect of SAR443122 on the use of rescue medication	• The frequency of use of rescue medications by category (eg, topical corticosteroids, topical calcineurin inhibitors, oral corticosteroids)

2 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 2 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Randomized	All screened participants who are randomly assigned to the IMP (by IRT) regardless of whether the intervention was received or not.
ITT	Same definition as above.
Efficacy	All randomized participants exposed to the IMP, with available Baseline assessment of the CLASI-A who did actually receive at least 1 complete dose of IMP and with at least 1 post IMP administration measurement. Participants will be analyzed according to the intervention they actually received.
Pharmacodynamic (PD)	All randomized and treated participants with at least one post-baseline value of the PD endpoint analyzed*. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic (PK)	All randomized and treated participants without any important deviation related to IMP administration, for whom the PK data are considered interpretable. Participants having received only placebo will not be part of the PK population.
PK/PD	All participants being included in both the PK and the PD populations will be included in the PK/PD population. In addition, participants being included in the PD population and having received only placebo will be part of the PK/PD population.
Safety	All randomized participants exposed to the IMP (regardless of the amount of treatment administered) are included in the safety population. Participants will be analyzed according to the intervention they actually received.
Population without trial impact (disruption) due to COVID-19	Any participant: • without any critical or major deviation related to COVID19 • and who didn't permanently discontinue treatment due to COVID19 • and who didn't permanently discontinue study due to COVID19.

CLASI-A: Cutaneous Lupus Erythematosus Disease Area and Severity Index - A, ICF: informed consent form, IMP: investigational medicinal product, PK: pharmacokinetic, PD: pharmacodynamic
Note: "Screened" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process.
*PD endpoints include exploratory biomarkers

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

For any participant randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be reported separately.

For participants receiving more than one study intervention during the study, the intervention group for as-treated analyses will be the intervention group of the study intervention received the most (based on the amount of study intervention administered). In case of equality, the SAR443122 intervention group will be used. The intervention group for as-randomized analyses will be the as-randomized intervention group.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

In general, unless otherwise specified, continuous data will be summarized using the number of observations available, mean, Standard Deviation (SD), median, Q1, Q3, minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants, as appropriate.

The baseline value of efficacy parameters is defined as the Day 1 assessment value except for e-Diary data (Peak Pruritus NRS and Peak Pain NRS) or otherwise specified. If not available, the last available Screening assessment value will be used. Day 1 is defined as the day of first IMP. For participants randomized and not exposed to IMP, Day 1 is defined as the day of randomization.

The baseline for weekly average Peak Pruritus NRS and Peak Pain NRS is defined as the average of daily non-missing scores obtained during the week prior to first IMP intake (Day 1).

The baseline value of the other parameters is defined as the last available value prior to the first dose of investigational medicinal product (IMP) if the participant is treated, or the last available value up to randomization if the participant is not exposed to IMP.

Unless otherwise specified, analyses will be performed by intervention group (and overall, for baseline and demographics characteristics).

Participants whose stratification data are entered incorrectly within the IRT system (eg, participant randomized in stratum “baseline use of chloroquine or hydroxychloroquine = no” instead of “baseline use of chloroquine or hydroxychloroquine = yes”) will nonetheless be considered as randomized and analyzed using the correct stratum values for all analyses.

Given the potentially low number of participants per stratum, the following modifications may be conducted for all analyses:

- Disease subtype stratification factor may be removed from the analysis model;
- The following combination of geographical regions and countries may be performed: Europe + North America + Australia versus Latin America + Eurasia + India.

Observation period

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the time between informed consent signature and first Investigational Medicinal Product (IMP) administration.
- The **Treatment-Emergent (TE) period** is defined as the period from the first IMP administration up to the End-Of-Study (EOS) visit (included). It may be split further into the following periods:

- **On-treatment period**, defined as the time from the first IMP administration to the last administration of the IMP + 5 days (last day included).
- **Residual treatment period**, defined as the time after end of the on-treatment period to the EOS visit (EOS included).

- The **post-treatment period** is defined as the time starting after the TE period.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

3.2.1 Definition of endpoint

The primary endpoint is the percent change from baseline in Cutaneous Erythematosus Disease Area and Severity Index activity (CLASI-A) sub-score at Week 12.

The CLASI (see Section 5.7) is a clinician rated scale designed to assess the disease activity and damage in CLE in adults. It is composed of 56 items covering two dimensions: the disease activity (CLASI-A) and the disease damage (CLASI-D). The domains covered by the two as follows:

- CLASI-A disease activity
  - Erythema
  - Scale/Hypertrophy
  - Recent hair loss/Alopecia (clinically not obviously scarred)
  - Mucous membrane lesions
- CLASI-D disease damage
  - Dyspigmentation
  - Scarring/Atrophy/Panniculitis
  - Clinically judged scarring of the scalp (including scarring alopecia)

Each of the two domains can be scored individually, with a higher score indicating a more severe skin disease. CLASI-A sub-score ranges from 0 to 70, with the following cut-offs: 0-9 indicating mild disease, 10-20 indicating moderate disease, and 21-70 indicating severe disease. Damage is scored on a scale of 0-56, using the parameters of dyspigmentation and scarring, with higher scores indicating worse disease damage. Scores are given for different anatomical locations and are based on the worst area involved.

Besides mucocutaneous ulcerations and hair loss, active inflammatory skin pathology scored in the CLASI-A includes erythema and scale/hypertrophy in 13 distinct body areas (scalp, ears, nose and malar area, rest of face, V-area neck (frontal), post neck and shoulders, chest, abdomen, back and buttocks, arms, hands, legs, feet), mucous membrane lesions and alopecia due to active lupus. The CLASI-A is the sum of the above item scores.

The CLASI-D considers dyspigmentation, skin scarring and/or panniculitis of the aforementioned 13 body areas.

The CLASI is assessed at Screening, Day 1, Week 4, Week 8, Week 12 (EOT) and Week 16 (EOS) visits.

Missing item(s) will lead to missing domain(s) and total score(s).

3.2.2 Main analytical approach

The primary analysis of the percent change from baseline in CLASI-A at Week 12 will be performed on the Efficacy population through a mixed model with repeated measurements (MMRM) over time within participant. All post-baseline available data of planned visits until Week 12 (EOT) will be taken into account.

The model will include fixed effects for disease subtype (DLE, SCLE), baseline use of chloroquine or hydroxychloroquine (Yes, No), geographical region (Asia Pacific, Eurasia, Europe, Latin America, North America), post-baseline visit, study intervention group, baseline CLASI-A, visit by study intervention group interaction, and visit-by-baseline CLASI-A interaction.

This model will be run assuming an unstructured covariance pattern. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Kenward-Roger adjustment.

Point estimate and two-sided 90% confidence interval (CI) for the difference of mean percent change between the 2 groups (SAR443122 versus placebo) at Week 12 will be derived from the linear model framework.

If MMRM model fails to achieve convergence due to complexity of model specification, other covariance structures may be tested by order of decreasing complexity (eg, heterogeneous Toeplitz (TOEPH), antedependence (ANTE(1)), heterogeneous autoregressive ((ARH(1)), Toeplitz (TOEP), autoregressive (AR(1)), compound symmetry (CS) or variance components (VC)); some fixed effect (eg, visit-by-baseline CLASI-A interaction) might also be removed from the model.

If model assumptions appear not to be met, alternative statistical methods may be applied, eg, robust ANCOVA may be conducted instead.

The following “intercurrent event” strategy will be followed:

- Taking selected prohibited/rescue medication (see Table 3) prior to Week 12: data after event occurrence will be set to missing. Data after event occurrence will be set to missing for descriptive statistics.
- Discontinuation of study treatment prior to Week 12 for any other reason: Off-study treatment data up to Week 12 will be included in the analysis.

Table 3 - Prohibited medications/rescue medications that impact efficacy

Medication	Comment	Data to be set as missing after taking medication in the main statistical analysis[a]
Topical corticosteroids and/or topical calcineurin inhibitors initiated after Day 1	No IMP discontinuation	Yes (Ticked 'RESCUE THERAPY' in CRF page)
One short course of oral corticosteroids of up to 10 days initiated after Day 1	No IMP discontinuation	Yes (Ticked 'RESCUE THERAPY' in CRF page)
Initiation or increase the dose of chloroquine or hydroxychloroquine or any other anti-malarial used for CLE treatment after Day 1	No IMP discontinuation	Yes (Ticked 'RESCUE THERAPY' in CRF page)
Topical immunosuppressants beyond a stable regimen of low to medium potency topical corticosteroids and/or topical calcineurin inhibitors initiated after Day 1	IMP to be discontinued	Yes (Identified during blinded review of deviations)
Discontinuation or decrease the dose of chloroquine or hydroxychloroquine after Day 1	No IMP discontinuation	Yes (Identified during blinded review of deviations)
Systemic treatments for cutaneous or systemic lupus erythematosus or immunosuppressive therapy for autoimmune disease (eg, cyclosporin, dapsone, methotrexate, mycophenolate mofetil, thalidomide, azathioprine, systemic retinoids, belimumab, anti-TNF mAbs, B and/or T cell targeted immunosuppressive therapies) initiated after Day 1	IMP to be discontinued	Yes (Identified during blinded review of deviations)
Systemic corticosteroids for more than 10 days initiated after Day 1	IMP to be discontinued	Yes (Identified during blinded review of deviations)
Intralesional and intra-articular corticosteroids initiated after Day 1	IMP to be discontinued	Yes (Identified during blinded review of deviations)

a When yes, data to be set as missing after taking medication. When no, data is not set to missing.

Blinded review of prohibited/rescue treatment (medication or procedure) based on Table 3 will be implemented before database lock by considering the type of medication or procedure, indication, dose, timing and frequency.

In addition, no imputation of missing endpoint data will be done as they will be handled directly in the mixed model with repeated measurements assuming they are missing at random (MAR).

The reason for non-available primary endpoint might be provided in a table (including premature study discontinuation, premature EOT visit, taking selected prohibited/rescue medication [see Table 3] prior to Week 12).

3.2.3 Sensitivity analysis

No sensitivity analysis will be performed. However, supplementary analyses will be performed as described in the section below.

3.2.4 Supplementary analyses

The following supplementary analyses will be performed:

Intent-to-treat analysis (including all data after taking the prohibited and/or rescue medications)

The data collected after taking selected prohibited/rescue medications will be included in this supplementary analysis to evaluate the robustness of the primary analysis results with respect to the method of handling data while taking the prohibited/rescue medications. This analysis will be performed on the ITT population where the participants will be analyzed according to the intervention they were allocated to. All post-baseline available data of planned visits until Week 12 (EOT) will be included into the analysis. Participants with missing CLASI-A at baseline will not be included in the analysis.

Hybrid method analysis (the worst-observation carried forward (WOCF) and last-observation carried forward (LOCF))

The percent change from baseline in CLASI-A at Week 12 will be analyzed on the Efficacy population using an analysis of covariance (ANCOVA) model with disease subtype, baseline use of chloroquine or hydroxychloroquine, geographical region, study intervention group and baseline CLASI-A as fixed effects.

A hybrid method will be used to handle data while taking the prohibited/rescue medications and missing data:

- Data after event occurrence will be set to missing and imputed using the WOCF approach: the participant's worst postbaseline value on or before the time of the event will be used to impute missing endpoint value (for participants whose postbaseline values are all missing, the participant's baseline will be used to impute the missing endpoint value).
- Missing endpoint data will be imputed using the LOCF approach.

Point estimate and two-sided 90% confidence interval for the mean differences between the 2 groups (SAR443122 versus placebo) at Week 12 will be provided.

Additional covariates (smoking status at baseline and average postbaseline sun exposure without sun protection)

A supplementary analysis of the percent change from baseline in CLASI-A at Week 12 will be explored by introducing smoking status at baseline (yes, no) and average postbaseline sun exposure without sun protection (in hours) as fixed effects to the analysis model defined above.

The average postbaseline sun exposure without sun protection will be calculated based on the non-missing values up to Week 12. For participants whose postbaseline values are all missing, the participant's baseline will be used to impute the missing value. Participants whose postbaseline and baseline values are all missing will be excluded from the analysis.

Point estimate and two-sided 90% confidence interval for the mean differences between the 2 groups (SAR443122 versus placebo) at Week 12 will be provided.

Tipping point analysis

In addition to the supplementary analyses planned above, a tipping point analysis based on multiple imputation (MI) method might be explored on the Efficacy population to evaluate the robustness of the results from the primary analysis to deviations from the MAR assumption.

The steps to perform the tipping point analysis will be as follows:

1. Data collected after taking selected prohibited/rescue medications will be set to missing while off-study treatment data up to Week 12 will be included in the analysis;
2. Missing data will be imputed using MI under the MAR assumption. The imputation number will be 1000;
3. All imputed Week 12 percent change from baseline in CLASI-A in the SAR443122 intervention group will be artificially penalized by adding a penalty term in each complete dataset;
4. The percent change from baseline in CLASI-A at Week 12 will be analyzed using an analysis of covariance (ANCOVA) model with disease subtype, baseline use of chloroquine or hydroxychloroquine, geographical region, study intervention group and baseline CLASI-A as fixed effects in each complete dataset;
5. Results will be combined across complete datasets using Rubin's rule;
6. Steps 3 to 5 will be repeated with penalty increased as needed to evaluate the impact on decision making.

See Section 5.5 for the sample SAS code for the imputation and the analysis.

Other analyses

Point estimate and two-sided 90% confidence interval (CI) for the difference of mean percent change between the 2 groups (SAR443122 versus placebo) at Week 4 and Week 8 will be derived from the MMRM model as presented for the primary analysis and intent-to-treat supplementary analysis.

Time profile plots of point estimates of the mean percent change from baseline in CLASI-A (+/- SE) will be presented by study intervention group and visit, and for the difference between the 2 groups (SAR443122 versus placebo) (with 90% CI).

The cumulative distribution function of the percent change from baseline in CLASI-A will be plotted by study intervention group at Week 12.

Descriptive statistics of raw data, change and percent change from baseline will be provided by visit and study intervention group. Additional descriptive statistics could be provided by stratum and combination of stratum if applicable. A listing of data observed after taking selected prohibited/rescue medication (see Table 3) will be provided as well.

In addition, mean raw data, change and percent change from baseline in CLASI-A with the corresponding standard error will be plotted over time by study intervention group. Spaghetti plots may be provided as well to visualize the behaviors of the participants.

3.3 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints analyses described in this section will be performed on the Efficacy population.

3.3.1 Definition of endpoints

The secondary endpoints are as follows:

- The proportion of patients with PhysGA disease activity of 0 or 1 (disease free or almost disease free) at Week 12

The Physician's Global Assessment of disease activity (PhysGA- disease activity) is a 5 point-Likert scale instrument designed to assess physician-reported disease activity ranging from 0 ("Not active at all") to 4 ("Extremely active").

The PhysGA disease activity is assessed at Screening, Day 1, Week 4, Week 8, Week 12 (EOT) and Week 16 (EOS) visits.

- The change from baseline in patients reported daily worst itch using itch-NRS at Week 12
- The change from baseline in patients reported daily worst pain using pain-NRS at Week 12

The Peak Pruritus NRS is a single item PRO tool that patients will use to report the maximal intensity of their pruritus (itch) daily, using a 24-hour recall period. Patients will be asked to rate their worst itch on a 0 ("No itch") to 10 ("Worst itch imaginable") NRS.

The Peak Pain NRS is a single item PRO tool that patients will use to report the maximal intensity of their CLE-related pain (skin, oral, genital) during a daily 24-hour recall period. Patients will be asked to rate their worst pain on a 0 ("No pain") to 10 ("Worst pain imaginable") NRS.

Patients will complete the Peak Pruritus NRS and Peak Pain NRS daily up to Week 12 (EOT) visit.

The weekly average Peak Pruritus NRS and Peak Pain NRS scores at each postbaseline visit will be used for analyses. It will be defined as the average of daily non-missing scores within the week preceding the given visit.

In case a patient does not attend a visit, the theoretical visit date will be used for derivation.

- The proportion of CLASI-A50 and CLASI-A75 responders at Week 12

The CLASI-A50/75 response is defined as a patient achieved a decrease by at least 50%/75% of CLASI-A sub-score from baseline.

- The change from baseline in CLASI components' score over time

See Section 3.2.1 for a description of the CLASI.

CLASI component's scores used for analysis will be CLASI-A, CLASI-D and CLASI subcomponent's scores (eg, Erythema, Scale/Hypertrophy, Scarring/Atrophy/Panniculitis scores).

- The proportion of patients with IGA-CLE score of 0 or 1 (clear or almost clear) at Week 12

Investigator's Global Assessment for Cutaneous Lupus Erythematosus (IGA-CLE) is a ClinRO that allows for clinicians to assess the overall disease activity of CLE using a 5-point scale: 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), and 4 (severe). The Severity of CLE is determined by descriptions of a combination of 3 plaque characteristics: erythema, scale, elevation. Erythema is the primary characteristic that should influence the rating, with other characteristics considered secondarily. Telangiectatic change should not be considered in the rating. The assessment does not require the presence of all four characteristics, the severity is averaged over the observed characteristics.

The IGA-CLE ClinRO was added in this study following FDA's demand. Since the implementation of this specifically developed ClinRO on sites happened after study start, some participants had already performed their Week 12 visit beforehand. As a result, participants with missing data resulting from the implementation, at their respective site, of the IGA-CLE ClinRO after their Week 12 visit will not be included into the analysis of this endpoint.

The IGA-CLE is assessed at Screening, Day 1, Week 4, Week 8, Week 12 (EOT) and Week 16 (EOS) visits.

- The change from baseline to Week 12 in the Oral Health Impact Profile (OHIP-14) for patients with oral lesions at baseline

The OHIP-14 is a PRO questionnaire that measures people's perception of dysfunction, discomfort and disability attributed to oral conditions in adults. It is composed of 14 items that assess seven different dimensions, considering the perception of the individual in relation to the impact of oral conditions in the physical, psychological and social well-being in the last month. Each of the 14 items has a set of possible answers distributed in a Likert scale (0 = never, 1 = hardly ever. 2 = occasionally 3 = fairly often, 4 = very often), which represents the frequency that the individual perceives the impact of oral health on seven dimensions: functional limitation (2 items), physical pain (2 items), psychological discomfort (2 items), physical disability (2 items), psychological disability (2 items), social disability (2 items) and handicap (2 items). The OHIP-14 scores can range from 0 to 56 and are calculated by summing the ordinal values for the 14 items. The domain scores can range from 0 to 8. Higher OHIP-14 scores indicate worse oral-health-related quality of life.

Item(s) answered "Don't know" will be considered as missing. Missing item(s) will lead to missing domain(s) and total score.

The OHIP-14 is assessed at Day 1 and Week 12 (EOT) visits.

- The change from baseline in SKINDEX-29+3 total score at Week 12

SKINDEX-29 is a PRO measure designed to assess the effects of skin disease on patients' health-related quality of life in adults. It is a generic instrument for skin and connective tissue diseases. It contains 29 items, distributed across the following domains: emotions (10 items: 3; 6; 9; 12; 13; 15; 21; 23; 26; 28), symptoms (7 items: 1; 7; 10; 16; 19; 24; 27), functioning (12 items: 2; 4; 5; 8; 11; 14; 17; 20; 22; 25; 29; 30); and one item about treatment that is not part of the total score (Item 18). Recall period is "during the past week". Each item is rated on a 5-point Likert scale (never, rarely, sometimes, often, all the time). Individual items are scored from 0 to 100 in 25-point increments with 100 representing maximal disability. The Skindex 29+3 (also called SkindexLupus) includes a fourth subscale (3 items: 31-33) to assess lupus-specific issues, ie, photosensitivity (Items 31; 33) and alopecia (Item 32). Domain scores are the average of items in a given domain. The total score (0 to 100, with a higher score indicating a worse quality of life) is defined as the average of all items.

More than 25% of items missing in a given domain (resp. overall) will lead to missing domain score (resp. total score). Any participant for whom emotions, symptoms and functioning domains score are missing will lead to exclusion of the participant from the analysis.

The SKINDEX-29+3 is assessed at Day 1 and Week 12 (EOT) visits.

3.3.2 Main analytical approach

Secondary efficacy endpoints that measure binary responses

Each binary endpoint (PhysGA-disease activity, IGA-CLE, CLASI-A50 and CLASI-A75) will be analyzed using a Cochran-Mantel-Haenszel (CMH) method stratified by disease subtype (DLE, SCLE), baseline use of chloroquine or hydroxychloroquine (Yes, No) and geographical region (Asia Pacific, Eurasia, Europe, Latin America, North America).

Point estimate and two-sided 90% confidence interval for the treatment difference (SAR443122 versus placebo) in proportion at Week 12 will be provided based on the weighted average of treatment differences from each strata using CMH weights as described below.

Let $\hat{p}_{0i}$ and $\hat{p}_{1i}$ denote the proportions of responders in the SAR44322 and placebo intervention groups from strata *i*, and n_{0i} and n_{1i} be the sample sizes in the SAR44322 and placebo intervention groups from strata *i*. Then the weighted average of treatment differences between SAR44322 and placebo will be estimated as $\hat{Y} = \Sigma w_i \hat{Y}_i$, where $\hat{Y}_i = \hat{p}_{1i} - \hat{p}_{0i}$ and $w_i = (1/n_{0i} + 1/n_{1i})^{-1} / (\Sigma((1/n_{0i} + 1/n_{1i})^{-1})) = [n_{0i}n_{1i}/(n_{0i} + n_{1i})] / [\Sigma(n_{0i}n_{1i}/(n_{0i} + n_{1i}))]$ is CMH weight for strata *i*. The associated two-sided 90% CI for the difference can be calculated as $(\hat{Y} - 1.645 * SE(\hat{Y}), \hat{Y} + 1.645 * SE(\hat{Y}))$, where $SE(\hat{Y}) = [\Sigma w_i^2 \text{ var}(\hat{Y}_i)]^{1/2}$, and

$$\text{var}(\hat{Y}_i) = \frac{\hat{p}_{0i}(1-\hat{p}_{0i})}{n_{0i}} + \frac{\hat{p}_{1i}(1-\hat{p}_{1i})}{n_{1i}} .$$

In case of no event in a cell for a strata, continuity correction will be made (ie, 0.5 will be added to each cell of the 2x2 table) for that strata for variance calculation only. No continuity adjustment will be applied for estimating the weighted average of treatment difference. The continuity correction will be applied to estimate variance for constructing 90% CI for the overall difference.

The proportion of responders in each study intervention group will be provided as well.

Participants who took prohibited/rescue medication (see Table 3) prior to Week 12 will be considered as non-responders.

Participants with missing binary endpoint data at Week 12 will be considered as non-responders.

Descriptive statistics

The observed proportion of CLASI-A50 and CLASI-A75 responders will be summarized descriptively by visit and study intervention group.

In, addition, PhysGA-disease activity and IGA-CLE scores will be summarized as ordinal variables by visit and study intervention group. Bar charts showing the distribution of severity categories will be provided as well by visit and study intervention group. If needed, a missing category will be included.

Data after taking selected prohibited/rescue medications (see Table 3) will be set to missing for descriptive statistics.

Secondary efficacy endpoints that measure continuous or ordinal responses

Secondary efficacy endpoints that measure continuous or ordinal responses (Peak Pruritus NRS, Peak Pain NRS, CLASI-A, SKINDEX-29+3) other than CLASI-D, CLASI subcomponent's scores and OHIP-14 will be analyzed using an analysis of covariance (ANCOVA) model with disease subtype (DLE, SCLE), baseline use of chloroquine or hydroxychloroquine (Yes, No), geographical region (Asia Pacific, Eurasia, Europe, Latin America, North America), study intervention group and relevant baseline endpoint measurement as fixed effects.

Point estimate and two-sided 90% confidence interval for the mean differences between the 2 groups (SAR443122 versus placebo) at Week 12 will be provided.

Endpoint data after taking prohibited/rescue medication (see Table 3) prior to Week 12 will be set to missing and imputed using the worst-observation carried forward (WOCF) approach as described in Section 3.2.4.

Missing endpoint data at Week 12 will be imputed using the LOCF approach.

Specifically for Peak Pruritus NRS and Peak Pain NRS, a multiple imputation (MI) approach may be used in addition to impute missing endpoint data (including missing data at baseline).

Descriptive statistics

As appropriate, descriptive statistics of raw data and change from baseline will be provided by visit and study intervention group.

In addition, mean raw data and change from baseline with the corresponding standard error will be plotted over time by study intervention group for weekly-averages Peak Pruritus NRS and Peak Pain NRS.

For CLASI-D and CLASI subcomponent's scores, only descriptive statistics of raw data and change from baseline may be provided by visit and study intervention group.

For OHIP-14, only descriptive statistics of raw data and change from baseline will be provided on the total score by visit and study intervention group.

Data after taking selected prohibited/rescue medications (see Table 3) will be set to missing for descriptive statistics.

Other secondary endpoints analyses are defined in Section 3.6.2 (AE, SAE, AESI), Section 3.6.3.1 (laboratory, vital signs and ECG abnormalities) and Section 3.7.1.1 (PK).

3.4 EXPLORATORY ENDPOINT(S) ANALYSIS

3.4.1 Definition of endpoints

The exploratory endpoints are as follows:

- Change from baseline at Week 12 in each of the sub-scores of the SKINDEX-29+3

See Section 3.3.1 for a description of the SKINDEX-29+3. Each of the four sub-scores of the SKINDEX-29+3 (emotion, symptoms, functioning, lupus specific) will be used for descriptive analysis.

- Change from baseline at Week 12 in the patient's global impression of disease severity (PGIS)

The PGIS is a 4-Point Likert scale instrument designed to assess patient's evaluation of the severity of their disease over the past week ranging from "None" to "Severe".

The PGIS is assessed at Day 1 and Week 12 visits.

- Evaluation of patient's global impression of change (PGIC) in overall disease at Week 12

The PGIC is a 7-Point Likert scale instrument designed to assess patient's-reported evaluation of change in their disease overall in regard to start of study medication. The scale is ranging from "Very much better" to "Very much worse".

The PGIC is assessed at Week 12 visit.

- Evaluation of physician's global assessment of change in disease activity (PhysGAC disease activity) at Week 12

See Section 3.3.1 for a description of the PhysGA - disease activity.

The Physician's Global Assessment of Change in disease activity is a 7-Point Likert scale instrument designed to assess physician-reported evaluation of change in patient's cutaneous lupus erythematosus activity overall in regards of start of treatment. The scale is ranged from "Very much improved" to "Very much worse".

The PhysGAC disease activity is assessed at Week 12 visit.

- Change from baseline in active joint count assessment (28 joint assessment) at Week 12

Twenty-eight-joint assessment is used to assess CLE related joint inflammation by counting the number of active swollen and tender joints. An active joint is defined as joint with swelling within joint not due to deformity and/or joint with tenderness.

The 28 joint assessment is done at Day 1, Week 4, Week 8, Week 12 and Week 16 visits.

- Change from baseline in Safety of Estrogens in Lupus Erythematosus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) over time

The SELENA-SLEDAI (see Section 5.8) has been developed to measure the disease activity in patients with SLE for use in clinical trials. It has been developed to determine global improvement and performed in effective and reliable manners in studies. This is a weighted index in which signs and symptoms, laboratory tests for each of the nine organ systems are given a weighted score and summed up if present at the time of the visit or in the preceding 10 days. The maximum theoretical score for the SELENA-SLEDAI is 105 (all 24 descriptors present simultaneously) with 0 indicating inactive disease.

The SELENA-SLEDAI is assessed at Day 1 and Week 12 visits.

Missing item(s) will lead to missing total score.

- Change from baseline to Week 12 in Genital Erosive Lichen Planus (GELP) total score for female patients with genital lesions at baseline

Genital Erosive Lichen Planus score (see Section 5.9) is a scoring system for clinical assessment of GELP in women. The GELP scoring system is based on a simple grading (0-3) of area of involvement, degree of erythema, number of erosions, number of striae and patient-reported pain induced by pressuring the involved area with a cotton swab. Area of genital involvement, erythema, striae, number of erosions and pain are registered and scored 0-3 (0 is none) for each parameter. Vulval and vaginal involvement is assessed separately, resulting in a maximum GELP score of 30, with higher score indicating a higher symptom severity.

The GELP is assessed at Day 1 and Week 12 visits.

Missing item(s) will lead to missing total score.

- Photographic assessment of index lesions (Central imaging acquisition tool), oral lesions if present

As a minimum the body site(s) and lesion features assessed by Investigator of photographed skin lesion will be recorded. The Photographic assessment of index lesions is done at Baseline and Week 12 visits.

- The frequency of use of rescue medications by category (eg, topical corticosteroids, topical calcineurin inhibitors, oral corticosteroids)

Rescue medications will be assigned to the following categories ("topical corticosteroids", "topical calcineurin inhibitors", "oral corticosteroids", "anti-malarial"," immunosuppressants") according to the algorithm presented in Section 5.6.

3.4.2 Main analytical approach

Exploratory efficacy endpoints (28 joint assessment, SELENA-SLEDAI) will be analyzed on the Efficacy population using the same methodology as secondary efficacy for similar data (continuous or ordinal) except the endpoints below:

- Change from baseline at Week 12 in each of the sub-scores of the SKINDEX-29+3

Descriptive statistics of raw data and change from baseline will be provided for each sub-score by visit and study intervention group. Data after taking selected prohibited/rescue medications (see Table 3) will be set to missing for descriptive statistics.

- Change from baseline at Week 12 in the patient's global impression of disease severity (PGIS)

PGIS will be summarized as an ordinal variable by visit and study intervention group. Data after taking selected prohibited/rescue medications (see Table 3) will be set to missing for descriptive statistics.

- Evaluation of patient's global impression of change (PGIC) in overall disease at Week 12

PGIC will be summarized as an ordinal variable at Week 12 by study intervention group. Data after taking selected prohibited/rescue medications (see Table 3) will be set to missing for descriptive statistics.

- Evaluation of physician's global assessment of change in disease activity (PhysGAC disease activity) at Week 12

PhysGAC disease activity will be summarized as an ordinal variable at Week 12 by study intervention group. Data after taking selected prohibited/rescue medications (see Table 3) will be set to missing for descriptive statistics.

- Change from baseline to Week 12 in Genital Erosive Lichen Planus (GELP) total score for female patients with genital lesions at baseline

Descriptive statistics of raw data and change from baseline will be provided for GELP total score as well as vulval and vaginal involvement scores by visit and study intervention group. Data after taking selected prohibited/rescue medications (see Table 3) will be set to missing for descriptive statistics.

- The frequency of use of rescue medications by category (eg, topical corticosteroids, topical calcineurin inhibitors, oral corticosteroids)

The number (%) of participants experiencing at least one use of rescue medication after D1 and prior to Week 12 (and prior to Week 16 as needed) will be summarized for each category and overall by study intervention group.

In addition, if at least 5 events as mentioned above occur, the time (week) to first rescue medication for those participants will also be analyzed using Kaplan-Meier method and the duration of the rescue medication use may be summarized if applicable.

- Photographic assessment of index lesions (Central imaging acquisition tool), oral lesions if present

Listing of participants with index lesions will be provided. Further descriptive analyses may be explored if applicable.

3.5 MULTIPLICITY ISSUES

No multiplicity adjustment will be performed for this study.

3.6 SAFETY ANALYSES

All safety analyses will be performed on the safety population as defined in Section 2, unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.
- Safety data in participants who do not belong to the safety population (eg, exposed but not randomized) will be provided separately.

3.6.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and summarized within the safety population and within the efficacy population if relevant.

The following listings will be provided:

- Participants receiving IMP from specified batch.
- Randomization scheme (Strata, Block number, Order within the block, Randomization number, Study intervention group, Randomization date and time, Participant identifier, and Comments [if needed]).

Duration of IMP exposure

Duration of IMP exposure is defined as last IMP administration date – first IMP administration date + 1 days, regardless of unplanned intermittent discontinuations. If the date of the last dose of IMP is missing, the duration of IMP will be left as missing.

Duration of IMP exposure will be summarized quantitatively and categorically: <1, 1 to 2, 2 to 4, 4 to 8, 8 to 12, and >12 weeks.

Treatment compliance

A given administration will be considered noncompliant if the participant did not take the planned dose of treatment as required by the protocol until the date of last administration of IMP (ie, 6 capsules in the day). Missing exposure between first recorded on-site dosing date and first recorded e-Diary dosing date, identified during blinded review of the deviations before database lock, will be assumed to be exposure as planned for participants whom e-Diary device was initiated late. No other imputation will be made for participants with missing or incomplete data.

Percentage of treatment compliance for a participant will be defined as the number of days that the participant was compliant divided by the total number of days that the participant was planned to take from the first administration of IMP up to the actual last administration of IMP.

Treatment compliance will be summarized quantitatively and categorically: <80%, <90%, <95% and ≥95%.

Cases of symptomatic overdose (defined as at least 50% more than intended daily dose within one day) will be considered an AESI and will be listed as such.

3.6.2 Adverse events

General common rules for adverse events

All adverse events (AEs) will be coded to a Lower-Level Term (LLT), Preferred Term (PT), High-Level Term (HLT), High-Level Group Term (HLGT), and associated primary System Organ Class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database lock.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- Treatment-Emergent Adverse Events (TEAE)s: AEs that developed, worsened or became serious during the treatment-emergent period
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period

Similarly, the AE leading to deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods if applicable.

The primary focus of AE reporting will be on TEAEs.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. If the severity is missing for an AE, the severity will be left as missing.

The AE tables will be sorted as indicated in Table 4.

Table 4 - Sorting of AE tables

AE presentation	Sorting rules
SOC, HLGT, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs and PTs[a, b]

a Sorting will be based on the SAR443122 intervention group
b The table of all TEAEs presented by SOC, HLGT, HLT and PT will define the presentation order for all other tables (eg, treatment-emergent SAE), unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE
- Any severe TEAE
- Any treatment emergent SAE
- TEAE leading to death, if any
- Any TEAE leading to permanent intervention discontinuation
- Any TEAE leading to permanent study discontinuation
- Any treatment emergent AESI
- Any TEAE considered by the investigator as related to IMP

The AE summaries of Table 5 will be generated with number (%) of participants experiencing at least one event and sorted by the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs and PTs. Sorting will be based on SAR443122 intervention group (see Table 4).

Table 5 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, HLGT, HLT and PT
Common TEAE (≥5% across all groups)	Primary SOC, HLGT, HLT and PT
TEAE related to IMP as per Investigator's judgment	Primary SOC, HLGT, HLT and PT
TEAE by maximal intensity	Primary SOC, HLGT, HLT and PT
Treatment emergent SAE [*optional*]	Primary SOC, HLGT, HLT and PT
Treatment emergent SAE related to IMP as per Investigator's judgment [*optional*]	Primary SOC, HLGT, HLT and PT
TEAE leading to permanent intervention discontinuation [*optional*]	Primary SOC, HLGT, HLT and PT
TEAE leading to death (death as an outcome of the AE as reported by the Investigator in the AE page) [*optional*]	Primary SOC, HLGT, HLT and PT
Treatment emergent COVID19 related AE [*optional*]	Primary SOC, HLGT, HLT and PT

In addition, the all TEAE summary by Primary SOC, HLGT, HLT and PT will be performed by trial impact (disruption) due to COVID-19 and according to baseline use of chloroquine or hydroxychloroquine.

Optional tables mentioned in Table 5 are to be done in case of sufficient number of events. Otherwise only listings will be provided.

Adverse events of special interest

Adverse events of special interest (AESIs) will be selected for analyses as indicated in Table 6.

In case of sufficient number of events, the number (%) of participants experiencing at least one event will be provided for each event of interest. Otherwise only listings will be provided. Tables will be sorted as indicated in Table 4.

Table 6 - Selections for AESIs

AESIs	Selection
Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP	e-CRF specific tick box on the AE page
Symptomatic overdose (serious or non-serious) with IMP	e-CRF specific tick box on the AE page
Increase in ALT	e-CRF specific tick box on the AE page
Anemia	Combined AESIs eCRF tick-box
QTc ≥500 ms	Combined AESIs eCRF tick-box
New Lymphadenopathy	Combined AESIs eCRF tick-box

A listing of all AEs will be provided for participants treated but not considered as randomized, if any.

Adverse events that occur outside of the treatment emergent period will be listed separately.

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following variables will be analyzed. They will be converted into standard international units.

- Hematology:
  - Red blood cells and platelets and coagulation: hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, reticulocyte count, red blood cell count, platelet count
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry:
  - Metabolism: glucose [fasting], total protein, creatine phosphokinase
  - Electrolytes: sodium, potassium, calcium
  - Renal function: creatinine, creatinine clearance, blood urea nitrogen. Creatinine clearance will be derived with the equation of Cockroft and Gault using weight assessed at the same visit as creatinine
  - Liver function: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total and direct bilirubin
- Urinalysis:
  - Urinalysis for quantitative analysis: pH, specific gravity, proteins and glucose
- Vital signs: pulse rate, systolic and diastolic blood pressure according to position (semi-supine), respiratory rate, temperature
- ECG variables: heart rate, PR, QRS, QT, and corrected QTc (according to Fridericia)

Quantitative analyses

For laboratory variables, vital signs and ECG variables above, descriptive statistics for results and changes from baseline as appropriate will be provided for each planned visit, and for the last value during the on-treatment period. These analyses will be performed using central measurements only (when available), for laboratory variables and ECG variables.

For hemoglobin, neutrophils, platelet count, creatinine clearance, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total and direct bilirubin and QTcF, mean changes from baseline with the corresponding standard error will be plotted over time.

Analyses according to PCSA

Potentially Clinically Significant Abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock for patients. For laboratory parameters for which no PCSA criteria are defined, similar analyses will be done using out-of-normal ranges, if applicable.

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables, vital signs and ECG variables above, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

Additional analyses for potential drug-induced liver injury

If any, an intext listing of liver function tests data for participants with potential drug-induced liver injury ("ALT >3 ULN and Total bilirubin >2ULN" or "Direct bilirubin>35% of Total bilirubin and Total bilirubin >1.5 ULN") will be provided.

Additionally, listing of ALT increase documentation (including specific medical history, alcohol habits, associated signs and symptoms, trigger factors…) will also be provided for participants with one or more ALT increases greater than or equal to 2 ULN.

Listing of participants with QTc >480 msec and/or change from baseline QTc >60 msec

If any, an intext listing of participants with QTc >480 msec and/or change from baseline QTc >60 msec will be provided.

3.7 OTHER ANALYSES

3.7.1 Other variables and/or parameters

3.7.1.1 PK analyses

SAR443122 concentrations will be described in the SAR443122 intervention group on the PK population for each planned visit using the following descriptive statistics: mean, geometric mean, median, standard deviation, coefficient of variation, minimum, and maximum. These analyses will be performed by specific subgroups (eg, gender, BMI, age) if appropriate.

All concentration values below the lower limit of quantitation (LLOQ) will be treated as zero in all summary statistics. Geometric mean will not be computed in case at least one concentration is below LLOQ.

3.7.1.2 Biomarkers analyses

The Biomarker endpoints are as follows:

- Change from baseline in transcriptomic biomarkers from mRNA derived from skin biopsy and from blood
- Change from baseline of blood plasma biomarkers (eg, cytokine and chemokine levels) over time
- Demonstrate inhibition of pS166-RIPK1 in PBMC lysates with SAR443122 treatment compared to placebo in a subset of patients at Week 12
- Histologic changes in skin biopsies (Central pathologist)

Biomarker analyses will be described in a specific Biomarker SAP and reported separately.

3.7.1.3 PK/PD analyses

The analysis of PK/PD relationship will be described and reported separately.

3.7.2 Subgroup analyses

Analyses will be performed on the primary endpoint across the following subgroups if relevant (categories with fewer than 5 participants may be combined with other categories) using the same methodology as for the primary endpoint:

- Age group (<65, ≥65 years)
- Gender (Male, Female)
- Geographical region (Asia Pacific, Eurasia, Europe, Latin America, North America).
- Disease subtype (SCLE, DLE)
- Baseline use of chloroquine or hydroxychloroquine (yes, no)
- Baseline CLASI-A (severe, moderate)

The subgroup factor term and the subgroup-by-intervention group, subgroup-by-visit and subgroup-by-intervention group-by-visit interaction terms will be added in the primary model. In the case that the subgroup factor is identical or similar to a randomization strata factor, the strata factor will not be kept in the model.

If needed simpler modelling (eg, ANCOVA) may be considered instead.

In each subgroup, the treatment effects for the primary endpoint will be provided, as well as the corresponding 90% CI, using the same method as applied to the primary analysis. Forest plots will be provided.

3.8 INTERIM ANALYSES

An interim analysis is planned for this study.

The sponsor will make use of this interim analysis to facilitate internal operational decision on the compound development. The interim analysis will be performed when around 75% of the participants have completed study treatment or discontinued the study. The PK and PD relationship could also be explored before final database lock. The cut-off for the interim analysis is once the 65th participant reaches its Week 12 (EOT) visit (09-Jan-2023) or prematurely discontinue study intervention. The interim analysis or PK/PD analysis will not lead to changes in the conduct of the protocol other than stopping recruitment for this proof-of-concept study due to a positive decision based on the interim analysis or due to negative decision, indicating a lack of equipoise for continued recruitment of patients. The statistical analyses efficacy results based on this interim analysis will be considered as the main analyses for the study. As a result, any additional analyses performed in the future with additional patients will be considered as supplementary analyses only.

The interim analysis will evaluate the mean percent change from baseline in CLASI-A at Week 12 and other selected secondary efficacy endpoints on the Efficacy population, as well as the safety endpoints on the Safety population defined below:

Efficacy:

- The proportion of patients with PhysGA disease activity of 0 or 1 (disease free or almost disease free) at Week 12
- The change from baseline in patients reported daily worst itch using Peak Pruritus Numerical Rating Scale (itch-NRS) at Week 12.
- The change from baseline in patients reported daily worst pain using Peak Pain Numerical Rating Scale (pain-NRS) at Week 12.
- The proportion of CLASI-A50 and CLASI-A75 responders at Week 12.
- The proportion of patients with IGA-CLE score of 0 or 1 (clear or almost clear) at Week 12.

Safety:

- Total number and percent of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), and TEAEs leading to permanent study intervention discontinuation through end of study (EOS).
- Percent of potentially clinically significant abnormalities (PCSAs) in laboratory tests, electrocardiogram (ECG) or vital signs through end of study (EOS).

All analysis performed for this interim analysis are described in the Statistical Analysis Plan, but the following additional rules will apply for analyses performed at interim analysis:

- Efficacy and safety analyses will be conducted on all participants who did complete the treatment period or prematurely discontinued the study intervention at cut-off date.

The interim analysis will be performed by a separate statistical team, independent of the study team. The PK/PD analysis will be performed by a sponsor internal modeling and simulation team, also independent of the study team. Only those necessary for conducting the interim analysis, PK/PD analysis and those responsible for internal project planning/overall portfolio planning needs (eg, to aid in the planning of future studies) will have the access to the interim analyses results before study completion. A list of these individuals will be maintained.

All sponsor internal personnel with access to unblinding information will be asked to sign a study confidentiality agreement before having access to unblinding information. Study team and investigational sites will not have access to interim study results and continue to be blinded to individual randomization codes until study completion and database lock. Therefore the interim analysis will not lead to changes in the conduct of the protocol.

Result distribution, code release process and blinding strategy will be described in a pre-defined dissemination plan.

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the protocol amendment(s).

Major statistical changes in protocol amendment(s)

Amendment Number	Approval Date	Changes	Rationale
1	10-Dec-2021	Aligned the names of the analysis populations with current Sponsor's standard	To improve precision and clarity
2	22-Nov-2022	Added an interim analysis	To facilitate internal operational decision on the compound development

4 SAMPLE SIZE DETERMINATION

The sample size was derived with respect to the primary endpoint (percent change from Baseline in CLASI-A sub-score at Week 12) by applying the Quantitative Decision Making approach as described by Quan et al (1). Assuming a standard deviation of 45% and a reducing effect of 28% under active treatment, a sample size of 80 evaluable participants results in an overall probability for a positive decision of more than 50% and a negative decision probability of 20%. Up to 88 participants are expected to be randomly assigned to the IMP, expecting a total of 80 evaluable participants with approximately 40 evaluable participants per group.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AE:	adverse event
AESIs:	adverse events of special interest
ANCOVA:	analysis of covariance
BID:	twice a day
CI:	confidence interval, confidence interval
CLASI:	cutaneous erythematosus disease area and severity index
CLE:	cutaneous lupus erythematosus
ClinRO:	clinician reported outcome
CMH:	Cochran-Mantel-Haenszel
CRF:	case report form
DLE:	discoid lupus erythematosus
EOS:	end of study
EOT:	end of treatment
GELP:	genital erosive lichen planus
HLT:	high level term
ICF:	Informed consent form
IGA-CLE:	investigator's global assessment for cutaneous lupus erythematosus
IMP:	investigational medicinal product
IRT:	interactive response technology
ITT:	intent to treat
LLOQ:	lower limit of quantification
LLT:	lower-level term
LOCF:	last observation carried forward
MAR:	missing at random
MCMC:	Markov Chain Monte Carlo
MedDRA:	medical dictionary for regulatory activities
MI:	multiple imputation
MMRM:	mixed model with repeated measurements
OHIP-14:	oral health impact profile
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic
PGIC:	patient's global impression of change
PGIS:	patient's global impression of disease severity
PhysGA:	physician's global assessment of disease activity
PhysGAC:	physician's global assessment of change in disease activity
PK:	pharmacokinetic
PRO:	patient reported outcome
PT:	preferred term
SAP:	statistical analysis plan
SCLE:	subacute lupus erythematosus

SD: standard deviation
SELENA-SLEDAI: safety of estrogens in lupus erythematosus national assessment
SLE: systemic lupus erythematosus
SOC: system organ class
TE: treatment-emergent
TEAE: treatment-emergent adverse event
ULOQ: upper limit of quantification
WHO-DD: World Health Organization-drug dictionary
WOCF: worst observation carried forward

5.2 APPENDIX 2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in the analysis populations listed in Table 2 will be summarized. All exclusions from any analysis populations will be fully documented in the CSR.

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized. The number (%) of screen failures with inclusion criteria not met and/or exclusion criteria met will be provided in the screened population.

The number (%) of participants in the following categories will be provided:

- Screened participants
- Randomized but not exposed participants
- Randomized and exposed participants
- Participants who completed the study treatment period as per protocol
- Participants who did not complete the study treatment period as per protocol and main reason for permanent intervention discontinuation.
- Participants who completed the study period as per protocol.
- Participants who did not complete the study period as per protocol and main reason for study discontinuation.

Reasons for permanent study intervention and study discontinuation “adverse event” and “other reasons” will be split as related versus not related to COVID-19.

The number (%) of exposed and not randomized participants will also be summarized. In addition, the number (%) of participants screened, screened-failed, randomized, randomized and exposed, with permanent intervention discontinuation and with early study discontinuation will be provided by geographical region, country and site.

Listing of participants with permanent intervention discontinuation or with premature end of study (ie, who did not complete the study period as per protocol) will be provided for the safety population along with the main reason of discontinuations and related to COVID-19 or not, respectively.

Protocol deviations

All critical or major deviations potentially impacting efficacy analyses, randomization, and drug dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group. In addition the summary will be displayed separately as related versus not related to COVID-19, if applicable. They will also be listed in the randomized population. They will be displayed separately as related versus not related to COVID-19.

Emergency situation impact

A summary of visits impacted by COVID-19 pandemic will be provided for the safety population along with the description of the impact (visit not done, visit partially done on site/by phone, visit done but delayed), if applicable.

In addition, a listing of participants excluded from the population without trial impact (disruption) due to COVID-19 will be provided for the safety population along with the main reasons of exclusion.

If any, similar summary of visits and listing of participants impacted by any other emergency situation (eg, war in Ukraine) will be provided for the safety population.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, medical and surgical history and disease characteristics at baseline will be summarized using descriptive statistics in the safety population and in the efficacy population if relevant.

Demographic and baseline characteristics

- Age in years as quantitative variable and in categories (18 to <65, 65 to <85)
- Gender (Male, Female)
- Race (White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Multiple)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- CLE subtype (DLE, SCLE)
- Geographical region (Asia Pacific, Eurasia, Europe, Latin America, North America)
- Baseline use of chloroquine or hydroxychloroquine (Yes, No)
- Average daily sun exposure without sun protection in hours
- CLASI-A severity (Moderate [10-20], Severe [21-70])

Baseline safety and efficacy/PD parameters (apart from those listed above) will be presented along with the safety and efficacy/PD summaries.

All medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock. All medical history will be summarized by primary SOC and PT using a frequency table (number and % of participants) by study intervention group.

The following baseline disease characteristics will be summarized by study intervention group:

- Time since diagnosis of CLE in years (defined as randomization date – diagnosis date)
- Time since diagnosis of SLE in years (defined as randomization date – diagnosis date)

Partial diagnosis dates will be imputed as follows:

- Missing day will be imputed as 15th of the corresponding month, if only month is available.
- Missing month will be imputed as July of the corresponding year.
- Missing both month and day will be imputed as July 1st of the corresponding year.
- Missing year won't be imputed.

In case an imputed date of diagnosis is after the participant's screening date, the screening date will be used instead.

Prior or concomitant or post-treatment medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the participant used prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during study intervention period.
- Concomitant medications are any medications received by the participant concomitantly to the IMP during the on-treatment period.
- Post-treatment medications are those the participant took in the period running from the end of the concomitant medications period up to the end of the study.

A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant and post-treatment medications will be summarized for the safety population and in the efficacy population if relevant, by anatomic and therapeutic level. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

General data handling conventions

For parameters with evaluations before administration and in cases of rechecked value(s) for one participant, only the last observation will be used as baseline in descriptive statistics and derivations of other parameter values. After baseline, only observations planned in the protocol will be used in descriptive statistics.

The premature EOT visit is entered in eCRF if a patient prematurely discontinues the study intervention. These measurements may not be used in descriptive statistics but could be added in table footnote.

Furthermore, EOS visit measurements from patients who prematurely discontinue the study ("Subject Status" in "Completion of End of Study/Follow-up" page is not "Completed") may not be used in descriptive statistics as well, but could be added in table footnote.

For clinical laboratory parameters with nonnumeric values, the imputed values used for the descriptive statistics and/or the flags will be determined by considering the following rules:

- If database value is ' <X', the value used will be X/2
- If database value is ' >X', the value used will be X
- If database value is a range (eg, 'X – Y'), the values used will be (Y + X)/2

Heart rate is the generic term used indifferently for pulse rate or heart rate from vital signs or ECG assessments.

Data below the Lower Limit Of Quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the Upper Limit Of Quantification will be replaced by ULOQ value.

Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs and ECG will be used for computation of baseline, the last on-treatment value and analysis according to PCSAs grades, and the shift summaries for safety.

Efficacy

The baseline value of efficacy parameters is defined as the Day 1 (the day of first IMP) assessment value unless otherwise specified. If not available, the last available Screening assessment value will be used. Single domains/(sub)scales of efficacy parameters may have baseline on a different visit than the overall score.

EOS visits will only be included (if available) in descriptive statistics and not in efficacy models. Premature EOT visits will not be included in efficacy models as well.

5.5 APPENDIX 5 SAMPLE SAS CODE

Variables

Assuming disease subtype stratification factor is removed from the analysis model and the following combination of geographical regions and countries are performed: Europe + North America + Australia versus Latin America + Eurasia + India.

* treat – treatment (Placebo [0]; SAR443122 [1]);
* strata1 – baseline use of chloroquine or hydroxychloroquine (Yes [1]; No [0]);
* strata2 – region (Latin America + Eurasia + India [0]; Europe + North America + Australia [1]);
* value0 – CLASI-A value at baseline;
* pchange1 … pchange3 – CLASI-A percent change from baseline at each post-baseline visit;

If multivariate normality assumption appears not to be met for the percent change from baseline in CLASI-A, the raw CLASI-A values may be used in the imputation model instead. Alternative statistical methods may be applied as well, eg, data may be transformed for analysis.

Tipping point analysis

1. 1000 datasets with a monotone missing pattern will be obtained, induced by Markov Chain Monte Carlo (MCMC) method.

   ** Partial imputation to render monotone missing;*

   proc mi data= data out=monotone nimpute=1000 seed=35791;

   var strata1 strata2 treat value0 pchange:;

   mcmc chain=multiple impute=monotone;

   run;

2. For each of the imputed dataset with monotone missing pattern in step 1, the remaining missing data will be imputed using the regression method for the monotone pattern with adjustment for covariates. Missing data will be imputed with penalty in SAR443122 intervention group.

   ** To impute the missing data at post-baseline visits with penalty in SAR443122 intervention group;*

   proc mi data= monotone out= dat_imp nimpute=1 seed=57913;

   by _imputation_;

   class strata1 strata2 treat;

   var strata1 strata2 treat value0 pchange:;

   monotone method=reg;

   *mnar adjust (pchange3 / shift=&shift. adjustobs=(treat='1')); *1 denotes SAR443122 intervention group;*

   run;

3. Each of the 1000 imputed datasets will be analyzed using the appropriate ANCOVA model.

```
proc glm data= dat_imp;
        by _imputation_;
        class strata1 strata2 treat;
        model value3 = strata1 strata2 treat value0;
        lsmeans treat / stderr;
        estimate 'Diff SAR443122 versus Placebo' treat -1 1;
        ods output LSMeans=implsmeans Estimates=implsmeansdiff;
run;
```

4. Applying Rubin's rule to combine analysis results (point estimates and standard errors) from 1000 imputations using PROC MIANALYZE for the LS means and difference in LS means between SAR443122 and placebo.

```
proc sort data=implsmeans; by treat _imputation_; run;

proc mianalyze data=implsmeans;
        by treat;
        modeleffects lsmean;
        stderr stderr;
        ods output ParameterEstimates=lsmeans;
run;

proc mianalyze data=implsmeandiff;
        modeleffects estimate;
       stderr stderr;
       ods output ParameterEstimates=lsmeandiff;
run;
```

5.6 APPENDIX 6 SELECTION CRITERIA FOR RESCUE MEDICATION CATEGORIES

Rescue medications identified with the following groupings will be assigned to category "**anti-malarial**":

- CDG00132 "HYDROXYCHLOROQUINE_mono_and_multi_ingredients";
- CDG30011 "CHLOROQUINE_mono_and_multi_ingredients";
- CDG40130 "MEPACRINE_mono_and_multi_ingredients";

Rescue medications identified with the following groupings will be assigned to category "**topical corticosteroids**":

- CDG10390 "Super High potency Topical corticosteroid (For Rescue only)" with Route="TOPICAL";
- CDG10391 "High Topical corticosteroid (For Rescue Only)" with Route="TOPICAL";
- CDG40052 "Medium potency topical corticosteroids_Study level" with Route="TOPICAL";
- CDG40053 "Low potency topical corticosteroids_Study level" with Route="TOPICAL".

Rescue medications identified with following groupings will be assigned to category "**topical calcineurin inhibitors**":

- Chemical class "TOPICAL CALCINEURIN INHIBITOR" and Route="TOPICAL";

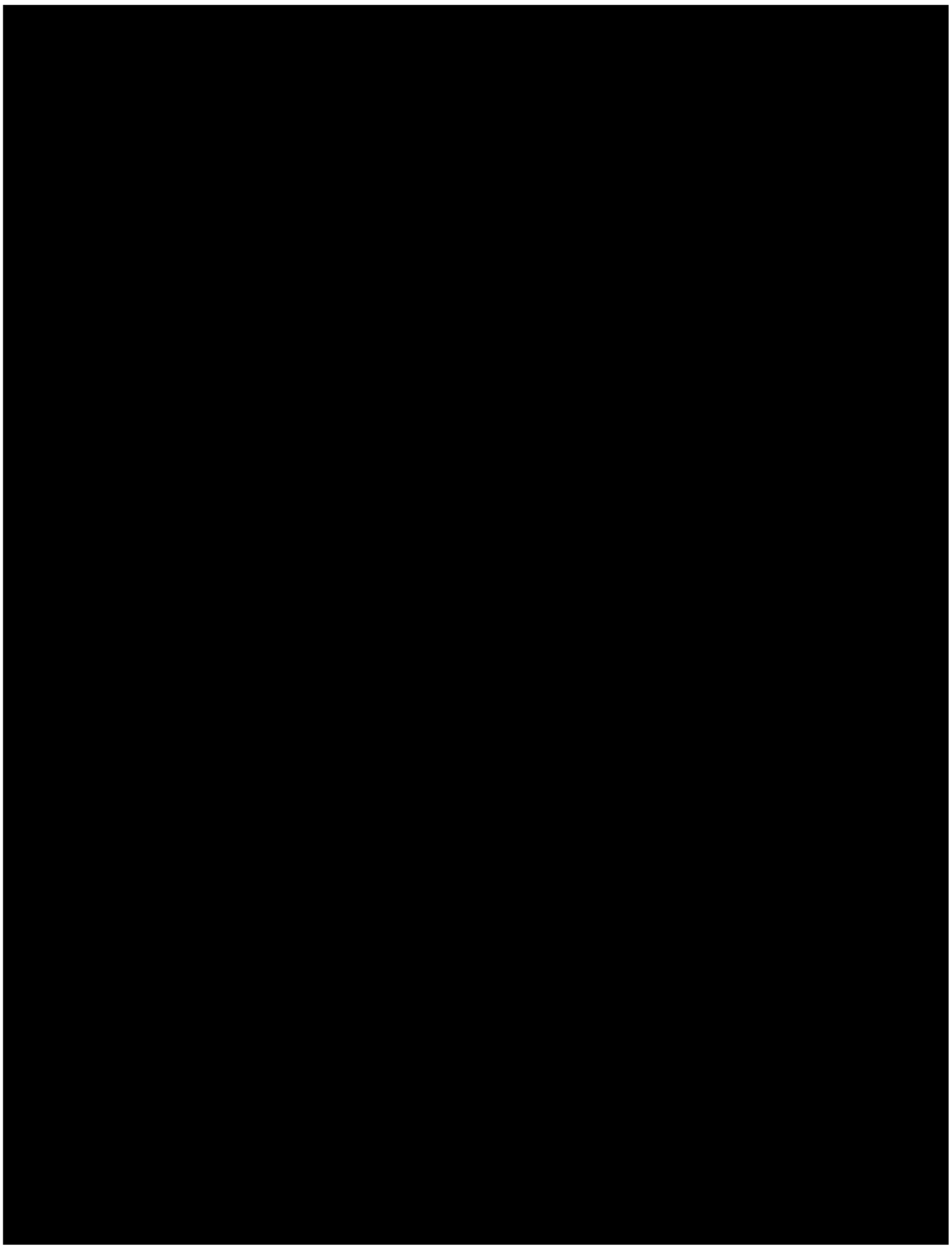
Rescue medications identified with following groupings will be assigned to category "**oral corticosteroids**":

- Chemical class "CORTICOSTEROIDS" and Route="ORAL";

Rescue medications identified with following groupings will be assigned to category "**immunosuppressant**":

- CDG00039 "AZATHIOPRINE_mono_and_multi_ingredients";
- CDG00120 "MYCOPHENOLATE_mono_and_multi_ingredients";
- CDG10270 "Thalidomide_mono_and_multi_ingredients";
- Chemical class "SELECTIVE IMMUNOSUPPRESSANTS";
- Standardized Medication Name "LENALIDOMIDE";

5.7 APPENDIX 7 SAMPLE OF CUTANEOUS LUPUS ERYTHEMATOSUS DISEASE AREA AND SEVERITY INDEX (CLASI)



5.8 APPENDIX 8 SAMPLE OF SAFETY OF ESTROGEN IN LUPUS ERYTHEMATOSUS NATIONAL ASSESSMENT – SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX (SELENA-SLEDAI)

SELENA-SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) INSTRUMENT SCORE

Check box: if descriptor is present at the time of visit or in the preceding 10 days.

Wt	Check if Present	Descriptor	Definition
8	☐	Seizure	Recent onset (last 10 days). Exclude metabolic, infectious or drug cause, or seizure due to past irreversible CNS damage.
8	☐	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations; incoherence; marked loose associations; impoverished thought content; marked illogical thinking; bizarre, disorganized or catatonic behavior. Exclude uremia and drug causes.
8	☐	Organic brain syndrome	Altered mental function with impaired orientation, memory or other intellectual function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
8	☐	Visual disturbance	Retinal and eye changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, optic neuritis, scleritis or episcleritis. Exclude hypertension, infection or drug causes.
8	☐	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.
8	☐	Lupus headache	Severe persistent headache: may be migrainous, but must be nonresponsive to narcotic analgesia.
8	☐	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis or hypertensive causes.
8	☐	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	☐	Arthritis	More than 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	☐	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	☐	Urinary casts	Heme-granular or red blood cell casts.
4	☐	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	☐	Proteinuria	New onset or recent increase of more than 0.5 gm/24 hours.
4	☐	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	☐	Rash	Ongoing inflammatory lupus rash.
2	☐	Alopecia	Ongoing abnormal, patchy or diffuse loss of hair due to active lupus.
2	☐	Mucosal ulcers	Ongoing oral or nasal ulcerations due to active lupus.
2	☐	Pleurisy	Classic and severe pleuritic chest pain or pleural rub or effusion or new pleural thickening due to lupus.
2	☐	Pericarditis	Classic and severe pericardial pain or rub or effusion, or electrocardiogram confirmation.
2	☐	Low complement	Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory.
2	☐	Increased DNA binding	>25% binding by Farr assay or above normal range for testing laboratory.
1	☐	Fever	>38°C. Exclude infectious cause.
1	☐	Thrombocytopenia	<100,000 platelets/mm^3.
1	☐	Leukopenia	<3,000 white blood cells/mm^3. Exclude drug causes.

_____ **TOTAL SCORE** (Sum of weights next to descriptors marked present)

5.9 APPENDIX 9 SAMPLE OF GENITAL EROSIVE LICHEN PLANUS (GELP) SCORE

Table 1 from "Vulvovaginal photodynamic therapy vs. topical corticosteroids in genital erosive lichen planus: a randomized controlled trial" by A.L.O. Helgesen et. al. British Journal of Dermatology, 173: 1156–1162. © British Association of Dermatologists. Reproduced by permission of John Wiley & Sons Inc.

6 REFERENCES

1. Quan H, Chen X, Lan Y, Luo X, Kubiak R, Bonnet N, et al. Applications of bayesian analysis to proof-of-concept trial planning and decision making. Pharm Stat. 2020;19(4):468-81.

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