AMENDED CLINICAL TRIAL PROTOCOL 02

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**
Protocol number:	**ACT16404**
Amendment number:	**02**
Compound number (INN/Trademark):	**SAR443122**
Brief title:	**Proof of concept study of SAR443122 in patients with cutaneous lupus erythematosus** **CLEan**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**1 avenue Pierre Brossolette** **91385 Chilly Mazarin Cedex** **France** **Manufacturer: Same as Sponsor**
Monitoring team's representative name and contact information	

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial protocol 02	All	22-Nov-2022, version 1 (electronic 2.0)
Amended Clinical Trial protocol 01	All	10-Dec-2021, version 1 (electronic 1.0)
Original Protocol		11-Dec-2020, version 1 (electronic 2.0)

Amended Clinical Trial protocol 02 (22 November 2022)

This amended clinical trial protocol 02 (amendment 02) is considered to be not substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union. Because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of this amendment is to include an interim analysis. The sponsor will make use of this interim analysis to facilitate internal operational decision on the compound development. For the details of the interim analysis, see Section 9.4.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 9.3 Statistical analyses	Added: The SAP will be developed and finalized prior to database lock or any interim analysis.	To provide more precision.
Section 9.4 Interim analysis	Added: 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 patients have completed study treatment or discontinued the study. The interim analysis will not lead to changes in the conduct of the protocol other than stopping recruitment for this proof of concept study due to clear efficacy signal at the time of the interim analysis or due to lack of an efficacy signal, indicating a lack of equipoise for continued recruitment of patients. The details including the pre-specified rules for stopping the recruitment will be described in the SAP.	An interim analysis is planned to facilitate internal operational decision on the compound development.

Section # and Name	Description of Change	Brief Rationale
	The interim analysis will evaluate the mean percent change from baseline in CLASI-A at Week 12 and other selected secondary efficacy endpoints, as well as the safety endpoints as needed. The PK and PD relationship could also be explored. 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 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	
Section 10.1.6 Dissemination of clinical study data; Study participants	Replaced “clinicalstudydatarequest.com” to “vivli.org”	To correct the website address for dissemination of clinical study data of study participants.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

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

Brief title:

Proof of concept study of SAR443122 in patients with cutaneous lupus erythematosus

Rationale:

SAR443122 is a novel, potent and selective Receptor-Interacting serine-threonine Protein Kinase1 (RIPK1) inhibitor. The RIP Kinase function involved in pro-inflammatory signaling via phosphorylated RIPK1/3 (pRIPK1/3) and phosphorylated mixed lineage kinase domain-like protein (pMLKL) leading to membrane pore formation, cell death and the release of danger-associated molecular patterns (DAMPs) is inhibited by SAR443122.

In interface dermatitis (ID), a group of skin autoimmune diseases, which is characterized by immune cell infiltration close to the basal membrane of the epidermis and cell swelling and death of the basal keratinocytes. A dysregulated immune response to keratinocyte damage caused by ultraviolet (UV) light and potentially other stimuli are considered drivers of ID which includes most cutaneous lupus erythematosus (CLE) forms.

All subtypes of cutaneous lupus can be triggered and worsened by sunlight. The manifestations of lupus on skin most often involves the scalp, face, ears, and/or other sun-exposed areas. Some patients may present oral and/or genital lesions. Sometimes patients may feel pain or itch. Skin lesion can lead to permanent damage such as depigmentation, scaring and even hair loss when the scalp is involved. CLE skin manifestations in sun exposed area like scalp and face can be disfiguring and are a significant cause of morbidity.

In Europe and the USA, the incidence of isolated CLE is ~4 cases per 100 000 persons per year. Skin involvement occurs in 70%-80% of all patients with systemic lupus erythematosus (SLE) during the course of their disease and patients with CLE can progress to SLE with internal organ systems involvement.

Existing options to treat subacute and chronic lupus are limited and the standards of care consist of repurposed drugs with limited evidence supporting their efficacy and with considerable safety issues. There is a high unmet need for therapies with novel mechanisms of action that target the inflammation in severe CLE and are more efficacious and safer than current treatment.

SAR443122 is proposed to target the chronic inflammation in participants with CLE which manifests as interface dermatitis, namely chronic cutaneous lupus erythematosus (CCLE)/discoid

lupus erythematosus (DLE) or subacute cutaneous lupus erythematosus (SCLE). RIPK1 inhibition may prevent the damage inflicted on keratinocytes and reduce the pro-inflammatory response to this damage, thereby ameliorating skin lesions and associated symptoms.

The available nonclinical and clinical data from the SAR443122 development program in healthy volunteers demonstrated that SAR443122 is well tolerated with a good safety profile which allows for high exposure and tissue penetration in the skin with the opportunity to achieve high exposure in target cells.

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
• 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)

Objectives	Endpoints
• 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 [$t_{1/2z}$])

Overall design:

This is a 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 SCLE or DLE.

The target population for the study is patients with histologically confirmed SCLE or DLE. Patients with acute CLE, drug induced lupus, certain chronic CLE subtypes (eg, LE timidus, lupus profundus, chilblain LE, LE-lichen planus overlap) or lupus like syndrome are excluded. Patients with SLE may be included provided they do not have significant involvement of the central nervous system (CNS), lung or kidney such as lupus nephritis.

The study will be blinded to investigators, patients and Sanofi as well as Sanofi contracted staff.

Participants will be randomized in a ratio of 1:1 to either SAR443122 or placebo arm. The randomization will be stratified by subtype of CLE (DLE or SCLE), baseline use of chloroquine or hydroxychloroquine (yes/no) and by region. 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 group.

Each participant will have a screening period of up to 4 weeks to assess eligibility, a treatment period of 12 weeks beginning from the day of randomization (Baseline, Day 1) and a 4-week post treatment follow-up period.

At screening, participants without a documented histological diagnosis of CLE within 1 year prior to Screening will need a biopsy during Screening period with a histological confirmation of CLE diagnosis before randomization. For participants with a documented histological diagnosis of CLE within 1 year prior to Screening, a biopsy will be performed at Baseline, while the eligibility related to CLE diagnosis will be based upon the historical documented result.

During the 12-week treatment period, participants will be assessed by investigators every 4 weeks and undergo clinical laboratory examinations for all protocol required assessments. Patient-reported disease symptoms (itch and pain) will be assessed on a daily basis within two weeks and at least 4 days prior to baseline and during the treatment period. Details are in Section 1.3.

The primary objective of the study is to assess disease activity compared with placebo at Week 12 as measured by the Cutaneous Lupus Erythematosus Disease Area and Severity Index (2, 3) activity (CLASI-A) sub-score. The secondary endpoints include Investigator's Global Assessment of CLE (IGA-CLE), Physician's Global Assessment of disease activity (PhysGA-disease activity) at Week 12, assessments of CLE-induced itch and pain evaluated separately daily

by a patient reported numerical rating scale, the comparison of CLASI-A50, CLASI-A75 responder rate, and change from baseline of CLASI individual components score (4). A quality of life instrument SKINDEX-29+3 will be used for quality of life assessment (5).

During the study, rescue medication may be used in cases where there is worsening of signs or symptoms of CLE per Investigator's assessment. If feasible, rescue medication should not be used for at least 4 weeks following the first administration of study intervention. Details are provided in Section 6.8.8.

An internal safety review committee (ISRC) will be established to oversee the welfare of the participants as well as the safety, scientific integrity of the trial. All members in the committee are independent of the study operational team members. Details regarding the composition, mandate and function of the internal safety review committee will be provided in the respective ISRC charter.

Brief summary:

This is a parallel, treatment, Phase 2, participants, outcome assessors and Investigator masked, 2-arm study to assess the efficacy and safety of SAR443122 compared to placebo in male and female participants aged 18 to 80 years with moderate to severe SCLE or DLE.

Number of participants:

A maximum of 88 participants will be randomized to study intervention with the goal of approximately 80 participants to complete the study and that are evaluable for the analysis of the primary endpoint.

Intervention groups and duration:

This study will include two treatment groups: SAR443122 and Placebo.

Total study duration per participant will be up 20 weeks including:

- A screening period of up to 4 weeks
- A treatment period of 12 weeks
- A post treatment follow-up period of 4 weeks

Study intervention(s)

Investigational medicinal product(s)

- Formulation: capsules of either SAR443122 100 mg or matching placebo
- Route(s) of administration: Oral route
- Dose regimen: 300 mg BID for 12 weeks

Non-investigational medicinal products(s)

- Rescue treatment may be used per investigators' judgement during the study. Topical corticosteroids and/or topical calcineurin inhibitors and/or one short course of oral corticosteroids of up to 10 days are allowed. Initiation of any new topical corticosteroids and/or topical calcineurin inhibitors and/or increase potency for treating CLE will be considered a rescue treatment. Only one course of oral corticosteroids of up to ten days duration is permitted. If other systemic rescue medications such as immunosuppressants (except initiation or increase the dose of chloroquine or hydroxychloroquine) are required, the patient should be permanently discontinued from the study drug but they should be encouraged to stay in the study until the end of the study.

Devices: Not applicable

Posttrial access to study medication: Not planned

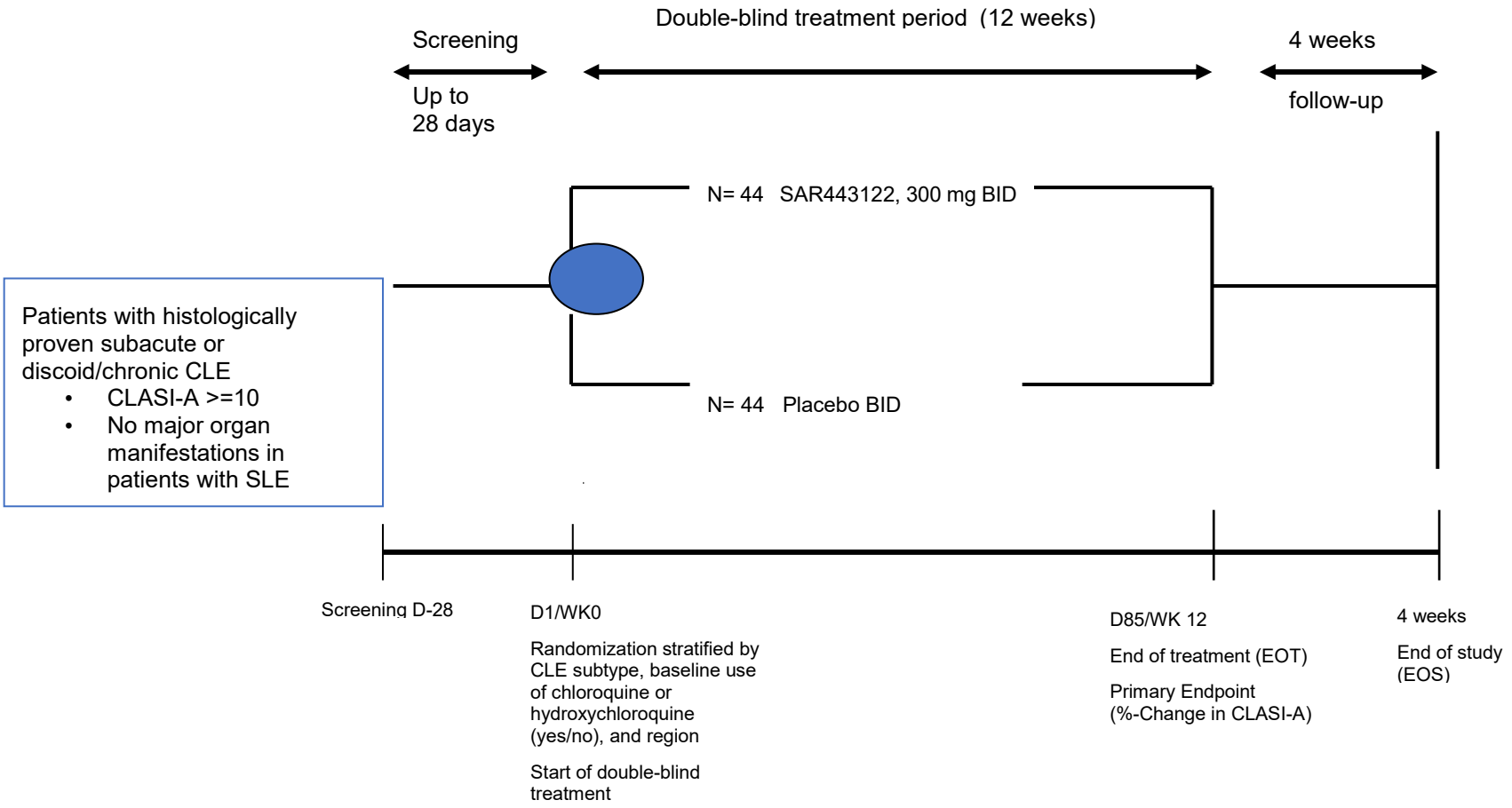
Statistical considerations:

- The sample size was derived to address the primary endpoint (percent change from Baseline to Week 12 in the CLASI-A sub-score) by applying the Quantitative Decision Making approach.

Data Monitoring/Other committee: Yes (ISRC - described previously)

1.2 SCHEMA

Figure 1 - Graphical study design



1.3 SCHEDULE OF ACTIVITIES (SOA)

	Screening (4 weeks)	Treatment phase				Follow-up
Visit	**V1**	**V2 Baseline**	**V3**[a]	**V4**	**V5 (EOT)**	**V6 (EOS)**
Day	**D-28 to D-1 (Maximum 28 days)**	**D1**	**D29 (±4)**	**D57 (±4)**	**D 85**	**D 113 (+4)**
Week		**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Patient demographics	X					
Medical/surgical history (includes substance usage[b]) and Family history of premature CV disease	X					
Prior medications history	X					
Concomitant medication (including sun protection[c])		X	X	X	X	X
12-lead electrocardiogram (ECG)	X				X	X[d]
Physical examination including vital signs[e]	X	X	X	X	X	X
Serology: Hepatitis B & C, and HIV[f]	X					
Antiphospholipid antibodies[g]		X				
Antihistone autoantibodies	X					
Tuberculosis (TB) testing[h]	X					
COVID-19 testing[h]	X					
Height	X					

	Screening (4 weeks)	Treatment phase				Follow-up
Visit	**V1**	**V2 Baseline**	**V3**[a]	**V4**	**V5 (EOT)**	**V6 (EOS)**
Day	**D-28 to D-1 (Maximum 28 days)**	**D1**	**D29 (±4)**	**D57 (±4)**	**D 85**	**D 113 (+4)**
Week		**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**
Weight	X				X	
Call IVRS	X	X Randomization	X	X	X	X
Investigational medicinal product (IMP)						
IMP daily intake (BID)[i]		X----------I				
IMP dispense		X	X	X		
IMP compliance (Patient diary)		X	X	X	X	
Safety						
Adverse event/SAE recording	X---------->					
Tuberculosis risk assessment		X			X	
Hematology, Chemistry	X	X	X	X	X	X[d]
Fasting lipids, glycosylated hemoglobin (HbA1c)	X					
Urinalysis[j]	X	X	X	X	X	
Serum pregnancy test (woman of childbearing potential [WOCBP] only)	X					
Urine pregnancy test (WOCBP only)		X	X	X	X	X
Efficacy assessment						
CLASI[k]	X	X	X	X	X	X

	Screening (4 weeks)	Treatment phase				Follow-up
Visit	**V1**	**V2 Baseline**	**V3[a]**	**V4**	**V5 (EOT)**	**V6 (EOS)**
Day	**D-28 to D-1 (Maximum 28 days)**	**D1**	**D29 (±4)**	**D57 (±4)**	**D 85**	**D 113 (+4)**
Week		**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**
IGA-CLE	X	X	X	X	X	X
PhysGA-disease activity	X	X	X	X	X	X
28-Joint assessment		X	X	X	X	X
SELENA-SLEDAI[l]		X			X	
GELP[n]		X			X	
OHIP-14[m]		X			X	
SKINDEX 29+3		X			X	
Itch-NRS/Pain-NRS[o]	<----------daily---------->					
Physician Global Assessment of Change in disease activity					X	
Patient Global Impression of change in disease					X	
Patient Global Impression of disease severity		X			X	
Skin examination with photography of index lesion(s)		X			X[u]	
PK and exploratory Biomarkers						
PK (plasma)[p]		X		X	X[u]	
pS166-RIPK1 (PBMC)[q]		X			X	X
Cytokine panel (Plasma)[r]		X	X	X	X	X
Chemokine Panel (Plasma)[r]		X	X	X	X	X

	Screening (4 weeks)	Treatment phase				Follow-up
Visit	**V1**	**V2 Baseline**	**V3**[a]	**V4**	**V5 (EOT)**	**V6 (EOS)**
Day	**D-28 to D-1 (Maximum 28 days)**	**D1**	**D29 (±4)**	**D57 (±4)**	**D 85**	**D 113 (+4)**
Week		**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**
RNA sequencing (Whole Blood) (optional)		X			X	
Marker for systemic lupus (anti-dsDNA-ab, C3, C4)[s]		X			X	
Markers for systemic lupus (antinuclear antibody [ANA], anti-Smith-ab)[s]		X				
Skin biopsy for histology, and RNA sequencing[t]	X[t]	X[t]			X[u]	
DNA sample (optional)		X				

Abbreviation: ANA = antinuclear antibody; BID = twice a day; CLASI = Cutaneous Erythematosus Disease Area and Severity Index; CV= cardiovascular; ECG = electrocardiogram; GELP= Genital Erosive Lichen Planus; HIV = human immunodeficiency virus; IGA-CLE = Investigator's Global Assessment of CLE; IMP = investigational medicinal product; NRS = Numerical Rating Scale ; OHIP = Oral Health Impact Profile; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamics; PK = pharmacokinetics; SAE = serious adverse event; SELENA-SEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index ; SLE = systemic lupus erythematosus; TB = tuberculosis; WOCBP = woman of childbearing potential

a In case of urgent COVID-19 pandemic situation requiring strict confinement of population, visit can be organized and done by video per PI's judgement. Appropriate measure should be put in place for laboratory procedures (eg, home nursing).

b Substances: drugs, alcohol, tobacco, and caffeine.

c Sun protection information includes the level of daily sun exposure and means for UV protection.

d Only if there are abnormal findings at Wk12 requiring follow-up.

e Full physical examination at screening only, including skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. A brief physical examination will be performed at remaining on-site visits and include, at a minimum, assessments of the skin, lungs, cardiovascular system, lymphatic system (include but not limited to cervical, axillary, inguinal and clavicular lymph nodes) and abdomen (liver and spleen).

f HBV and HCV serologies include: hepatitis B surface antigen (HBs-Ag), hepatitis B surface antibody (HBs-Ab), total hepatitis B core antibody (HBc-Ab), and hepatitis C antibody (HCV-Ab). In case of HBc-Ab positive and HBs-Ag negative, to assess patient's eligibility, HBV DNA will be performed locally as per Investigator's judgement.

g Antiphospholipid antibodies to be performed in patients with SLE.

h TB testing method will follow local guidelines and will be performed locally, in case that local guidelines is not available, QuantiFERON TB gold test will be performed either locally or centrally. COVID-19 testing will follow local guidelines and will be performed locally.

i Last IMP dose intake will be morning dose on-site on Day 85.

j To use dipstick, if any abnormality, send sample to central lab for testing. Urine microscopic examination (including pyuria, hematuria and urinary casts) and spot urine protein/creatinine ratio test will be performed at Baseline, Week 12, and when the SELENA-SLEDAI is assessed.

k CLASI assessment includes CLASI-A and CLASI-D.
l SELENA-SLEDAI will be assessed for all patients at Baseline and W12, if new suspicion of SLE during the study, additional assessment will be performed at the on-site visit closest to the suspicion.
m Only in patients with oral lesions diagnosed as lupus related at baseline.
n Only in patients with genital lesions as lupus related at baseline.
o NRS daily assessment will start within 2 weeks and at least 4 days prior to baseline.
p Sample collection : on Day 1, PK sampling within 2 to 5 hours after the first morning dose (around C_{max}); on Day 57 PK sampling just before or within 1 h before the morning dosing, within 2 to 5 hours after the first morning dose (around C_{max}) and within 7 to 10 hours after the morning doses , On Day 85 (or early EOT) for all participants, PK sampling just before or within 1 h before the morning dosing and within 2 to 5 hours after the first morning dose (around C_{max}).
q PBMC assay will be performed in patients with CLE in a subset of qualified sites.
r Cytokine panel and chemokine panel assays will be performed. Details of the assessment in the panels are provided in Section 8.6.
s To be measured at V2 and as needed if suspicion of systemic lupus during the study.
t Only skin lesion to be biopsied. For patients who have no documented histological diagnosis, biopsy will be performed at screening and at Week 12. For patients who have documented histological diagnosis, biopsy will be performed at V2 after other eligibility assessments done and at Week 12. In case that the patient is prematurely discontinued from IMP, biopsy will be performed at EOT instead of Week 12.
u To be performed at the end of treatment only, not required at Week 12 in case of premature end of treatment.

2 INTRODUCTION

SAR443122 is a novel, potent and selective Receptor-Interacting serine-threonine Protein Kinase1 (RIPK1) inhibitor for oral administration. RIP Kinase1 inhibition with SAR443122 results in the inhibition of tumor necrosis factor (TNF), interferon (IFN), toll-like receptor (TLR) 3/4 mediated cell death (necroptosis or apoptosis) and inflammation triggered by the release of danger-associated molecular patterns (DAMPs). SAR443122 has no effect on the scaffolding function of RIPK1 which is important for the Nuclear factor kB (NF-kB) dependent cell survival signaling downstream of the TNF-TNF receptor-1 complex. On the other hand, the RIP Kinase function involved in pro-inflammatory signaling via pRIPK1/3 and pMLKL leading to membrane pore formation, cell death and DAMP release is inhibited by SAR443122 (see SAR443122 Investigator Brochure for detailed information).

In skin autoimmune disease, such as CLE, we hypothesize that RIPK1 inhibition would be beneficial by a generalized dampening of the local pro-inflammatory milieu. CLE is manifested in the skin by increases in several pro-inflammatory cytokines as well as other mechanisms of cell death.

Normally, controlled cell death is a physiological mechanism to remove infected or damaged cells but is also exploited by pathogens to escape host defense. Interferon receptors and TLR3/4 receptors function as pathogen sensors of viral or bacterial components (PAMPs) or cell damage (DAMPs). Some pathogens modulate pro-inflammatory response after TNF receptor stimulation to escape innate immunity. Similar to response to infection, this process appears to be involved in certain autoimmune diseases such as CLE.

Interface dermatitis (ID), which includes most CLE forms, is characterized by immune cell infiltration close to the basal membrane of the epidermis and cell swelling and death of the basal keratinocytes. Initial stimulus might be different among certain skin diseases, but dominance of cytotoxic T cells and involvement of plasmacytoid dendritic cells are described in several ID positive skin diseases (6). Biopsy-derived T-cells from CLE patients are dominated by interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) positive cells (7). It was also demonstrated that ID is characterized by a shared transcriptome signature and CLE points towards a strong type I immune response. RIPK1 gets activated downstream of TNF receptor and IFN receptor activation as well as TLRs. Hence, primary pro-inflammatory cytokines involved in the pathophysiology of CLE are strongly linked to RIPK1 activation and downstream signaling demonstrated by hallmarks of RIPK1 signaling, phosphorylated RIPK1 (pRIPK1) and pMLKL (8). In conclusion, inhibition of RIPK1 downstream of TNF and IFN receptor activation are considered as a potential target to modulate the pathophysiology of CLE.

Three-month toxicity studies of SAR443122 in monkey and rat have shown no adverse events (AEs) at the highest doses tested ([redacted] mg/kg/day and [redacted] mg/kg/day, respectively). In the 3-month rat study, test article-related effects were limited to increases in mean body weight, mean body weight gain, and mean food consumption for males administered [redacted] mg/kg/day; a few minor clinical pathology changes in animals administered ≥[redacted] mg/kg/day, with no microscopic correlates; microscopically increased germinal center lymphocytes in the spleen of males and

females administered ≥[redacted] mg/kg/day, with correlative splenic weight increases in females administered [redacted] mg/kg/day; increased liver weights for males administered [redacted] mg/kg/day and females administered ≥[redacted] mg/kg/day; and increased kidney weights for females administered ≥[redacted] mg/kg/day. All findings exhibited reversibility and were considered not adverse. Due to the mild severity of findings and the lack of impact on the health and well-being of animals administered [redacted] mg/kg/day, effects for this dose were considered non-adverse. Thus, the no observed adverse effect level (NOAEL) is [redacted] mg/kg/day. This dose level corresponded to mean C_{max} and AUC values of [redacted] µM and [redacted] h*µM, respectively, in males and [redacted] µM and [redacted] h*µM, respectively, in females during Week 13 of the dosing phase.

In the 3-month monkey study, non-adverse, SAR443122-related, increases in the incidence and/or severity of mononuclear cell infiltrates or increased lymphocytes were observed in multiple tissues of animals administered ≥[redacted] mg/kg/day. Many of the findings were not found after the recovery phase, indicating reversibility. However, increased incidences and/or severities of mononuclear cell infiltrates persisted in the pancreas, lacrimal gland, kidney, sternum marrow (focal), tongue, and vagina. None of the findings in any dose group were considered adverse, thus, the NOAEL is [redacted] mg/kg/day. This dose level corresponded to mean C_{max} and AUC values of [redacted] µM and [redacted] h*µM, respectively, in males and [redacted] µM and AUC [redacted] h*µM, respectively, in females during Week 13 of the dosing phase.

SAR443122 was safe and well tolerated in healthy volunteers at exposures of up to 800 mg during the single dose part of the study, and up to 600 mg given once a day for 14 days during the multiple dose part of the study.

Following single oral dose administration of 10 to 800 mg SAR443122 in fasted conditions, median t_{max} was reached between [redacted] and [redacted]-hours post dosing. AUCs increased without major deviation from dose proportionality from [redacted] mg and then increased less than expected from dose proportionality from [redacted] mg. C_{max} increased less than expected by dose proportionality from [redacted] mg.

After once daily repeated administration for 14 days, there is no drug accumulation. The mean elimination half-life was estimated between [redacted] hours. Concomitant intake of a high fat meal did not modify the bioavailability of SAR443122 at 100 mg.

Sustained maximal target engagement, measured as RIPK1 phosphorylation inhibition (>90%), was sustained for 24, 48 and at least 72 hours after single doses of 100, 200 and 400 mg, respectively. During the multiple ascending dose (MAD) study the median inhibition achieved during the period of maximal inhibition of the 50 mg group was 88.5% whereas the 100 and 200 mg groups show a median inhibition greater than 90% (93.9% and 91.3% respectively). Duration of the period of maximal inhibition was longer in 100 and 200 mg groups (median: 58 hours and 65 hours respectively) than in 50 mg group (median: 22 hours) under multiple dosing.

The favorable safety profile allows for high exposure with the opportunity to achieve high exposure (>IC90, over 24 h) in target cells of carefully selected indications. The projected AUC following 12-weeks of administration to patients at 300 mg BID is [redacted] µM*h. Therefore, projected animal:human exposure ratios based on AUC are 10X and 2.8X for the rat 3-month and monkey 3-month, respectively.

A phase 1b, randomized, double-blinded, placebo-controlled study to evaluate the safety and immunomodulatory effect of the RIPK1 inhibitor SAR443122 in hospitalized patients with severe COVID-19 has started in July 2020.

In Europe and the USA, the incidence of isolated CLE is ~4 cases per 100 000 persons per year, which is slightly higher than the incidence of SLE (~3 cases per 100 000 persons per year) (9, 10, 11). CLE most often affects middle aged adults with a mean age at diagnosis of 54 years old. Skin involvement occurs in 70%-80% of all patients with SLE during the course of their disease and skin lesions are the first disease manifestation to present in 20%-25% of patients with SLE (11). Patients with CLE can progress to SLE with internal organ systems involvement. The rate of systemic manifestations depends on the underlying subtype of CLE; for example, acute cutaneous lupus erythematosus (ACLE) has the highest rate of systemic involvement (~90%), whereas localized DLE has the lowest (<5%) (10, 12).

All subtypes of cutaneous lupus can be triggered and worsened by sunlight. Acute CLE most often involves a prominent rash on the cheeks and nose ("butterfly rash"). Subacute CLE most often presents with an erythematous, scaly papules on sun-exposed areas of the body that evolve into plaques. It tends to have circular skin lesions or lesions that can look like psoriasis on sun-exposed skin. Discoid lupus starts out as a red to purple scaly rash on the scalp, face, ears, and other sun-exposed areas. Over time, discoid lupus may heal with discolored scarring and even hair loss when the scalp is involved. Sometimes patients may feel pain or itch (13). Skin lesion can lead to permanent damage such as depigmentation and scarring if not treated. CLE skin manifestations in sun exposed area like scalp and face can be disfiguring and are a significant cause of morbidity.

The adverse effects associated with exposure to UV light, in triggering and worsening disease activity, protection from exposure to direct sunlight is recommended for all patients with cutaneous lupus; though photoprotection does not always work and is not always feasible. Additionally, reduced sun exposure results in a decreased activation of vitamin D and the continuous or frequent use of corticosteroids increases the risk of osteoporosis. The guideline from the European Academy of Dermatology and Venereology recommends vitamin D supplementation for all patients with CLE to protect CLE patients against an increased risk of osteoporosis (14).

Topical glucocorticoids are the first-line treatment for CLE lesions because of their anti-inflammatory properties (14, 15). The primary indication for topical glucocorticoids is a localized DLE, patients with more extensive disease may show an inadequate response and are more prone to adverse effects. While topical calcineurin inhibitors are not approved for the treatment of CLE, they are frequently used as an alternative to topical corticosteroids. Unlike corticosteroids, these inhibitors do not induce skin atrophy, however, they are less effective than corticosteroids and carry a black box warning due to a potential tumor risk.

2.1 STUDY RATIONALE

Established systemic treatment in CLE

In the current guidelines, antimalarial drugs and glucocorticoids are both recommended as first-line treatment in patients with highly active or widespread lesions (14, 16). Antimalarial drugs (such as chloroquine, hydroxychloroquine and quinacrine) are the most frequently used systemic drugs in CLE. The mode of action of these relatively old antimalarial drugs is still under investigation, but all of these antimalarial drugs inhibit type I IFN production by immune-activated peripheral blood mononuclear cells (17). Both chloroquine and hydroxychloroquine are associated with important adverse drug reactions including QTc-prolongation and with long-term use there is a risk of potentially irreversible retinopathy.

The use of systemic glucocorticoids (SGCs) is recommended for severe or widespread active CLE lesions. However, to decrease the impact of adverse reactions associated with SGCs, there is an imperative to taper their use as soon as possible (14).

In patients with long-standing disease or high disease activity, other immunosuppressive and immunomodulatory drugs such as methotrexate, retinoids and dapsone are used (15). Approximately 30%-40% of patients with CLE are refractory to antimalarials. Methotrexate is recommended for use in refractory CLE, primarily SCLE (13), dapsone for recalcitrant CLE and bullous lupus erythematosus, and retinoids for selected patients with CLE (particularly patients with hypertrophic DLE) when they are unresponsive to other treatments. All other drugs, including mycophenolate mofetil and cyclosporine, are considered third-line therapies because of the lack of supporting clinical studies in CLE (14).

In summary, existing options to treat subacute and chronic cutaneous lupus are limited and the current mainstays of treatment are repurposed drugs with limited evidence supporting their efficacy and are associated with considerable safety issues, in particular if used long-term.

Patients using chloroquine and hydroxychloroquine for chronic treatment require regular ophthalmological screening to avoid potentially irreversible retinopathies, which increase sharply after 5-7 years of use. Among many other adverse effects, the same drugs may also cause QTc prolongation, which may be potentiated by other drugs.

Serious side effects such as fatal cardiac rhythm disturbances including Torsades de Pointes are uncommon but have been observed and may be underdiagnosed. Chronic use of oral corticosteroids has many serious adverse effects including osteoporosis, hypertension, diabetes, weight gain, increased vulnerability to infection, cataracts and glaucoma (eye disorders), and thinning of the skin. No drug has been specifically approved for the treatment of CLE and there is an unmet need for therapies with novel mechanisms of action that target the inflammation in severe CLE that are more efficacious and safer than current treatment.

2.2 BACKGROUND

Preclinical data support the application of RIPK1-inhibitors in ID, which includes CLE. Interface dermatitis characterized by immune cell infiltration close to the basal membrane of the epidermis,

and cell swelling and death of the undermost keratinocytes. This cell death is thought to contribute and propagate the inflammation seen in the skin diseases associated with ID. While the initial stimulus might be different among certain skin diseases, all ID is characterized by the dominance of cytotoxic T cells in the inflamed tissue and involvement of plasmacytoid dendritic cells. Biopsy-derived T-cells from CLE patients are dominated by IFN-γ and TNF- α positive cells. It was also demonstrated that ID is characterized by a shared transcriptome signature across different skin diseases, and CLE is associated with a strong type I immune response. RIPK1 gets activated downstream of TNF receptor and IFN receptor as well as TLRs signaling. Hence, primary pro-inflammatory cytokines involved in the pathophysiology of CLE are strongly linked to RIPK1 activation and downstream signaling as demonstrated by hallmarks of RIPK1 signaling, namely pRIPK1, pRIPK3 and pMLKL. In conclusion, inhibition of RIPK1 activity downstream of TNF and IFN receptor signaling is considered an important target to modulate the pathophysiology of cutaneous lupus erythematosus. Additional primary cell culture work based on human keratinocytes is ongoing to demonstrate the beneficial effect of RIPK1 inhibition on preventing or attenuating cell death in ID. In these ongoing assays we aim to demonstrate that through RIPK1 inhibition, dysregulation of cell death (apoptosis/necroptosis) is blocked and reduces overall inflammation.

2.3 BENEFIT/RISK ASSESSMENT

The available nonclinical and clinical data from the SAR443122 development program in healthy volunteers (78 receiving active drug) demonstrated that SAR443122 is well tolerated with a good safety profile to date. SAR443122 is proposed to target the chronic inflammation in participants with CLE which manifests as interface dermatitis, namely DLE or SCLE. A dysregulated immune response to keratinocyte damage caused by UV light and potentially other stimuli as described above are considered drivers of interface dermatitis. RIPK1 inhibition may prevent the damage inflicted on keratinocytes and reduce the pro-inflammatory response to this damage, thereby ameliorating skin lesions and associated itch and discoloration of said skin lesions.

More detailed information about the known and expected benefits and risks of SAR443122 may be found in the Investigator's Brochure.

2.3.1 Risk assessment

SAR443122 was safe and well tolerated in the first-in-human (FIH) study (TDU16339/TDR16341). There were no serious adverse events (SAEs), no severe treatment-emergent adverse events (TEAEs) and no deaths. There were no relevant treatment emergent potentially clinically significant abnormalities (PCSAs) for the laboratory values, vital signs, and ECG parameters.

TDU16339 Part 1a single dose ascending (SAD): Total of [redacted] healthy volunteers were enrolled: [redacted] subjects were enrolled into each of the [redacted], and treated with [redacted] mg, [redacted] mg, [redacted] mg, [redacted] mg, [redacted] mg or [redacted] mg of SAR443122 (or placebo), respectively. No adverse events of special interest (AESIs), or treatment related TEAEs leading to treatment discontinuation reported during the study.

TDU16339 Part 1b food effect and relative bioavailability study: Total of [redacted] healthy volunteers completed all three periods. There were no AESIs, or treatment related TEAEs leading to treatment discontinuation reported during the study.

TDR16341-Part2-MAD: Total of [redacted] healthy volunteers randomized and treated: Placebo: [redacted]; SAR443122 [redacted] mg: [redacted]; SAR443122 [redacted] mg: [redacted]; SAR443122 [redacted] mg: [redacted]; SAR443122 [redacted] mg: [redacted]. Treated [redacted] days with highest multiple dose at [redacted] mg QD x [redacted] days.

- Two AESI of alanine transaminase (ALT) elevation >2 x upper limit of normal (ULN), but <3 x ULN were reported, 1x on [redacted] mg and 1x on [redacted] mg dose. Both recovered, were asymptomatic and mild.

Based on the clinical FIH TDU16339-SAD and TDR16341-Part2-MAD, both in healthy volunteers, and nonclinical studies of SAR443122, no important risks were identified to date.

Based on the nonclinical studies, the potential risks are effect on immune system and anemia.

Table 1 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
[redacted]		

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
[redacted]		

2.3.2 Benefit assessment

Currently, there are no approved drugs for CLE. Limited existing options including antimalarial drugs, glucocorticoids, immunosuppressants and immunomodulators are often tried. All these drugs are repurposed drugs with limited evidence supporting their efficacy and with considerable side-effects. There is a high unmet medical need in patients with moderate to severe CLE.

Through RIPK1 kinase inhibition, SAR443122 is expected to inhibit the dysregulation of apoptosis/necroptosis observed in ID including CLE and downregulate the inflammation. Based on the mechanism of action, and even though the study is of short duration, the potential benefits would be:

- Reduction in disease activity score (CLASI-A)
- Reduction in itch
- Reduction in pain
- Reduction of cutaneous or systemic disease flares
- Reduction in oral or genital lesions
- Improvement in QoL

2.3.3 Overall benefit: risk conclusion

Based on the FIH clinical studies (TDU16339/TDR16341) SAR443122 was safe and well tolerated in healthy volunteers up to [redacted] mg given as a single dose and up to [redacted] mg given daily for [redacted] days. SAR443122 has demonstrated a satisfactory safety profile in the nonclinical toxicity studies and was not found to be genotoxic or phototoxic. The projected AUC following [redacted]-weeks of administration to patients at [redacted] mg BID is [redacted] µM*h. Therefore, projected animal:human exposure ratios based on AUC are [redacted]X and [redacted]X for the rat [redacted]-month and monkey [redacted]-month, respectively.

Risk management procedures and specific safety monitoring in particular to mitigate the potential risk of immune system disorder or anemia will be implemented (Section 2.3.1).

Based on the acceptable safety profile summarized above and the potential for considerable benefits on cutaneous lupus disease activity, on acute episodes and on long-term sequelae, the potential benefits outweigh the risks in the proposed study population.

3 OBJECTIVES AND ENDPOINTS

Table 2 - 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
• 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 [$t_{1/2z}$])

Objectives	Endpoints
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 pS166-RIPK1 in PBMC lysates with SAR443122 treatment compared to placebo in a subset of patients at Week 12
• 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)

3.1 APPROPRIATENESS OF MEASUREMENTS

The Cutaneous Erythematosus Disease Area and Severity Index (CLASI) is a validated clinical instrument with documented content validity and good psychometric properties (inter- and intra- rater reliability; ability to detect changes) (2, 18, 19, 20, 21). It is commonly used clinically to assess

disease activity (CLASI-A) and skin damage (CLASI-D) induced by CLE. The primary endpoint is to assess disease activity; measured by the CLASI-A sub-score. This choice is in line with the standard instrument for evaluation of disease activity and the study design publicly available.

To assess changes in skin lesions and potential early skin lesion improvement, the change of CLASI individual components from baseline will be evaluated, which occurs typically faster than other features of skin lesions.

As a secondary endpoint, overall disease activity will be assessed by the IGA-CLE. The IGA is widely used in several dermatological conditions with verbal descriptors specific for the assessment of the indication in which it is used. The IGA-CLE is under development to be specific for the assessment of CLE by expert dermatologists and rheumatologists.

The 5 point-lickert scale Physician's Global assessment of disease activity (PhysGA-disease activity) will provide a global evaluation of the disease activity as per investigator's evaluation. This instrument will be a secondary endpoint.

Numerical rating scale (NRS) is one of standard measurement instruments for evaluation of chronic symptoms and is a popular choice for all patients due to its simple format. The peak pruritus NRS (itch-NRS) assess worst itch in the past 24 hours features high reliability and concurrent validity. The peak pain NRS (pain-NRS) related to CLE is developed specifically for this study and will assess worst pain related to CLE in the past 24 hours.

GELP score is a scoring system for clinical assessment of genital lesions in women and it has been developed in lichen planus. For both the targeted CLE subtypes of the present study and lichen planus (LP) manifest interface dermatitis, CLE patients may present oral and/or genital lesions. These two clinical instruments validated in LP are considered as appropriate to assess oral and/or genital lesions in CLE patients. The results obtained from this study can serve for the larger study in CLE in the future.

As an exploratory endpoint, 28- joint assessment of tender and swollen joints has been frequently used to assess joints inflammation in patients with lupus. It has been identified to assess SAR443122 effect on joint involvement in CLE patients in this study.

Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) is an instrument for the assessment of systemic manifestations of lupus (22). It is a clinical instrument to assess the disease activity in patients with SLE. In the present study, SLE patients without major organ involvement will be allowed to participate, and CLE could progress to SLE in some patients. It is anticipated to administer the SELENA-SLEDAI in all patients enrolled in order to monitor the lupus disease activity and potential development of systemic disease. Potential effect of SAR443122 on the systemic manifestations of lupus will be explored with this instrument.

A quality of life questionnaire Skindex 29+3 (also called SkindexLupus) (5) will evaluate the effect of SAR443122 on patient's QoL. It includes Skindex-29 items and a set of 3 questions to assess lupus-specific issues, ie, photosensitivity and alopecia.

Patient's global impression of disease severity (PGIS) instrument will evaluate patient-reported impression of the disease severity while patient's global impression of change in disease activity (PGIC) and physician's global assessment of change in disease activity (PGAC) will evaluate patients and physicians evaluation of change in disease since the start of study medication, respectively. These scales will be used as anchor measure to validate psychometric properties of CLASI and patient reported outcomes (PROs) assessments used in the study.

The pharmacokinetic assessments used in this study are standard for the evaluation of the drug administrated BID.

The exploratory assessments related to DNA, RNA and biomarkers are selected based on the current knowledge from the literature and in-house research.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a 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 BID compared to matching placebo in patients with moderate to severe SCLE or DLE.

The target population for the study are patients with histologically proven SCLE or DLE. Patients with acute CLE, intermittent disease or drug induced lupus are excluded. Patients with SLE may be included provided they do not have significant involvement of the central nervous system (CNS), lung or kidney such as lupus nephritis.

The study will be blinded to investigators, patients and Sanofi as well as Sanofi contracted staff.

Participants will be randomized in a ratio of 1:1 to either SAR443122 or placebo arm. The randomization will be stratified by subtype of CLE (DLE or SCLE), baseline use of chloroquine or hydroxychloroquine, and by region. Up to 88 participants are expected to be randomly assigned to the IMP, expecting a total of approximately 80 evaluable participants with approximately 40 evaluable participants per group.

Each participant will have an up to 4 weeks screening period to assess the eligibility, 12 weeks treatment period counting from the day of randomization (Baseline, Day 1) and a 4-week post treatment follow-up period.

At screening, participants without a documented histological diagnosis of CLE within 1 year prior to Screening will have to perform biopsy and histological result should be obtained before randomization to confirm the eligibility related to CLE diagnosis. For participants who have a documented histological diagnosis of CLE within 1 year prior to Screening, biopsy will be performed at Baseline, the eligibility related to CLE diagnosis will be based upon the documented result.

During the 12 weeks treatment period, participants will be assessed by investigators every 4 weeks and undergo a series of clinical laboratory examinations for efficacy, safety, pharmacokinetic, pharmacodynamic and exploratory assessments. Patient reported daily disease symptoms (itch and pain) will be assessed on a daily basis within two weeks and at least 4 days prior to baseline and during treatment period. Details can be found in Section 1.3.

The primary objective of the study is to assess disease activity compared with placebo at Week 12 as measured by the CLASI-A sub-score, the Cutaneous Lupus Erythematosus Disease Area and Severity Index (2, 3) activity sub-score. The secondary endpoints include IGA-CLE score, PhysGA- disease activity at Week 12, assessments of CLE-induced itch and pain evaluated separately daily by a patient reported NRS, the comparison of CLASI-A50, CLASI-A75 responder rate, and-change from baseline of CLASI individual components score (4). The safety of SAR443122 will be assessed throughout the study. A quality of life instrument SKINDEX-29+3 will be used for quality of life assessment (5).

During the study, the rescue medication may be used in case of CLE worsening per investigator's medical judgement. If feasible, rescue medication should not be used for at least 4 weeks following the first administration of study intervention. Details can be found in Section 6.8.8.

An internal safety review committee (ISRC) will be established to oversee the welfare of the participants as well as the safety, scientific integrity of the trial. Details regarding the composition, mandate and function of the internal safety review committee will be provided in the respective charter.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This Phase 2a study is designed as a proof-of-concept study aimed at evaluating efficacy and safety of RIPK1 kinase inhibitor SAR443122 in patients with moderate and severe CLE (CLASI-A ≥10).

The target population are patients with CLE which manifest interface dermatitis, namely DLE or SCLE based upon the hypothesis that RIPK1 inhibition may prevent the damage inflicted on keratinocytes and reduce the pro-inflammatory response to this damage, thereby ameliorating skin lesions including oral and genital lesions and associated clinical manifestations such as itch and pain.

The proposed 12 weeks treatment duration is supported by the available preclinical and FIH studies and is consistent with the generally accepted time period to assess the clinical effect in patients with CLE.

Existing options for treatment of CLE are repurposed drugs with limited evidence supporting their efficacy and with considerable safety issues. A placebo-controlled and parallel arms study is appropriate to evaluate efficacy and safety of SAR443122 in this population. PK and various biomarkers will be evaluated in this early clinical development study as well.

This study is double-blind to minimize potential for bias on the part of the investigator, participant, or sponsor.

The randomization ratio is 1:1. Stratification by subtype of CLE, baseline use of chloroquine or hydroxychloroquine (yes/no), and by region allows to minimize the influence of potential confounding factors such as the disease subtype, background treatment and seasonality on the participant's response to the study treatment.

Given that the study is placebo-controlled and is the first study of SAR443122 in patients with CLE, during the study, rescue medication may be used, to mitigate any potential risk related to CLE worsening.

An Internal Safety Review Committee which is independent to study team will oversee the welfare of the participants as well as adverse drug effects.

While there is no formal statistical hypothesis testing performed, the sample size was derived with respect to the primary endpoint (see Section 9.1). Thus, it is anticipated that the current sample size of approximately 80 evaluable patients may demonstrate a reduction of disease activities in

the active treatment arm measured by CLASI-A sub-score at Week 12, among other secondary clinical outcomes.

The knowledge gained from this study could be confirmed with a larger trial to demonstrate a clinically significant effect of RIPK1 inhibition in CLE.

4.2.1 Participant input into design

Potential participants have not been involved in the design of this clinical trial.

4.3 JUSTIFICATION FOR DOSE

Recently released clinical data from a competitor (23) and internal preclinical data in chronic inflammatory CNS disease, suggest that very high levels of RIPK1 kinase activity inhibition are required to have a clinical effect and that exposure needed to reach this high level of inhibition is higher in chronic inflammatory disease than in healthy subjects. Therefore, a daily dose of 600 mg of SAR443122 administered as 300 mg twice daily orally for 12 weeks is proposed. A BID regimen is selected to optimize drug plasma concentrations and reduce PK fluctuation during the entire dosing interval and thus to maintain maximum levels of inhibition. SAR443122 was well tolerated after single oral doses up to 800 mg and at multiple daily doses up to 600 mg in healthy subjects. Of note, a maximal tolerated dose was not established in either of these clinical studies of healthy volunteers. Predicted exposure for a 300 mg dose administered BID provides a safety margin of 5 x in terms of C_{max} and 2.8 x in terms of AUC as compared to the exposure reached at the NOAEL in monkeys.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit (End of Study visit, EOS) as shown in the Schedule of Activities (Section 1.3).

The end of the study is defined as the date of the last visit of the last participant in the study globally.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be 18 to 80 years of age inclusive, at the time of signing the informed consent

Type of participant and disease characteristics

I 02. Participants with cutaneous lupus erythematosus either in the form of discoid/chronic cutaneous lupus erythematosus or subacute cutaneous lupus erythematosus for at least 3 months before Screening

I 03. Participants with histologically confirmed and documented diagnosis within one year prior to Screening or during Screening period prior to randomization

I 04. Active cutaneous lupus erythematosus skin lesions and a CLASI-A ≥10 both at Screening and Baseline

I 05. Participant who is candidate for systemic treatment per Investigator's judgement

Sex, contraceptive/barrier method and pregnancy testing requirements

I 06. All

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants

Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 5 days after the last dose of IMP, corresponding to time needed to eliminate study intervention(s) (eg, 5 terminal half-lives)

- Refrain from donating sperm.

PLUS, either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below
  - A male condom and an additional highly effective contraceptive method as described in Appendix 4 Contraceptive and barrier guidance (Section 10.4) when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.

b) Female participants

A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

- Is a woman of non-childbearing potential (WONCBP) as defined in Appendix 4 Contraceptive and barrier guidance (Section 10.4).

OR

- Is a WOCBP and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 4 Contraceptive and barrier guidance (Section 10.4) during the study intervention period and for at least 2 days, corresponding to the time needed to eliminate any study intervention(s) (eg, 5 terminal half-lives) plus 30 days (a menstrual cycle) after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period.
  - A WOCBP must have a negative highly sensitive pregnancy test (urine and/or serum as required by local regulations) at Screening and Baseline visits before the first administration of study intervention, see Section 10.2 Pregnancy testing.
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

c) Local regulations regarding contraception for male and female participants (see Section 10.4.2).

Informed Consent

I 07. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. In countries where legal age of majority is above 18 years, a specific ICF must also be signed by the participant's legally authorized representative.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Systemic lupus erythematosus according to the 2012 SLICC criteria (24) with major organ involvement such as lupus nephritis, cardiopulmonary involvement (eg, interstitial lung disease, pulmonary hypertension, pleuritis, pericarditis, myocarditis, and endocarditis), neuropsychiatric involvement, vasculitis, antiphospholipid syndrome (APS) on or requiring chronic anticoagulation, significant hematological and/or gastrointestinal involvement. Concurrent findings of malar rash, constitutional symptoms, alopecia, arthralgia/arthritis, myalgia, oral/nasal ulcers, Sjogren syndrome, Raynaud's phenomenon, sub-clinical pericardial and/or pleural effusions are permitted. Please consult the Sponsor for related SLE manifestations if unclear related to eligibility.

E 02. Suspected or proven drug induced lupus erythematosus, including patients with positive antihistone autoantibody tests.

E 03. Diagnosed with certain subtypes of CCLE (such as Lupus erythematosus tumidus, Chilblain, lupus panniculitis, lichenoid cutaneous lupus/lichen planus overlap syndrome).

E 04. Autoimmune disease(s) other than systemic lupus erythematosus (eg, systemic sclerosis, myositis, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, multiple sclerosis, Behcet’s disease etc).

E 05. Active skin diseases that may interfere with the study or study assessments (eg, Psoriasis).

E 06. History of significant cardiovascular diseases/conditions, clinically significant renal, hepatic, metabolic (eg, poorly controlled diabetes mellitus demonstrated by screening HbAc1 ≥9%), neurologic, hematologic, ophthalmologic, respiratory, gastrointestinal, cerebrovascular or other significant medical illness or disorder which, in the judgment of the Investigator, could interfere with the study or require treatment that might interfere with the study.

E 07. History of any malignancy except history of adequately treated basal cell carcinoma or in situ cervical carcinoma.

E 08. Patients with active tuberculosis (TB) or non-tuberculous mycobacterial infection, or a history of incompletely treated active or latent TB per local guidelines will be excluded from the study unless it is documented by a specialist that the participant has been adequately treated and can now start treatment with the RIPK1 kinase inhibitor. Also excluded from the study are patients with a positive PPD test, Mantoux test or Quantiferon-TB Gold test at Screening indicating latent tuberculosis or another mycobacterial infection. Positive PPD or Mantoux is acceptable if can be explained by a documented BCG-vaccination. The method of tuberculosis testing will be selected on a country-by country basis, according to local guidelines. If Quantiferon-TB Gold test is used as per local guidelines, patients with positive or 2 confirmed indeterminate Quantiferon-TB Gold tests at screening (regardless of prior treatment status) will be excluded.

E 09. History of HIV infection or positive HIV serology at screening.

E 10. Participants with any of the following result at screening:

- Positive (or indeterminate) HBs Ag or,
- Positive total HBc Ab confirmed by positive HBV DNA or,
- Positive HCV Ab.

E 11. History of recurrent or recent serious infection (eg, pneumonia, septicemia) within 4 weeks of screening, infection requiring hospitalization or intravenous antibiotics, antivirals or antifungals within 4 weeks of screening or chronic bacterial infections deemed unacceptable, as per Investigator's judgement.

E 12. Recurrent or active herpes zoster within 2 months prior to screening.

E 13. Prolonged QTcF ≥450 ms (by Fridericia formula) or clinically significant findings on ECG per Investigator's assessment at Screening or during Screening period.

E 14. Exposure to another investigative drug (monoclonal antibodies as well as small molecules) prior to Visit 1, within the period specified as follows: an interval of less than 6 months or <5 PK half-lives for investigative monoclonal antibodies, and an interval of less than 30 days or <5 PK half-lives, whichever is longer prior to Screening, for investigative small molecules.

E 15. Surgery within 4 weeks prior to the screening visit or with planned surgery during the study.

E 16. Positive COVID-19 screening test, suspected of COVID-19 infection or known exposure to COVID-19 during the screening period.

E 17. History of COVID-19 infection within 4 weeks prior to Screening; history of mechanical ventilation or extracorporeal membrane oxygenation (ECMO) due to COVID-19 infection within 3 months prior to Screening or with residual significant complications from COVID-19 making it unsafe for the participant to enter this study.

E 18. Cannot avoid excessive UV exposure (such as use of tanning equipment and/or sun exposure [eg, beach vacation]) 4 weeks prior to baseline and during the study. Routine sun exposure through work (eg, farmer, construction worker, etc) are permitted but requires the use of sun block (recommend to use sun block with SPF 50 or higher) to sun exposed areas for at least 4 weeks prior to baseline and during the study.

Prior/concomitant therapy

E 19. Concomitant treatment with topical immunosuppressants beyond a stable regimen of low to medium potency topical corticosteroids and/or topical calcineurin inhibitors during the study and two weeks before baseline visit.

E 20. Initiation and/or changes in dosage of chloroquine/hydroxychloroquine within 12 weeks prior to Screening visit (or during Screening period) and/or the dose exceeding 2.3 mg/kg/day for chloroquine or 400 mg/day for hydroxychloroquine.

E 21. Systemic treatments (except for the study medication) for cutaneous or systemic lupus erythematosus or immunosuppressive therapy for autoimmune disease other than the study medication including:

- cyclosporin and dapsone within 4 weeks prior to baseline visit.
- methotrexate within 6 weeks prior to baseline visit.
- mycophenolate mofetil (MMF), thalidomide, azathioprine, systemic retinoids, belimumab as well as any anti-TNF mAbs, B and/or T cell targeted immunosuppressive therapies within 2 months or 5 half-lives prior to baseline visit, whichever is longer as well as during the study.

E 22. Systemic corticosteroids treatment <4 weeks before baseline visit.

E 23. Live vaccine(s) within 1 month prior to Screening, or plans to receive such vaccines during the study.

Prior/concurrent clinical study experience

E 24. Participation in another clinical study 60 days before baseline visit.

Diagnostic assessments

E 25. Any of the following laboratory abnormalities at the Screening visit:

- Hemoglobin <10 g/dL.
- Absolute neutrophil count (ANC) <1500 /mm^3 (or <1000/mm^3 for participants of African descent).
- Platelet <100 000 /mm^3.
- Creatinine clearance <60 mL/min using Cockcroft-Gault equation.
- ALT or AST or ALP >1.5 x ULN.
- Total bilirubin >1.5 x ULN or total bilirubin between > ULN and ≤1.5 ULN and associated with > ULN conjugated bilirubin unless documented Gilbert's syndrome.

Retest can be done to reassess the eligibility during Screening period as per investigator's judgement that observed abnormality is not clinically significant and not consistent with patient's medical history.

Other exclusions

E 26. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 27. Any country-related specific regulation that would prevent the participant from entering the study - see Appendix 8 of the protocol (Section 10.8 country-specific requirements).

E 28. Individuals with established dependency on drugs or alcohol, per the judgement of the investigator.

E 29. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 30. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the ICH-GCP Ordinance E6).

E 31. Any specific situation during study implementation/course that may rise ethics considerations.

E 32. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

No restrictions are required.

5.3.2 Caffeine, alcohol, and tobacco

The information of one’s regular use of alcohol and tobacco should be recorded in eCRF.

5.3.3 Activity

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 additional time. Rescreened participants should be assigned with a new participant number. The participant number for the initial screening will be recorded in the rescreening eCRF.

Participants who are rescreened must sign a new informed consent and all screening visit procedures must be repeated except biopsy done in previous screening visit. There is no requirement for a waiting period between the screen failure date and the rescreen date.

5.5 CRITERIA FOR TEMPORARILY DELAYING (ENROLLMENT/RANDOMIZATION/ADMINISTRATION OF STUDY INTERVENTION)

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Appendix 9 (Section 10.9): Contingency measures for a regional or national emergency that is declared by a governmental agency should be considered for screening, enrollment, randomization, and administration of study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

6.1.1 Investigational medicinal product

Table 3 - Overview of study interventions administered

Arm name	SAR443122	Placebo
Intervention labels	SAR443122	Placebo
Type	Drug	Drug
Dose formulation	Capsules	Capsules
Unit dose strength(s)	100 mg	N/A
Dosage level(s)	3 capsules (300 mg) BID	3 capsules BID
Route of administration	Oral[a]	Oral
Use	Experimental	Placebo
IMP or NIMP	IMP	IMP
Packaging and labeling	IMP will be provided in double blind kit labeled as required per country requirement	IMP will be provided in double blind kit labeled as required per country requirement
[Current/Former name(s) or alias(es)]	DNL758	Not applicable

a The IMP can be taken with or without food.

The SAR443122/placebo may be supplied at the site or from the PI/site/Sponsor to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 9 (Section 10.9): Contingency Measures for a regional or national emergency that is declared by a governmental agency.

6.1.2 Non-investigational medicinal product

Rescue treatment may be used per investigators' judgement during the study. Topical corticosteroids and/or topical calcineurin inhibitors and/or one short course of oral corticosteroids of up to 10 days are allowed. Initiation of any new topical corticosteroids and/or topical calcineurin inhibitors and/or increase potency, or initiation of oral corticosteroid for treating CLE will be considered a rescue treatment.

If other systemic rescue medications such as immunosuppressants are required (except initiation or increase the dose of chloroquine or hydroxychloroquine), the patient should be permanently discontinued from the study drug but they should be encouraged to stay in the study until the end of the study.

6.1.3 Devices

Not applicable.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.9).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for DTP shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Methods of assigning participants to treatment arm

The randomized treatment kit number list is generated centrally by Sanofi.

The IMPs are packaged in accordance with this list.

All participants will be centrally assigned to randomized study intervention using an interactive response technology (IRT). The Sanofi Clinical Supply Chain team will provide the randomized treatment kit number list to the IRT. The IRT system generates the participant randomization list and allocates the intervention number and the corresponding treatment kits to the participants according to it.

The Investigator or designee will obtain the treatment kit numbers at randomization (Day 1, Baseline) and subsequent scheduled dosing visits via IRT that will be available 24 hours/day. Although the kit numbers will vary for the individual participant, the treatment group assignment and randomization will not change throughout the study.

Treatment kits will be dispensed at the study visits summarized in SoA (Section 1.3). Returned study treatment kits should not be re-dispensed to the participants.

Participants will be randomized in 1:1 ratio to treatment arms described in Table 3. Randomization will take place on Baseline/Day 1 and will be stratified by subtype of CLE (DLE versus SCLE), baseline use of chloroquine or hydroxychloroquine (Yes versus No), and by region. Sub-type of CLE and baseline use of chloroquine or hydroxychloroquine will be entered in the IRT before randomization takes place.

A participant cannot be randomized more than once in the study.

Methods of blinding and code breaking during the study

SAR443122 100 mg and matching placebo will be provided in identically and visually indistinguishable capsules.

The investigator, other staff members, as well as the participant will remain blinded and will not know the participant's intervention assignment during the study.

- The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted (eg, in case of available antidote). Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, he/she may, at his/her discretion, contact the Sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

6.4 STUDY INTERVENTION COMPLIANCE

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and patient's e-Diary. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. IMP kits are delivered by Investigator during on-site visits for the following 4 weeks administrations at home. IMP kits (used, unused and partially used) are returned by the participant at each visit. In case of DTP process, the IMP kits can be provided and returned by the carrier (if defined in the contract). Compliance will be assessed by e-Diary records and counting returned capsules during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of SAR443122/placebo capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.5 DOSE MODIFICATION

Not applicable for this study.

6.5.1 Retreatment criteria

Not applicable.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Not applicable.

6.7 TREATMENT OF OVERDOSE

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should assess the participant, and then:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until SAR443122 can no longer be detected systemically (at least 5 days).
3. Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document appropriately in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.8 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

6.8.1 Prohibited medications

Any medications listed in exclusion criteria (E 19, E 20, E 21, E 22 and E 23) should not be initiated during the study except what specifically mentioned in rescue medicine section (Section 6.8.8).

6.8.2 Topical corticosteroids

Stable regimen of low to medium potency topical corticosteroids (Appendix 10, Section 10.10.1) are allowed from baseline if they are initiated 2 weeks before baseline. No modification including formulation or regimen change is allowed during the study, except that the patient develops an AE not related to CLE requiring the modification. The modification and AE must be recorded in the eCRF.

Any increase of potency of principal active, initiation a new topical corticosteroid due to CLE worsening will be considered as rescue medication and should be appropriately recorded as described in Section 6.8.8.

6.8.3 Systemic corticosteroids

Participants should not receive systemic corticosteroids within 4 weeks prior to the baseline. During the study, oral corticosteroids can be used as rescue medication as described in Section 6.8.8. If the participant develops an AE for a condition not related to CLE that requires the oral corticosteroid treatment, the sponsor must be notified timely (eg, within 1 working day). The allowed cumulative dose of oral corticosteroid is equivalent prednisone <60 mg/day x 10 days, taking into account rescue oral corticosteroid if any.

6.8.4 Intra-articular, intralesional, intranasal, and inhaled corticosteroids

Intralesional and Intra-articular corticosteroids are not allowed during the study.

Intranasal and inhaled corticosteroid are authorized as needed for treating conditions other than CLE.

6.8.5 Chloroquine and hydroxychloroquine

If patients receive chloroquine, hydroxychloroquine at baseline, the dose should be stable for at least 12 weeks prior to Screening visit and not exceed 2.3 mg/kg/day for chloroquine, 400mg/day for hydroxychloroquine. No change is allowed during the Screening period. Whenever possible, the dose should be stable during entire study period except that the patient develops an AE not related to CLE or SLE requiring the modification. The modification and AE must be recorded in the eCRF.

6.8.6 Nonsteroidal anti-inflammatory drugs, topical anesthetics, acetaminophen and other analgesic

Paracetamol/Acetaminophen, at doses of ≤2 grams/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the Investigator, if they do not interfere with the study including any study assessments.

6.8.7 Drug interaction

6.8.8 Rescue medications

Topical corticosteroids and/or topical calcineurin inhibitors and/or one short course of oral corticosteroids of up to 10 days are allowed as rescue medications. If other systemic rescue medications such as immunosuppressants (except initiation or increase the dose of chloroquine or hydroxychloroquine) are required, the patient should be permanently discontinued from the study drug, but they should be encouraged to stay in the study until the end of the study.

Subjects requiring rescue therapy (addition or increase of any systemic or topical treatments) beyond baseline will be considered non-responders.

Rescue medication should not be used for at least 4 weeks following the first administration of study intervention, if feasible. The date and time of rescue medication administration as well as the name, route of administration, reason for starting and dosage regimen of the rescue medication must be recorded.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated. Remaining visits will be performed, details are in Section 7.1.1.1.

See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

The IMP will be permanently discontinued in case of the following events:

- Clinically significant infections such as:
  - Opportunistic infections
  - Active TB
  - COVID-19 infections (positive-PCR or suspected active COVID-19 infection)
- New adenopathy of unknown cause
- New diagnosed malignancies
- Initiation of systemic rescue medication except one short course of oral corticosteroid <10 days and/or chloroquine or hydroxychloroquine
- Significant laboratory abnormalities (See Appendix 6 [Section 10.6]):
  - ALT >5 ULN or ALT >3 ULN with concomitant total bilirubin >2 ULN (unless patient with documented Gilbert's syndrome)
- Hb <8 g/dl of unknown cause
- Symptomatic overdose
- Pregnancy in female participant
- Any AEs, per Investigator's judgement that discontinuation of study intervention is in best interest of the participant

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation before making a decision of definitive discontinuation of the IMP for the concerned participant.

7.1.1.1 Handling of participants after permanent intervention discontinuation

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the definitive early discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP (end of treatment [EOT] visit) including skin biopsy sample and PK sample, if appropriate. Then, all the remaining visits and associated procedures prespecified in the SOA will be performed, except skin biopsy, pharmacokinetic samples, and photography at Week 12.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Liver chemistry stopping criteria

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in the algorithm (Section 10.6) or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant.

7.1.3 QTc stopping criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval after enrollment), the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE or AESI (Section 8.3.8).

7.1.4 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs (Section 10.6) or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency [Section 10.9]). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

A temporary discontinuation >7 consecutive days will lead to permanent discontinuation.

7.1.5 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 9 (Section 10.9): Contingency Measures for a regional or national emergency that is declared by a governmental agency.

7.1.5.1 Study intervention restart or rechallenge after liver stopping criteria met

Study intervention restart or rechallenge after liver chemistry stopping criteria (Section 7.1.2) are met by any participant in this study is not allowed.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed. The clinician reported outcome (ClinRO) mentioned in the SoA will be used when copyright is obtained (if applicable).
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Patient-reported outcome (PRO) questionnaires should be completed by the participants before the consultation and/or clinical tests, in a quiet place (at home in e-diary and at clinic). The questionnaires should be completed by the participants themselves, independently from their physician, the study nurse, or any other medical personnel and without any help from friends or relatives.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 9 (Section 10.9): Contingency Measures for a regional or national emergency that is declared by a governmental agency.

8.1 EFFICACY ASSESSMENTS

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3).

8.1.1 Cutaneous lupus Erythematosus Disease Area and Severity Index (CLASI)

The CLASI 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 (2): 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)

It has a current recall period and takes approximately 5 minutes to complete. 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 (3). 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.

The CLASI is a validated clinical instrument with documented content validity and good psychometric properties (inter- and intra- rater reliability; ability to detect changes) (2, 18, 19, 20, 21). A 4-point or 20% decrease in CLASI-A score represents the minimal clinically important change (MCIC) (3).

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.

Whenever possible, the same patient should be assessed by the same Investigator throughout the study.

The CLASI is provided in Appendix 10 (Section 10.10.2).

Clinicians will complete the CLASI as per SoA (Section 1.3).

8.1.2 Physician Global Assessment of disease activity (PhysGA- disease activity) for cutaneous lupus erythematosus

The Physician's Global Assessment of disease activity (PhysGA- disease activity) is a 5 point-Lickert scale instrument designed to assess physician-reported disease activity ranging from "Not active at all" to "Extremely active". This instrument has been developed internally for this study in CLE. Whenever possible, the same patient should be assessed by the same Investigator throughout the study.

The PhysGA-disease activity is provided in Appendix 10 (Section 10.10.3).

Clinicians will complete the PhysGA-disease activity as per SoA (Section 1.3).

8.1.3 Physician Global Assessment of Change in cutaneous lupus erythematosus activity (PGAC)

The Physician's Global Assessment of Change in cutaneous lupus erythematosus (PGAC) 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".

Whenever possible, the same patient should be assessed by the same Investigator throughout the study.

The PGAC is provided in Appendix 10 (Section 10.10.3).

Clinicians will complete the PGAC as per SoA (Section 1.3).

8.1.4 Patient-reported Numerical Rating Scale (NRS)

The Peak Pruritus NRS (itch-NRS) is a single item PRO tool that patients will use to report the intensity of their pruritus (itch) during a daily recall period. Patients will be asked to rate their worst itch on a 0 ("No itch") to 10 ("Worst itch imaginable") NRS by answering the following question: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?"

The Peak Pruritus NRS has been validated in atopic dermatitis adult and adolescent patients; a threshold for clinically relevant, within-person response was found to be 2-4 points (25).

The Peak Pain NRS (Pain-NRS) is a single item PRO tool that patients will use to report the intensity of their CLE-related pain (skin, oral, genital) during a daily recall period. Patients will be asked to rate their worst pain on a 0 ("No pain") to 10 ("Worst pain imaginable") NRS by answering the following question: "On a scale of 0 to 10, with 0 being 'no pain' and 10 being the 'worst pain imaginable', how would you rate your pain at the worst moment due to your lupus during the previous 24 hours?".

The Pain-NRS has been developed specifically for the present study.

The itch-NRS and Pain-NRS are provided in Appendix 10 (Section 10.10.4).

Patients will complete the Peak Pruritus NRS and Peak Pain NRS daily, as per the SoA (Section 1.3).

If acetaminophen or other analgesics or topical anesthesia are used for pain relief, the participant will be requested to rate his/her pain just before the next administration.

8.1.5 Investigator's Global Assessment for Cutaneous Lupus Erythematosus (IGA-CLE)

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.

Whenever possible, the same patient should be assessed by the same Investigator throughout the study.

The IGA-CLE is provided in the Appendix 10 (Section 10.10.8)

Clinicians will complete the IGA-CLE as per SoA (Section 1.3).

8.1.6 Oral Health Impact Profile 14-item version (OHIP-14)

The OHIP-14 is a PRO questionnaire that measures people's perception of dysfunction, discomfort and disability attributed to oral conditions in adults (26). 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) (26). 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. OHIP-14 shows good reliability, validity and precision.

The OHIP-14 is provided in Appendix 10 (Section 10.10.5).

Patients will complete the OHIP-14 as per the SoA (Section 1.3).

8.1.7 SKINDEX-29+3

Skindex-29 is a PRO measure designed to assess the effects of skin disease on patients' health-related quality of life in adults (27, 28). It is a generic instrument for skin and connective tissue diseases. It contains 29 items, distributed across the following domains: emotions (10 items), symptoms (7 items), functioning (12 items); and one item about treatment that is not part of the total score. 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 to100 in 25-point increments with 100 representing maximal disability.

The measurement properties of the instrument have been extensively documented in various skin diseases, including CLE and SLE patients (3, 29, 30, 31). No data is available on the ability of the instrument to detect changes in CLE/SLE. Important impact on health-related quality of life is defined as a 9.38-point and a 7.37-point improvement in the Emotions and Symptoms subscales of Skindex-29, respectively (32).

The Skindex 29+3 (also called SkindexLupus) (5). It includes a fourth subscale (3 questions) to assess lupus-specific issues, ie, photosensitivity and alopecia. Two items, ''I worry about going outside because the sun might flare my disease'' and ''My skin disease prevents me from doing outdoor activities'' relate to photosensitivity. The average of these two items was used to generate a photosensitivity subscale. Construct validity (item-total correlations; known-group validity) has been documented (33, 34, 35).

The SKINDEX-29+3 is provided in Appendix 10 (Section 10.10.6).

Patients will complete the SKINDEX-29+3 as per the SoA (Section 1.3).

8.1.8 Patient Global Impression of disease severity (PGIS) and Patient Global Impression of Change (PGIC) in cutaneous lupus erythematosus

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

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 PGIS and PGIC are provided in Appendix 10 (Section 10.10.7).

Patients will complete the PGIS and PGIC as per the SoA (Section 1.3).

8.1.9 28-Joint assessment

Twenty- eight-joint assessment will be 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.

Twenty- eight joints include proximal interphalangeal joints (10 joints), metacarpophalangeal joints (10), wrists (2), elbows (2), shoulders (2) and knees (2).

8.1.10 Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI)

The SELENA-SLEDAI has been developed to measure the disease activity in patients with SLE for use in clinical trials (22). It has been developed to determine global improvement and performed in effective and reliable manners in studies (36).

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. A reduction of ≥4 points in the SELENA-SLEDAI score from baseline is considered to be a clinically meaningful improvement (37).

Clinicians will complete the SELENA-SLEDAI as per the SoA (Section 1.3).

8.1.11 Genital Erosive Lichen Planus (GELP) score

Genital Erosive Lichen Planus score is a scoring system for clinical assessment of GELP in women (38). 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.

Clinicians will complete the GELP as per the SoA (Section 1.3).

8.1.12 Photography of Index Lesion

Index lesions will be photographed at baseline. The same lesions will be photographed at EOT visit to evaluate their progression.

Index lesion should include at least biopsied lesion and non-biopsied lesions. The lesion with the highest disease activity score as assessed by CLASI-A by Investigator at baseline should be selected. If more than one lesion is evaluated with the same highest score, it is up to Investigator to select some of those lesions or decide to photography all of them. If oral lesions present at baseline, oral lesion should be selected as well.

The body site(s) and lesion features assessed by Investigator of photographed skin lesion will be recorded in the eCRF.

The detailed information will be provided in the photography user guide.

8.2 SAFETY ASSESSMENTS

This section presents safety assessments other than AEs which are presented in Section 8.3.

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical examinations

A targeted physical examination including lung auscultation and assessment of consciousness will be performed at time points according to Section 1.3. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the participant's medical history.

- A full physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems, skin, nasal cavities, eyes, and ears. Height (screening only) and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, lymphatic system (include but not limited to cervical, axillary, inguinal and clavicular lymph nodes) and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any new finding or worsening of previous finding should be reported as a new adverse event.

8.2.2 Vital signs

Vital signs, including systolic and diastolic blood pressure, pulse rate, temperature and respiration rate, will be collected and recorded at the time points according to Section 1.3.

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed. The site of temperature measurement should be recorded in the eCRF, and the same site should be used throughout the study for the same patient.
- Blood pressure and pulse measurements will be assessed in semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.

8.2.3 Electrocardiograms

A standard 12-lead ECG will be performed at time points according to Section 1.3. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT (identify QTcF) intervals will be recorded in the eCRF. The ECG strips or reports will be retained with the source.

- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 7 for QTcF withdrawal criteria and any additional QTcF readings that may be necessary.

8.2.4 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency. Additional clinical laboratory tests may be performed based on the investigator's clinical judgement.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

A laboratory manual will be provided to study sites with additional information for laboratory parameters assessed centrally.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention should be repeated until the

values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or severe AE or dose modification), then the results must be recorded in the eCRF.

8.2.5 Suicidal ideation and behavior risk monitoring

Not applicable.

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.3.8.

The definitions of unsolicited and solicited adverse events can be found in Appendix 3 (Section 10.3).

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.1 Time period and frequency for collecting AE and SAE information

All SAEs will be collected from the signing of the informed consent form (ICF) until the follow-up visit at the time points specified in the SoA (Section 1.3).

All AE will be collected from the signing of the ICF at the time points specified in the SoA (Section 1.3).

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3).

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, and AEs of special interest (as defined in Section 8.3.8), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Adverse events that are considered expected will be specified in the reference safety information (Investigator's Brochure).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

- An Investigator who receives an Investigator safety report describing a SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

It is the responsibility of the investigator to report to the sponsor (or designee), any pregnancy occurring in a female study participant or a female partner of male participant, during the study.

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until the outcome of the pregnancy. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Cardiovascular and death events

Cardiovascular and death events should be reported to the sponsor and/or health authority per reporting rules for AEs or SAEs if seriousness criteria met.

8.3.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable.

8.3.8 Adverse event of special interest

Adverse event of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

- 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;

  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Appendix 4 [Section 10.4])
- Symptomatic overdose (serious or nonserious) with IMP.
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as at least 50% more than intended daily dose within one day.
- Increase in alanine transaminase (ALT)
  - ≥3 X ULN (for participants with normal baseline) or
  - >3 X ULN AND at least 2-fold increase from baseline value (for participants with abnormal baseline).
- Other AESI:
  - Anemia (Hb <8 g/dL).
- Other project specific AESI(s)
  - QTc ≥500 ms (per QTcF).
  - New Lymphadenopathy.

8.3.9 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.3.9.1 Medical device deficiencies

Not applicable.

8.4 PHARMACOKINETICS

Samples for SAR443122 PK analyses will be collected at the following timepoints as mentioned in (Section 1.3):

- On Day 1, PK sampling within 2 to 5 hours after the first morning dose (around C_{max});

- On Day 57 PK sampling just before or within 1 h before the morning dosing, within 2 to 5 hours after the first morning dose (around C_{max}) and within 7 to 10 hours after the morning doses;
- On Day 85, PK sampling just before or within 1 h before the morning dosing and within 2 to 5 hours after the first morning dose (around C_{max}).

Procedures for PK sample management and analysis will be described in the laboratory manual.

A maximum of 2 samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

The actual date and time (24-hour clock time) of each sample, and associated IMP intake will be recorded.

8.4.1 Pharmacokinetics handling procedure

Instructions for the collection and handling of biological samples will be provided by the Sponsor in the laboratory manual.

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained. At visits during which plasma samples for the determination of multiple aspects of study intervention will be taken, one sample of sufficient volume can be used.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.4.2 Bioanalytical method

SAR443122 will be assayed by a validated LC/MS method. The details of the bioanalytical method will be specified in the laboratory manual.

8.4.3 Pharmacokinetic parameters

SAR443122 concentrations at selected time points after IMP intake will be reported using descriptive statistics. Additional PK parameters such as C_{max}, t_{max}, and $AUC_{0\text{-}tau}$ and elimination half-life [$t_{1/2z}$] at steady state will be estimated using a population PK approach. These parameters will be presented in a separate, stand-alone report.

8.5 GENETICS

All participants will undergo skin punch biopsies. The first biopsy will be before the randomization (either at screening or at Baseline) and the second at EOT visit. Transcriptomic analysis (RNA sequencing) will be performed on skin samples obtained from biopsies, to explore changes related to treatment and/or disease progression compared to baseline and placebo controls to evaluate their association with the observed clinical responses to SAR443122.

Participants will be asked whether they will consent to the collection of an optional blood sample for the isolation of DNA and RNA. These materials will be used for exploratory genomic and transcriptomic analysis, respectively.

Blood samples for DNA or RNA isolation will be collected at the timepoints indicated in SoA (Section 1.3) from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

Blood samples for RNA isolation will be collected at the timepoints indicated in SoA from participants who have consented to participate in the gene expression analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA or RNA seq extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 5 (Section 10.5) for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual.

8.6 BIOMARKERS

Blood and skin biopsy samples collected from subjects in this study may be used to identify and measure biomarkers (including optional collections of blood for DNA and/or RNA as discussed in Section 8.5) related to the study drug. These samples will be used for scientific research to support this study protocol. The information gained from these samples may be used to design or improve methods for analyzing, comparing, or combining study data. Plasma from whole blood will be used for exploratory research including the development of PD assays and/or exploration of target- and disease-related exploratory biomarkers related to RIP kinase-1 inhibition such as cytokines, lipids, metabolites, proteome, cellular markers, immune cell phenotypes, and other inflammatory biomarkers. All samples, including any for assay development will be shipped to the Sponsor or a designated laboratory.

Blood samples for biomarkers related to CLE will be collected by venipuncture at the timepoints indicated in SoA (Section 1.3). Procedures for collecting, processing and shipping of these samples are provided in the laboratory manual.

Samples will be tested for changes related to treatment and/or disease progression compared to baseline and placebo controls to evaluate their association with the observed clinical responses to SAR443122, including:

- **PBMC**: Whole blood will be collected for PBMC isolation. RIPK1 phosphorylation at Serine-166 (pS166-RIPK1) will be measured in lysates prepared from collected PBMCs using a qualified fit-for-purpose assay.

- **Cytokines Panel, Chemokines Panel, and disease related biomarkers**: Blood plasma will be used for the tests.
  - The cytokine panel includes validated assays for: [redacted]
  - The chemokine panel includes validated assays for: [redacted].
  - The disease related biomarkers are referred to as C3, C4, anti-dsDNA-Ab as well as other CLE biomarkers.
- **Skin Biopsy for Immunohistochemistry (IHC)**: Skin samples obtained from punch biopsies will be used for Immunohistochemistry and histology analysis.

Samples will remain confidential. These samples, and any additional samples derived from the original samples, may be stored and analyzed for up to 15 years after the study ends and the final results are reported (or according to local regulations). The Sponsor and its authorized representatives will ensure that samples are destroyed at the end of the storage period.

The timing of the PD assessments, including blood collections, to be performed during the study may be subject to change based on the ongoing review of the data. Furthermore, additional blood samples may be taken from each subject per treatment period per safety purpose. Any changes to the scheduled timepoints of PD assessments will be agreed with the Sponsor.

8.7 IMMUNOGENICITY ASSESSMENTS

Not applicable.

8.8 HEALTH ECONOMICS

Not applicable.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants (see Section 10.1.3) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

For participants who consent to the future use of biological samples, the left-over samples may be used after the study ends for future research related either to the drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions.

For this same purpose above, some clinical laboratory data generated in this study from participants who consent to will be shared with researchers as a third part. Participant's coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 25 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

In the event future research is conducted for other purposes not listed above, the study participants will be informed of those purposes and will be given means to object to those research projects. An additional written consent will be obtained from participants if this is the case.

Data and samples will be used in compliance with the information provided to participants in the ICF Part 2 (future research) and any applicable data protection laws.

All study participant data and samples will be coded such that no participant direct identifiers will be linked to them. Coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

The samples will be stored for a maximum of 15 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study participant who has requested the destruction of his/her samples).

Participant's coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 25 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

9 STATISTICAL CONSIDERATIONS

9.1 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 (39). 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.

9.2 POPULATIONS FOR ANALYSES

The following populations are defined (Table 5):

Table 5 - Populations for analyses

Population	Description
Screened	All participants who sign the ICF.
Randomized	All screened participants who are randomly assigned to the IMP (by IRT) regardless of whether the intervention was received or not.
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.
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.
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.

CLASI-A: Cutaneous Lupus Erythematosus Disease Area and Severity Index - A, ICF: informed consent form, IMP: investigational medicinal product, PK: pharmacokinetic.

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.

9.3 STATISTICAL ANALYSES

The statistical analysis plan (SAP) will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and a subset of secondary endpoints. The SAP will be developed and finalized prior to database lock or any interim analysis.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9): Contingency measures for a regional or national emergency that is declared by a governmental agency.

9.3.1 General considerations

Descriptive analyses will include summarization of quantitative variables (using n, mean, standard deviation, inter quartile range, median, minimum, and maximum) and qualitative data (by reporting absolute and relative frequencies).

The baseline value of efficacy parameters is defined as the Day 1 pre-dose assessment value unless otherwise specified.

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.

9.3.2 Primary endpoint(s)

The primary analysis will be performed on the Efficacy population through a mixed model with repeated measurements (MMRM) will be fitted to estimate the difference in percent change in CLASI-A from Baseline at Week 12. The model includes fixed effects for baseline CLASI-A, post-baseline visit, geographical region, disease subtype, baseline use of chloroquine or hydroxychloroquine, intervention group, visit by intervention group interaction, and visit-by-baseline CLASI-A interaction. Stratification factors will be included in the analysis model if a sufficient number of participants per stratum is available. Details will be specified in the SAP. Repeated measurements for each post-baseline visit are taken within subject (Table 6). Point estimate and two-sided 90% confidence interval for the difference of mean percent change between the 2 groups (SAR443122 versus placebo) will be derived from the linear model framework.

Table 6 - Primary endpoint analysis

Primary endpoint	Statistical analysis methods
Percent change in CLASI-A score from Baseline to Week 12.	The difference to placebo of mean percent change from Baseline in CLASI-A at Week 12 will be derived using a mixed model with repeated measurements (MMRM) including fixed effects for baseline CLASI-A, post-baseline visit, geographical region, disease subtype, baseline use of chloroquine or hydroxychloroquine, intervention group, visit-by- intervention group interaction, and visit-by-baseline-CLASI-A interaction. Repeated measurements for each post-baseline visit are taken within subject. Point estimate with 90% confidence interval for the difference of mean percent change at Week 12 between the 2 groups (SAR443122 versus placebo) will be derived.

CLASI-A: Cutaneous Lupus Erythematosus Disease Area and Severity Index - A.

Observed mean and mean percent change from Baseline in the primary endpoint will be summarized descriptively by intervention group and visit.

Details on the handling of participants requiring rescue medication will be detailed in the SAP.

9.3.3 Secondary endpoint(s)

Analysis of secondary efficacy endpoints will be performed on the Efficacy population.

The secondary endpoints defined as proportion of patients with Phys-GA disease activity being either 0 or 1 at Week 12 and proportion of patients with IGA-CLE of 0 or 1 (clear or almost clear) at Week 12 (Table 7) will be calculated using a logistic regression model with treatment, geographical region, disease subtype, baseline use of chloroquine or hydroxychloroquine, and subtype by intervention group interaction as fixed effects. Stratification factors will be included in the analysis model if a sufficient number of participants per stratum is available. Details will be specified in the SAP. A 90% confidence interval for the difference in proportions will be provided by back-transformation to the natural scale of the corresponding 90% confidence interval for the log-odds ratio.

Table 7 - Selected secondary endpoints analyses

Secondary endpoint	Statistical analysis methods
Proportion of patients with PhysGA-disease activity at Week 12 being either 0 or 1	The difference in proportion of subjects with PhysGA-disease activity in 0 or 1 will be estimated based on a logistic regression model with treatment, geographical region, disease subtype, baseline use of chloroquine or hydroxychloroquine, and subtype-by-intervention group interaction as fixed effects. A 90% confidence interval for the difference will be provided.
Proportion of patients with IGA-CLE score of 0 or 1 (clear or almost clear) at Week 12	The difference in proportion of subjects with IGA-CLE score of 0 or 1 will be estimated based on a logistic regression model with treatment, geographical region, disease subtype, baseline use of chloroquine or hydroxychloroquine, and subtype by intervention group interaction as fixed effects. A 90% confidence interval for the difference will be provided.

PhysGA-disease activity: Physicians Global Assessment of disease activity; IGA-CLE: Investigator's Global Assessment for Cutaneous Lupus Erythematosus.

The observed proportion of subjects with PhysGA-disease activity in 0 or 1 and with IGA-CLE score in 0 or 1 will be summarized descriptively by intervention group and visit, respectively.

Secondary endpoints other than adverse events, PCSAs, laboratory tests, ECG parameters, vital signs or pharmacokinetic parameters will be summarized descriptively by intervention group and visit, and their change from baseline will be presented where applicable.

Summaries of adverse events, PCSAs, laboratory tests, ECG parameters, vital signs as well as pharmacokinetic parameters are described in Section 9.3.5 below.

Additional details on further analyses of secondary endpoints will be provided in the SAP.

9.3.4 Exploratory endpoint(s)

Details on the analysis of exploratory endpoints will be provided in the SAP.

9.3.5 Analyses of safety data

The safety evaluation will be based upon the review of the individual values (clinically significant abnormalities), descriptive statistics (summary tables, figures) and, if needed, on statistical analysis (appropriate estimations, confidence intervals). No statistical significance tests will be performed on safety data.

Potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor, according to predefined criteria/thresholds based on literature reviews and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG parameters.

All the safety analyses will be performed using the safety population.

For all safety data variables, the following observation periods are defined and used for classification of AEs, determination of on-treatment PCSA values, and the last on-treatment value for laboratory and vital sign parameters:

- The pre-treatment period is defined as the time between informed consent signature and the first IMP administration.
- The treatment-emergent (TE) period is defined as the time from the first IMP administration up to the EoS visit (EoS included). It may be split further into the following periods:
  - On treatment period, defined as the time from the first IMP administration up 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.

9.3.5.1 Adverse events

9.3.5.1.1 Definitions

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; version in use by the Sponsor at the time of database lock). Clinical judgment should be used to determine the severity of AEs as described in Section 10.3.3.

Adverse events 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 AEs: 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 deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment period.

Analysis of all adverse events

Adverse event incidence table will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment emergent AESI (defined with a PT or a prespecified grouping), all treatment emergent SAEs and all TEAEs leading to permanent treatment discontinuation.

The AE summaries will be generated with number (%) of participants experiencing at least one event.

Deaths will also be analyzed if applicable.

Analysis of AEs, SAEs, AESIs, deaths and PCSAs are summarized in Table 8 and will be detailed in the SAP.

Table 8 - Safety analyses

Safety measures	Statistical analysis methods
Adverse events • AEs • TEAEs • SAEs • AEs leading to IMP discontinuation or study withdrawal • AEs leading to death • AESIs • PCSAs	Treatment-emergent adverse event incidence tables will be presented by system organ class, high-level group term, high-level term, and preferred term for each intervention group and overall, showing the number (n) and percentage (%) of participants experiencing a TEAE. Multiple occurrences of the same event in the same participant will be counted only once in the tables. The denominator for computation of percentages will be the safety population within each intervention group. In addition, TEAEs will be described according to maximum intensity and relation to the IMP. Adverse events that occur outside the treatment emergent period will be listed separately. Proportion of patients with at least 1 TEAE, treatment emergent SAE, AESI, TEAE leading to death, and TEAE leading to definitive treatment discontinuation will be tabulated by intervention group and overall. The incidence of PCSAs occurring during the TE period will be summarized by intervention group overall and by baseline status.

AE: adverse event, AESI: adverse event of special interest, IMP: investigational medicinal product, PCSA: potentially clinically significant abnormality, SAE: serious adverse event, TEAE: treatment-emergent adverse event.

9.3.5.2 Vital signs

Vital signs (respiration rate, temperature, pulse rate and blood pressure) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics for each intervention group.

9.3.5.3 Clinical safety laboratory

Laboratory results (hematology or clinical chemistry) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics for each intervention group.

9.3.5.4 Electrocardiogram

Electrocardiogram parameters will be summarized by intervention group as raw data and change from baseline to each assessment time with descriptive statistics based on the data collected.

9.3.6 Analyses of pharmacokinetic data

9.3.6.1 Pharmacokinetic parameters

SAR443122 concentrations at selected time points will be reported by intervention group using descriptive statistics on the Pharmacokinetic population.

Further details on the analysis of PK parameters will be described in the SAP.

9.3.6.2 Pharmacokinetic/Pharmacodynamic analysis

The analysis of PK/PD relationship will be described in the SAP.

9.4 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 patients have completed study treatment or discontinued the study. The interim analysis will not lead to changes in the conduct of the protocol other than stopping recruitment for this proof of concept study due to clear efficacy signal at the time of the interim analysis or due to lack of an efficacy signal, indicating a lack of equipoise for continued recruitment of patients. The details including the pre-specified rules for stopping the recruitment will be described in the SAP.

The interim analysis will evaluate the mean percent change from baseline in CLASI-A at Week 12 and other selected secondary efficacy endpoints, as well as the safety endpoints as needed. The PK and PD relationship could also be explored.

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 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.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR).
- The protocol, protocol amendments, ICF, Investigator Brochure, [IDFU] and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.

- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participants, and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the Global Data Protection Regulation (GDPR) and of the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s). Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc).
- A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 9 (Section 10.9): Contingency Measures for a regional or national emergency that is declared by a governmental agency.

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because they are expected to modify the drug response and because they are required by regulatory agencies (eg, on African American population for the FDA). They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study.
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:

- The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
- Sanofi's Binding Corporate Rules for intra-group transfers.

- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committee structure

10.1.5.1 Internal Safety Review Committee

This study will establish an unblinded ISRC which is independent from study team and Investigators to conduct the review of safety data (all AEs, including SAE and AESIs) as well as selected clinical laboratory parameters, and to make recommendations to the study team regarding the continuation, modification including additional safety measures, a temporary halt or termination of the trial. The assessment of available safety data and selected clinical laboratory data (as defined in the ISRC charter) will be done periodically. Enrollment may be held during the safety review only on the recommendation of the ISRC at their discretion. The ISRC chair may call for Ad hoc meetings at any point if the ongoing safety report data warrants this measure in their judgement. The structure, membership and exact responsibilities of the ISRC are detailed in the respective charter.

10.1.6 Dissemination of clinical study data

Study participants

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to vivli.org.

Individual participant data and supporting clinical documents are available for request at vivli.org. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: vivli.org.

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organizations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in CRF completion instructions.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Monitoring Plan.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is considered the first act of screening and will be the study start date.

Study/Site termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio.
  - Discontinuation of further study intervention development.
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
  - Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 9 will be performed.
- For tests to be performed by the central laboratory, local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing.

Table 9 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	
	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	RBC indices:
	MCV
	MCH
	%Reticulocytes
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry	
	Blood urea nitrogen (BUN)
	Creatinine
	Creatinine phosphokinase (CPK)
	Glucose [fasting]
	Potassium
	Sodium
	Calcium
	Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase[a]
	Total and direct bilirubin
	Total protein
Urinalysis	• Specific gravity
	• pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick
	• Microscopic examination (including pyuria, hematuria and urinary casts)
Spot Urine test	• Urine protein test
	• Urine creatinine test

Laboratory tests	Parameters
Pregnancy testing	• Serum or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[b]
Other screening tests	• Please refer to Section 1.3 for a complete list of screening test • All study-required laboratory tests will be performed by a central laboratory with the exception of: - TB screening testing - COVID-19 screening testing - Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) - Hepatitis B DNA testing as needed The results of each test must be entered into the eCRF.

NOTES:
a If alkaline phosphatase is elevated, consider fractionating.
b Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results (eg, PK/PD) that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of unsolicited and solicited AE

- An unsolicited adverse event is an adverse event that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

- Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected during interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any adverse event that, at any dose:

a) **Results in death**

b) **Is life-threatening**

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) **Requires inpatient hospitalization or prolongation of existing hospitalization**

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) **Is a congenital anomaly/birth defect**

f) **Other situations:**

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
    - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
  - Development of drug dependence or drug abuse
  - ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN
  - Suicide attempt or any event suggestive of suicidality
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
  - Bullous cutaneous eruptions

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. "Severe" is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor and/or health authority. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** the Sponsor and/or health authority**.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the health authority and the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in Investigator study file.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in Investigator study file.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below).

- A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods include:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry eligibility.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first administration of study intervention, additional evaluation should be considered.

10.4.2 Contraception guidance

- If locally required, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly effective methods[b] that have low user dependency Failure rate of <1% per year when used consistently and correctly.
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly effective methods[b] that are user dependent Failure rate of <1% per year when used consistently and correctly.
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] - oral - intravaginal - transdermal - injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] - oral - injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c Male condoms must be used in addition to hormonal contraception

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

- For the Unite Kingdom, acceptable forms of effective contraception include:
  - Established use of oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation;

- Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS);
- Bilateral tubal occlusion;
- Male sterilization (provided that the partner is the sole sexual partner of the WOCBP study participant and that the sterilized partner has received medical assessment of the surgical success).

- True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive the IMP.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

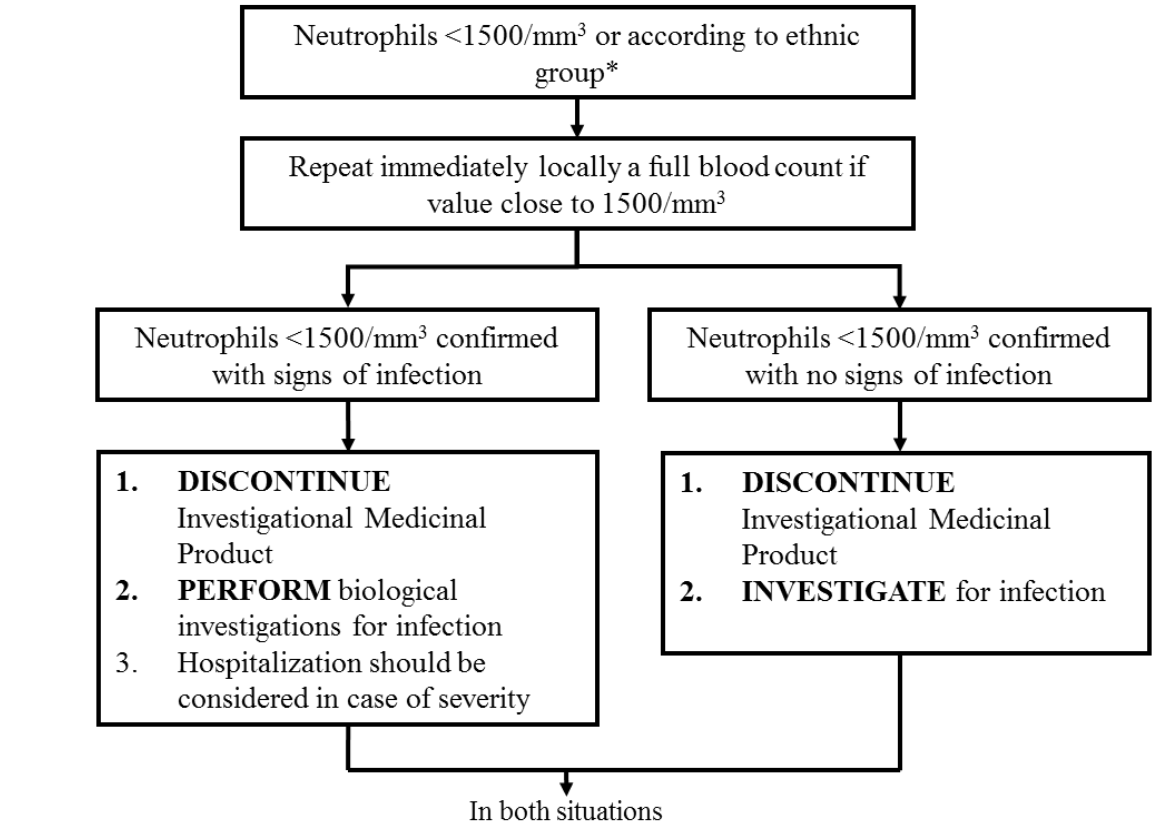
10.5 APPENDIX 5: GENETICS

Use/Analysis of DNA/RNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA and RNA analysis from consenting participants. Skin biopsy sample will be collected for RNA analysis from study participant.
- DNA/RNA samples will be used for research related to SAR443122 or CLE and related diseases. They may also be used to develop tests/assays including diagnostic tests related to SAR443122 and/or RIPK1 kinase class and CLE. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA/RNA samples will be analyzed for changes related to treatment and/or disease progression compared to baseline and placebo controls to evaluate their association with the observed clinical responses to SAR443122. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to SAR443122 or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The Sponsor will store the genetic samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on SAR443122 or study interventions of this class or CLE and related diseases continues but no longer than 15 years or other period as per local requirements.

10.6 APPENDIX 6: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS AND STUDY INTERVENTION RECHALLENGE GUIDELINES

NEUTROPENIA

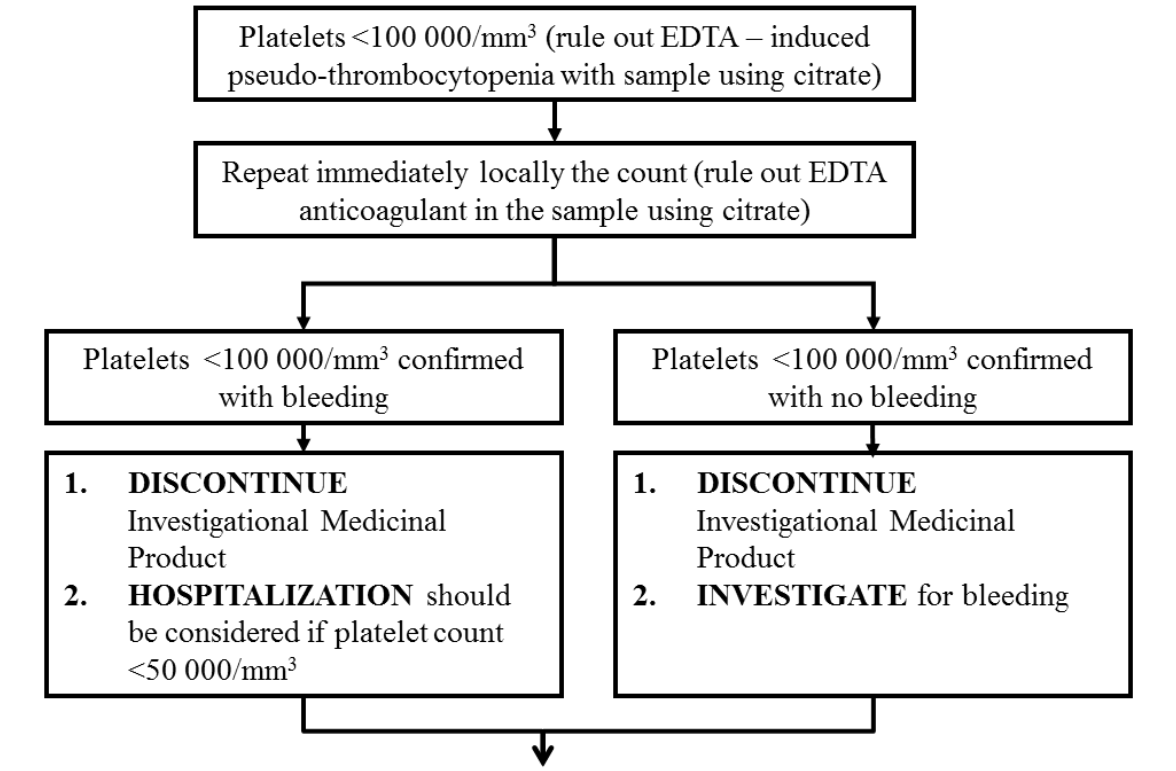


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts, Absolute Neutrophil Count (ANC)
   - Infectious serologies to be performed locally, according to clinical symptoms / medical history
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)**
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

***** For individuals of African descent, the relevant value of concern is <1000/mm3

Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.3.3 is met.

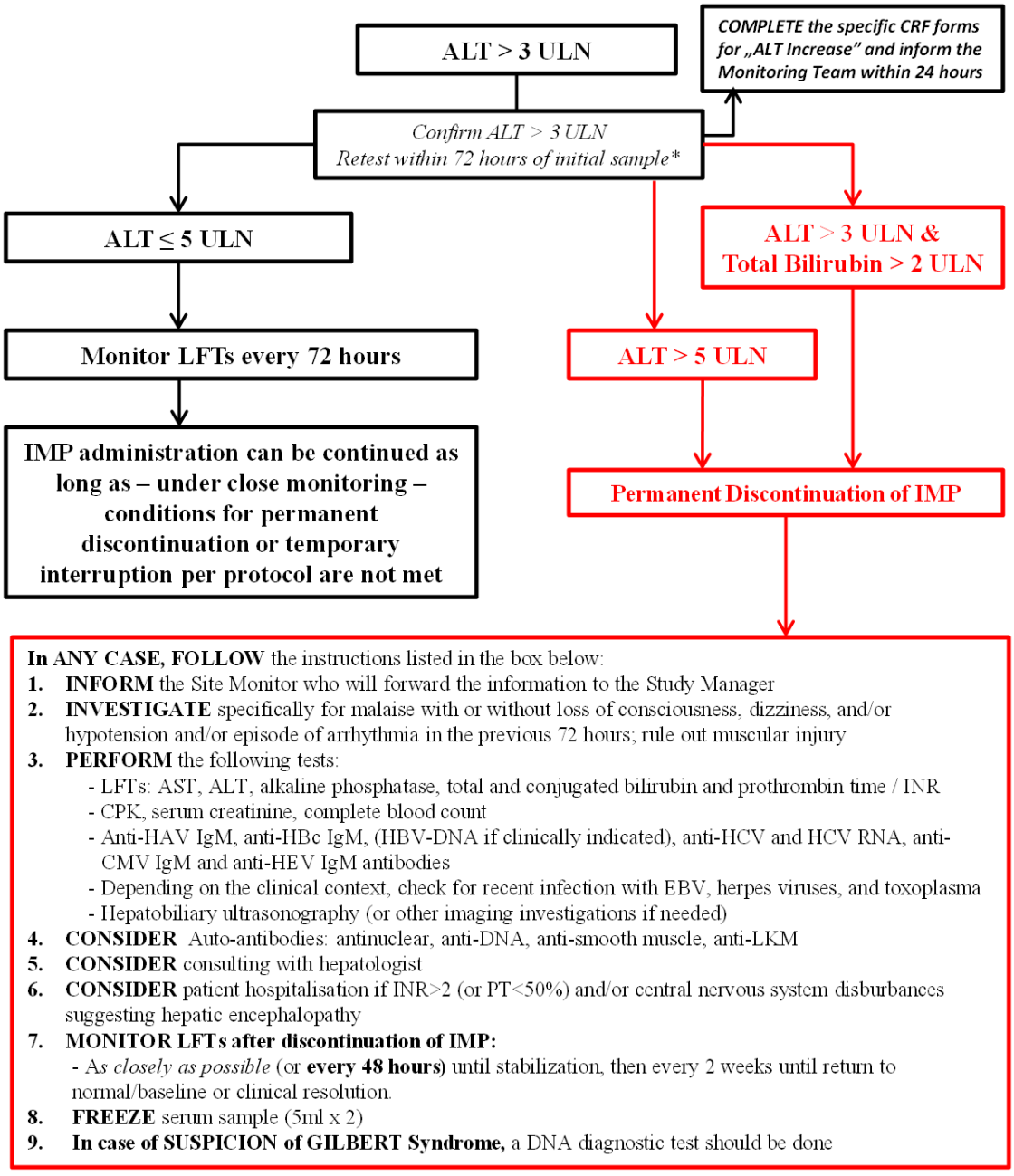
THROMBOCYTOPENIA



3. **INFORM** the local Monitor
4. **QUESTION** about alcohol habits, any drug intake including quinine (drinks), heparin administration, aspirin, immunotherapy, etc.
5. **PERFORM** or collect the following investigations:
   - Complete blood count, schizocytes, creatinine
   - Locally:
     - Bleeding time and coagulation tests (INR or PT, aPTT, D-Dimers)
     - Infectious serologies to be performed according to clinical symptoms / medical history
6. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)**
7. **DECISION** for bone marrow aspiration to be taken in specialized unit
8. **MONITOR** the platelet count every day for at least one week and then regularly until it returns to normal

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.3.3 is met.

INCREASE IN ALT



In ANY CASE, FOLLOW the instructions listed in the box below:

1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM, (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** consulting with hepatologist
6. **CONSIDER** patient hospitalisation if INR>2 (or PT<50%) and/or central nervous system disburbances suggesting hepatic encephalopathy
7. **MONITOR LFTs after discontinuation of IMP:**
   - As *closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to normal/baseline or clinical resolution.
8. **FREEZE** serum sample (5ml x 2)
9. **In case of SUSPICION of GILBERT Syndrome,** a DNA diagnostic test should be done

*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

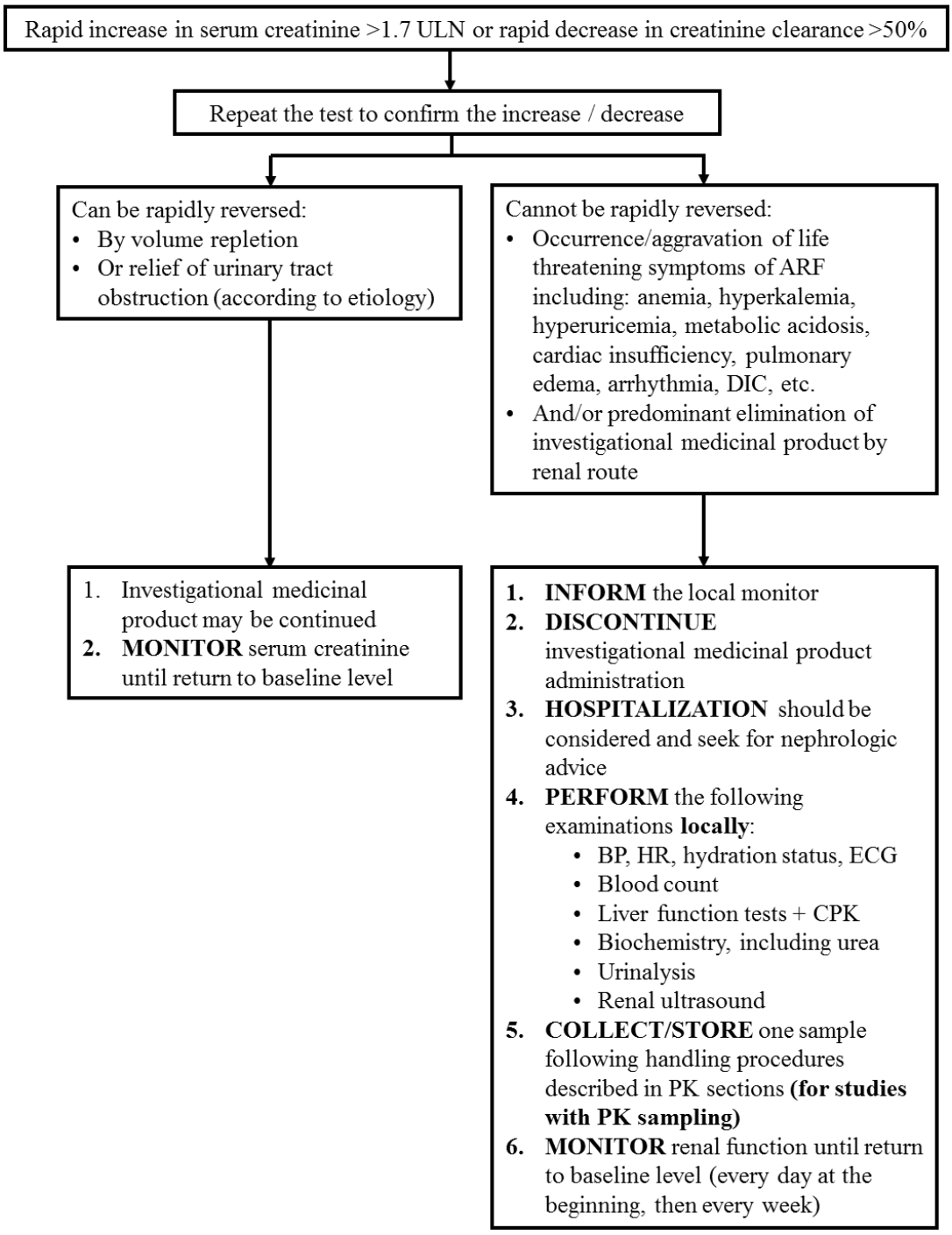
Note:

"Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.

See Section 10.3.3 for guidance on safety reporting.

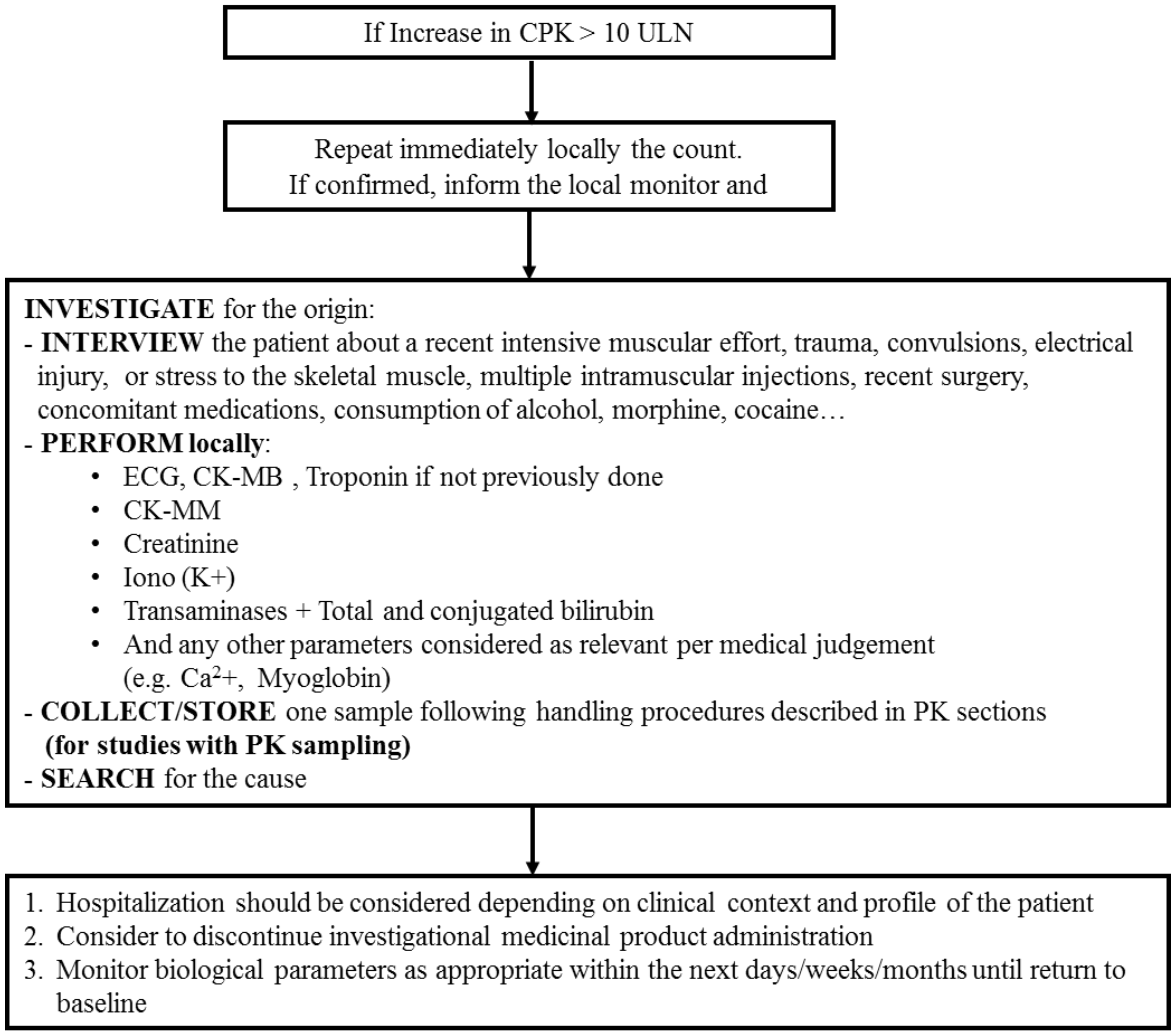
Normalization is defined as ≤ ULN or baseline value, if baseline value is > ULN.

INCREASE IN SERUM CREATININE in patients with normal baseline (creatininemia between 45 µmol/L and 84 µmol/L)



Increase in serum creatinine is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.3.3 is met.

INCREASE IN CPK OF NON-CARDIAC ORIGIN AND NOT RELATED TO INTENSIVE PHYSICAL ACTIVITY



Increase in CPK is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting adverse events in Section 10.3.3 is met.

10.7 APPENDIX 7: AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

For country-specific contraceptive guidance, see Section 10.4.2.

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement must be obtained prior to the implementation of these procedures for the duration of the emergency.

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical trial should be proposed, and screening/enrollment/randomization/administration of study intervention may be temporarily delayed.

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

Contingencies implemented due to emergency will be documented.

The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local labs).

Study assessments and procedures

Use of local clinic or laboratory locations may be allowed when central labs analyses cannot be performed due to a government declared national emergency.

If onsite visits are not possible:

- remote visits (eg, phone call, virtual consultation, etc) or home visits (eg, home nurses, home health vendor, etc) may be planned for the collection of possible safety and/or efficacy data (eg, adverse events, blood sampling, patient-reported questionnaires, etc)
- visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely [eg, vital signs, physical examination, ECG, CLASI-assessment and other physician-assessed questionnaires, index lesion photography, biopsy]. Possibility of visit extension and duration of such extension must be discussed on a case by case basis with the Sponsor considering first of all subject's safety and best interests.

If onsite visits are possible and there is a need to reduce the time spent on site to a minimum, combined-approach can be considered:

- during onsite visit, the focus should be on IMP dispensation, collection of safety information (vital signs, physical examination, adverse events), safety blood collection (mainly biochemistry and hematology) and efficacy endpoints (eg, CLASI, PhyGA-disease activitiy, IGA-CLE if applicable, etc). However, all efforts should be made to perform the measurements of other parameters for efficacy endpoints. These would include photography and biopsy.
- And to complete other assessments that can be obtained in a remote fashion.

Study intervention

The following contingencies may be implemented to make clinical supplies available to the participant for the duration of the emergency.

- The Direct-to-Patient (DTP) supply of IMP from the PI/site/Sponsor via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant.
- Delivery by authorized staff during home visits, following clear defined procedures (IMP shipment process, safety protection of patients and staff, data protection etc).

If a participant has to stop IMP due to a regional or national emergency (eg, COVID-19), reinitiation of IMP can only occur once the Investigator has determined, according to his/her best judgement, that the contribution of the IMP(s) to the occurrence of the epidemic event (eg, COVID-19) was unlikely and the selection criteria for the study are still met. Reinitiation of the study intervention will be done under close and appropriate clinical/and or laboratory monitoring.

Statistical analyses

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

10.10 APPENDIX 10: ADDITIONAL APPENDICES

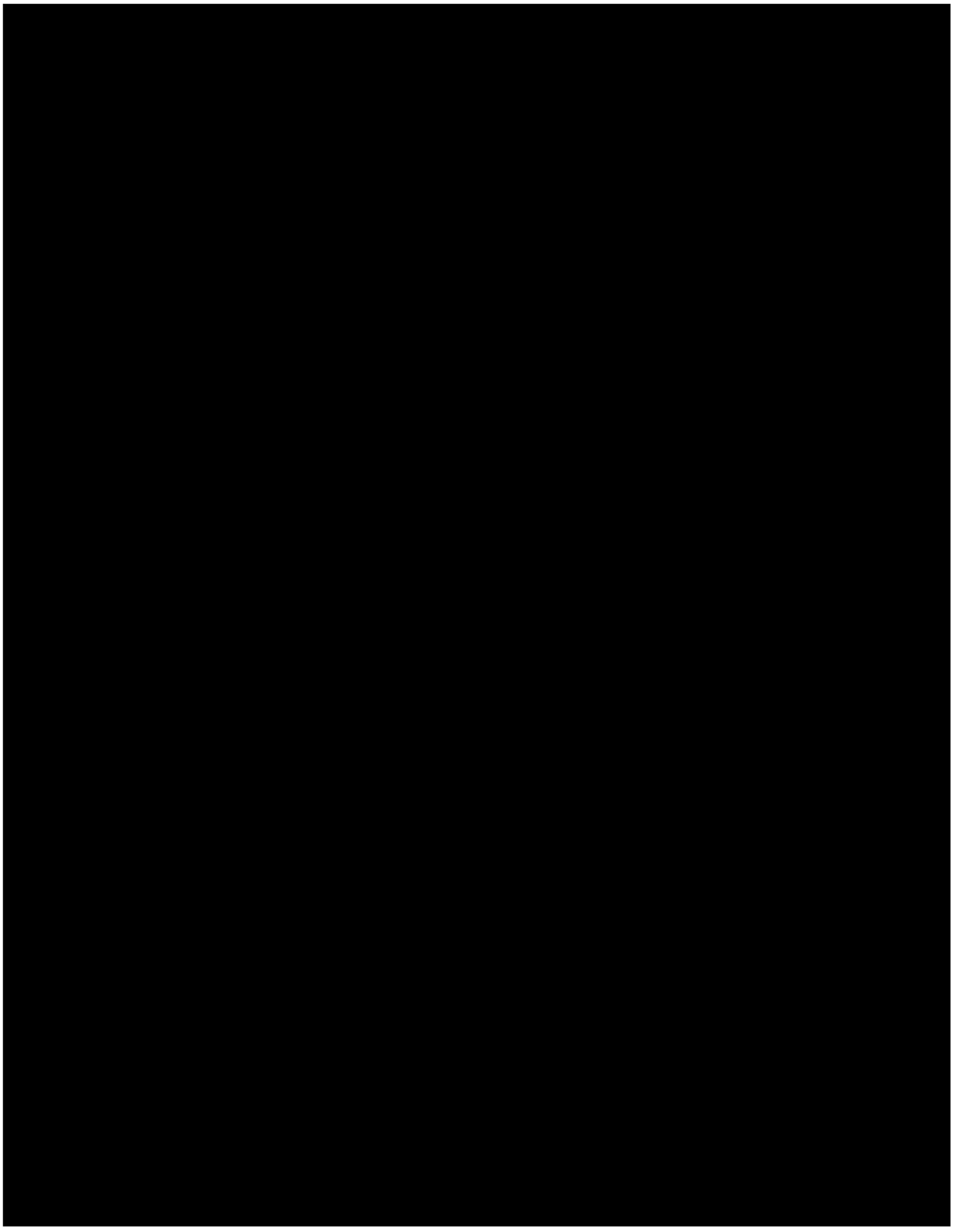
10.10.1 List of topical corticosteroids

This list is indicative and not exhaustive.

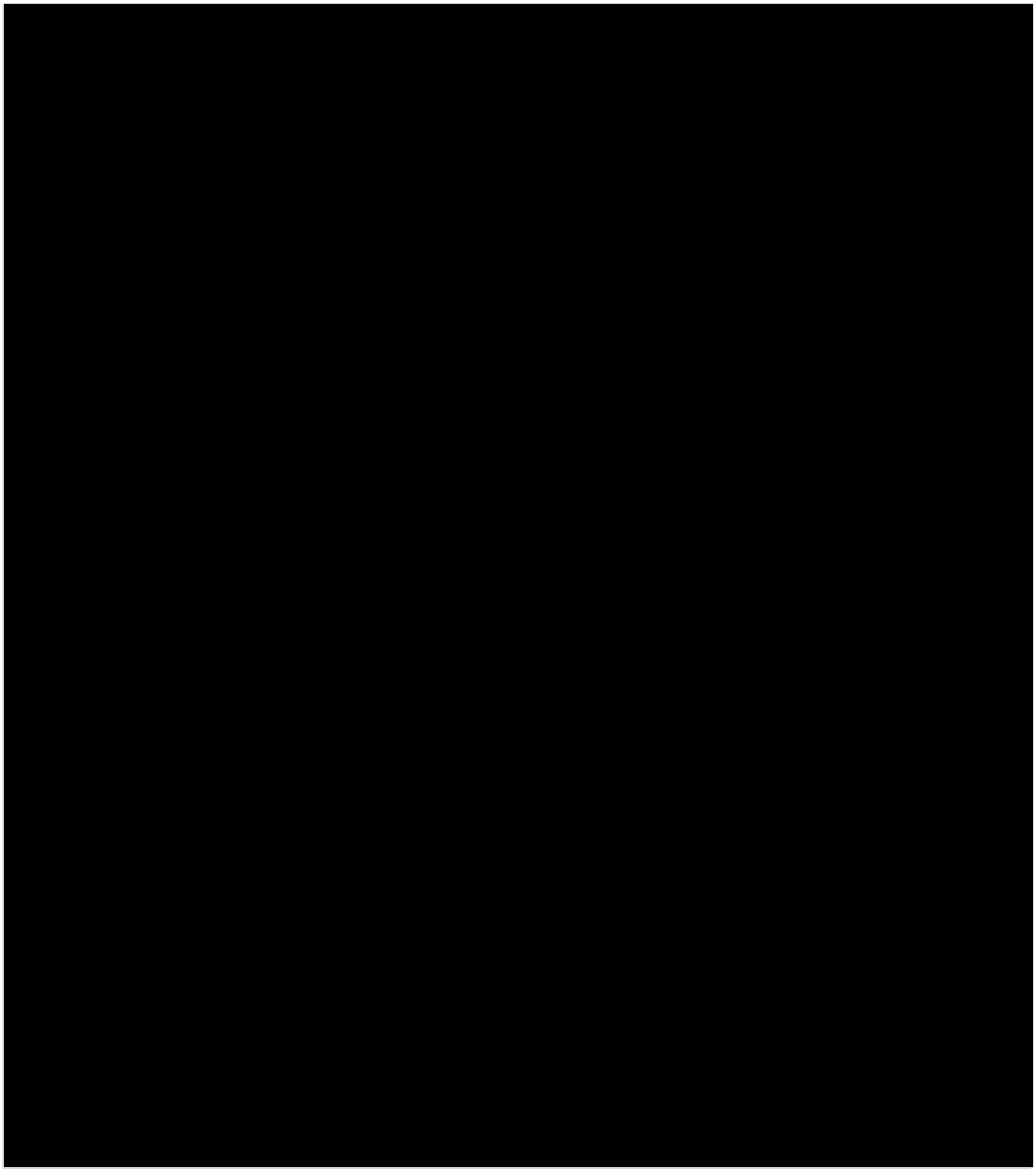
Topical corticosteroid	Formulation(s)	Strength
Super High potency (For Rescue only)		
Betamethasone dipropionate, augmented	Ointment	0.05%
Clobetasol propionate	Solution, Foam, Cream, Ointment	0.05%
Diflorasone diacetate	Ointment	0.05%
Halobetasol propionate	Cream, Ointment	0.05%
High (For Rescue Only)		
Amcinonide	Lotion, Cream, Ointment	0.1%
Betamethasone dipropionate	Foam, Cream, Ointment	0.05%
	Cream, Ointment	0.025%
	Cream, Ointment, Solution, Lotion, Gel	0.064%
Betamethasone butyrate propionate	Lotion, Cream, Ointment	0.05%
Betamethoasone valerate	Ointment, Foam	0.05%
	Cream, Ointment	0.12%
Deprodone propionate	Cream, Ointment	0.3%
Desoximetasone	Cream, Ointment	0.25%
Dexamethasone propionate	Lotion, Cream, Ointment	0.1%
Dexamethasone valerate	Cream, Ointment	0.12%
Diflorasone diacetate	Cream, Ointment	0.05%
Diflorcortolone valerate	Solution, Cream, Ointment	0.01%
Difluprednate	Lotion, Cream, Ointment	0.05%
Fluocinonide	Solution, Gel, Cream, Ointment	0.05%
Halcinonide	Solution, Cream, Ointment	0.1%
Mometasone furoate	Ointment	0.1%
Medium Potency		
Betamethasone dipropionate	Lotion	0.02%
Betamethasone valerate	Foam, Lotion, Cream	0.1%
	Lotion, Cream	0.12%
Clobetasone butyrate	Lotion, Cream, Ointment	0.05%
Desoximetasone	Cream	0.05%
Fludroxycortide	Cream, Tape	0.05%, 4 µg/m^2
Flumethasone pivalate	Lotion, Cream, Ointment	0.02%
Fluocinolone acetonide	Solution, Cream, Ointment	0.025%

Topical corticosteroid	Formulation(s)	Strength
Hydrocortisone butyrate	Lotion, Cream, Ointment	0.1%
Hydrocortisone valerate	Cream, Ointment	0.2%
Mometasone furoate	Lotion, Cream	0.1%
Prednicarbate	Cream	0.1%
Prednisolone	Cream, Ointment	0.5%
Prednisolone acetate	Ointment	0.25%
Prednisolone valerate acetate	Lotion, Cream, Ointment	0.3%
Triamcinolone acetonide	Lotion, Cream, Ointment	0.1%
Low Potency		
Alclometasone dipropionate	Cream, Ointment	0.05%
	Ointment	0.1%
Desonide	Foam, Gel, Cream, Ointment	0.05%
Dexamethasone sodium phosphate	Lotion, Cream, Ointment	0.1%
	Cream, Ointment	0.05%
Fluocinolone acetonide	Solution, Cream	0.01%
	Spray	0.007%
Hydrocortisone acetate	Lotion, Cream, Ointment	≤1%
Methylprednisolone	Ointment	0.1%

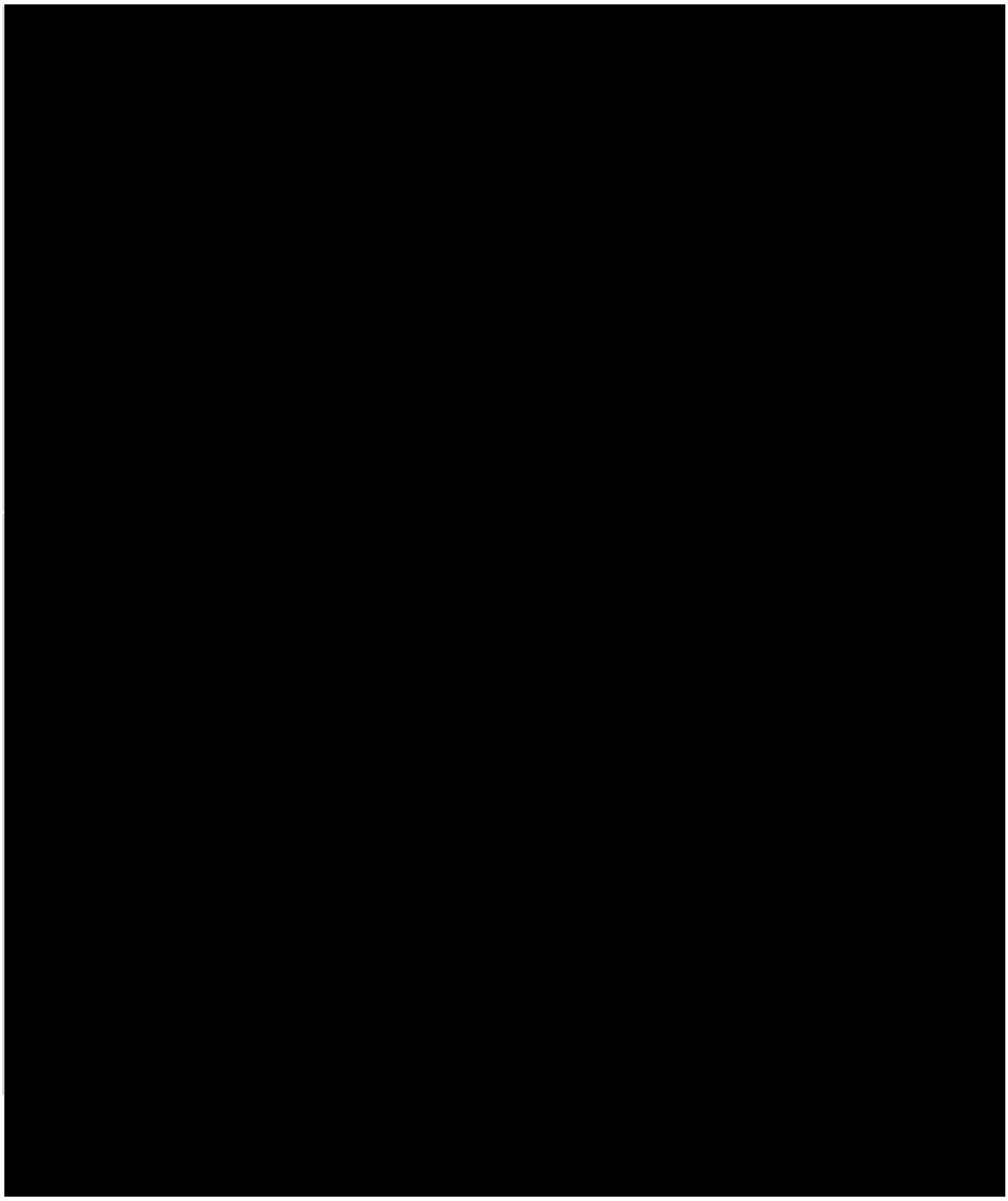
10.10.2 Sample of Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)



10.10.3 Sample of Physician Global Assessment of disease activity (PhysGA- disease activity) and Physician Global Assessment of changes in cutaneous lupus erythematosus activity (PGAC)



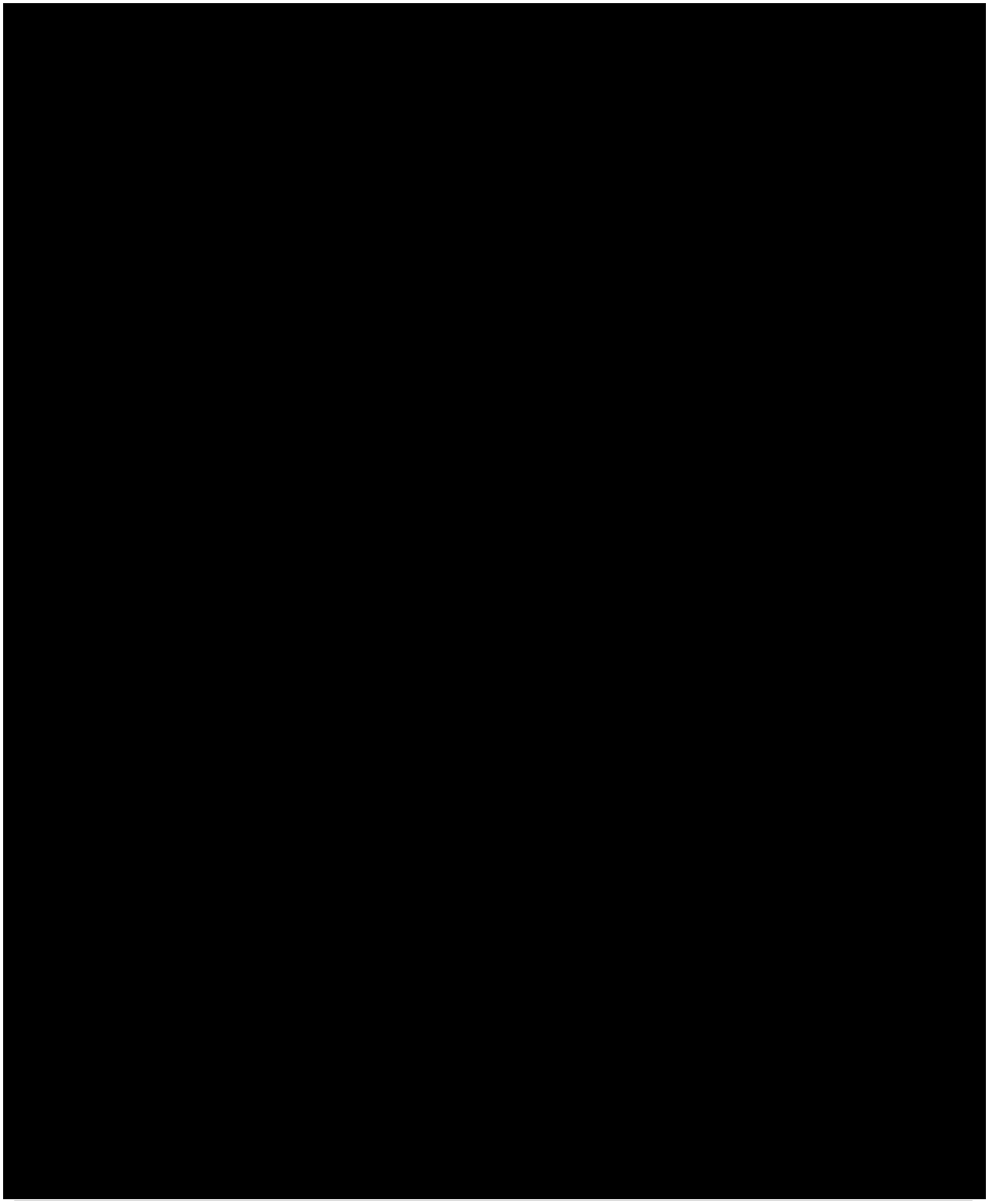
10.10.4 Sample of Patient-Reported Peak Pruritus Numerical Rating Scale (itch-NRS) and Peak Pain Numerical Rating Scale (Pain-NRS)

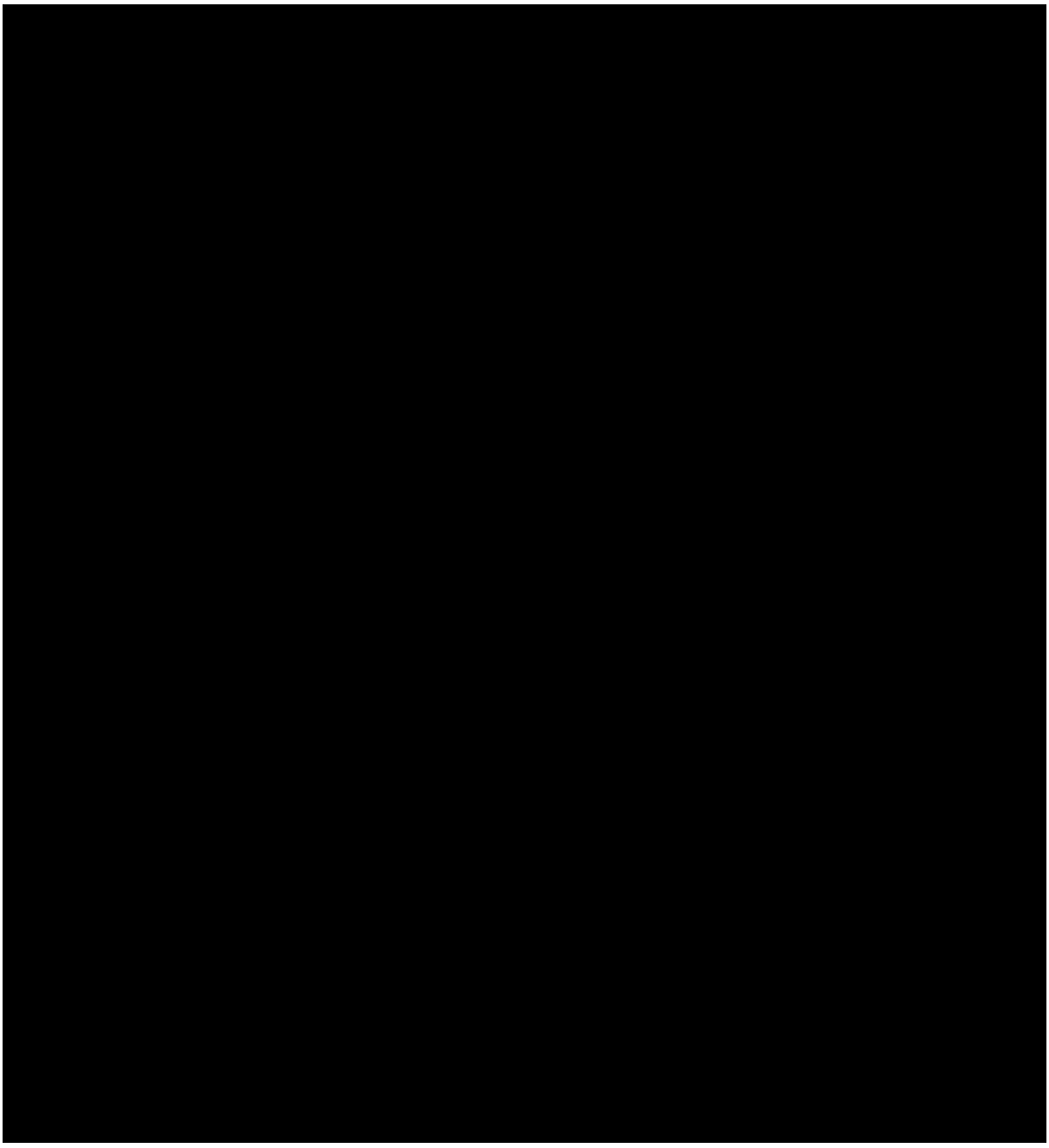


10.10.5 Sample of Oral Health Impact Profile (OHIP-14)

The University of North Carolina at Chapel Hill
School of Dentistry

Oral Health Impact Profile





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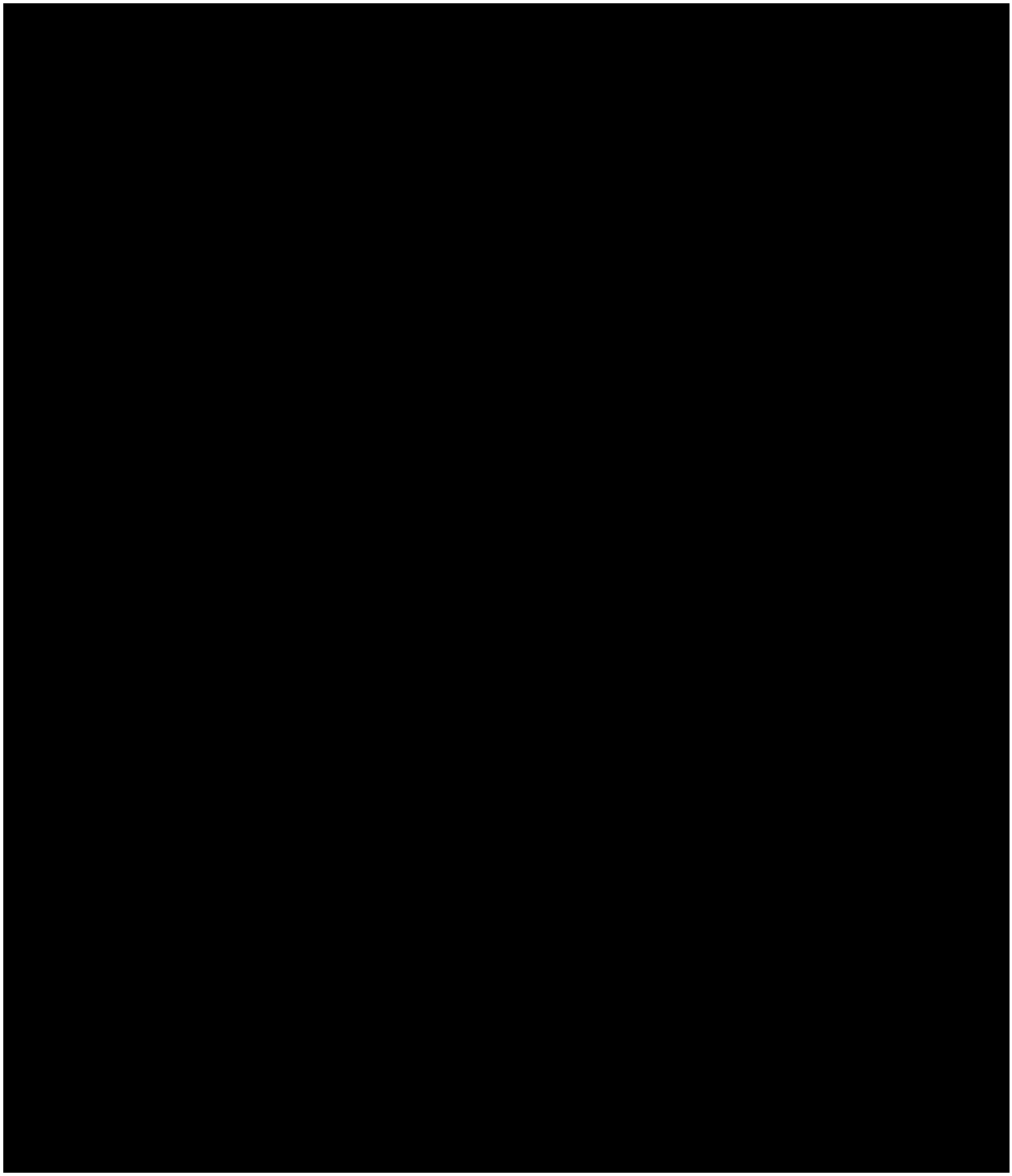
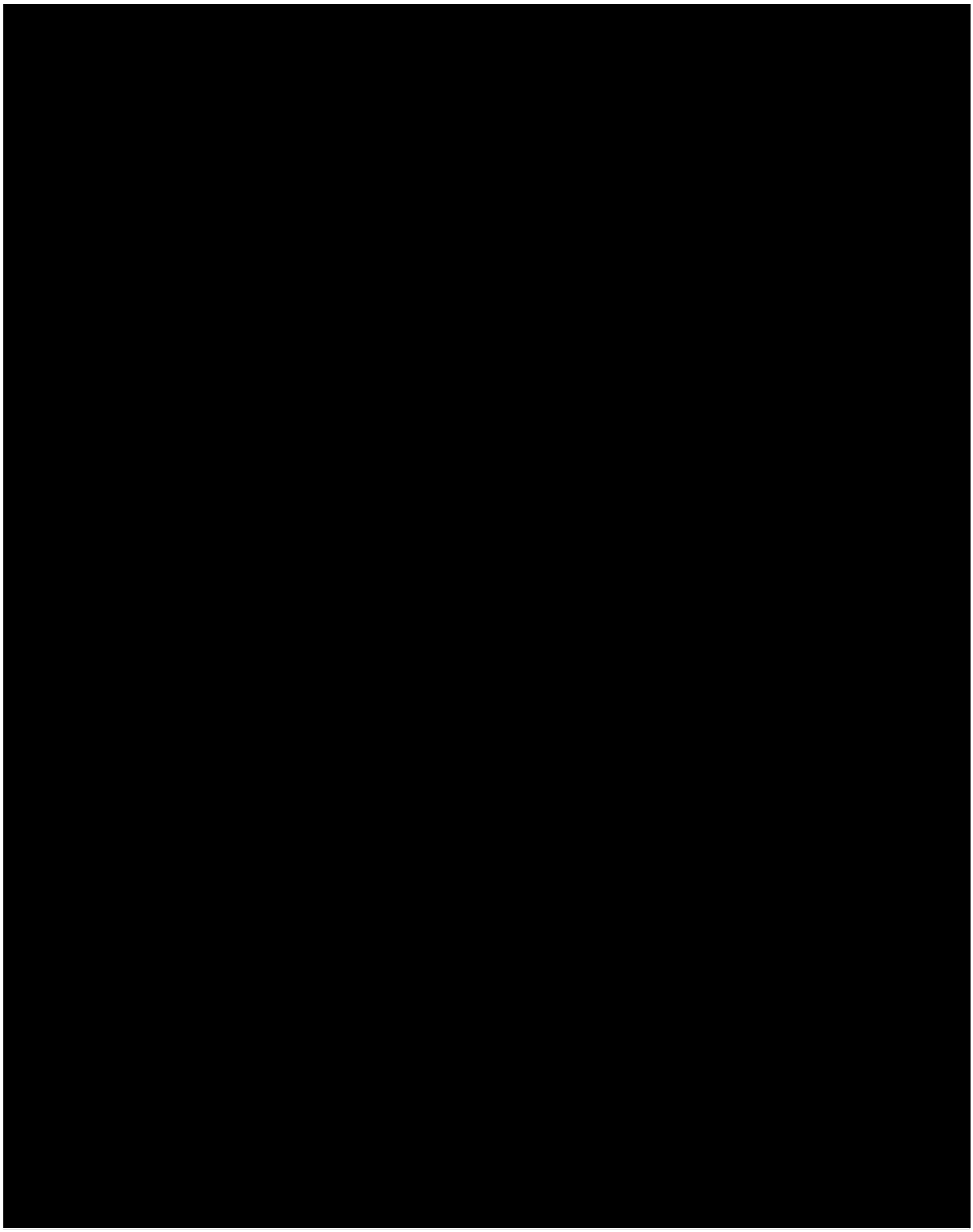
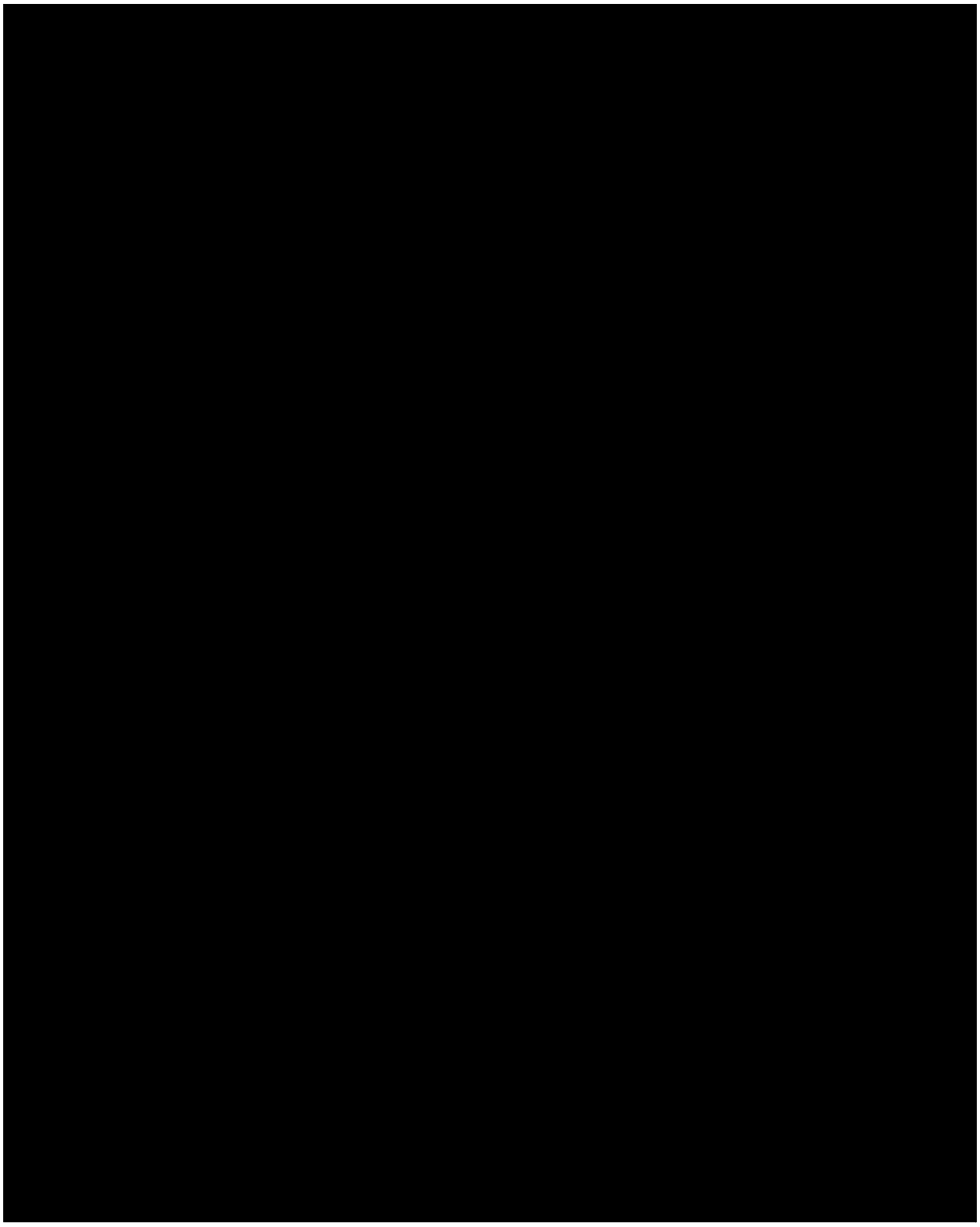
10.10.6 Sample of SKINDEX-29+3

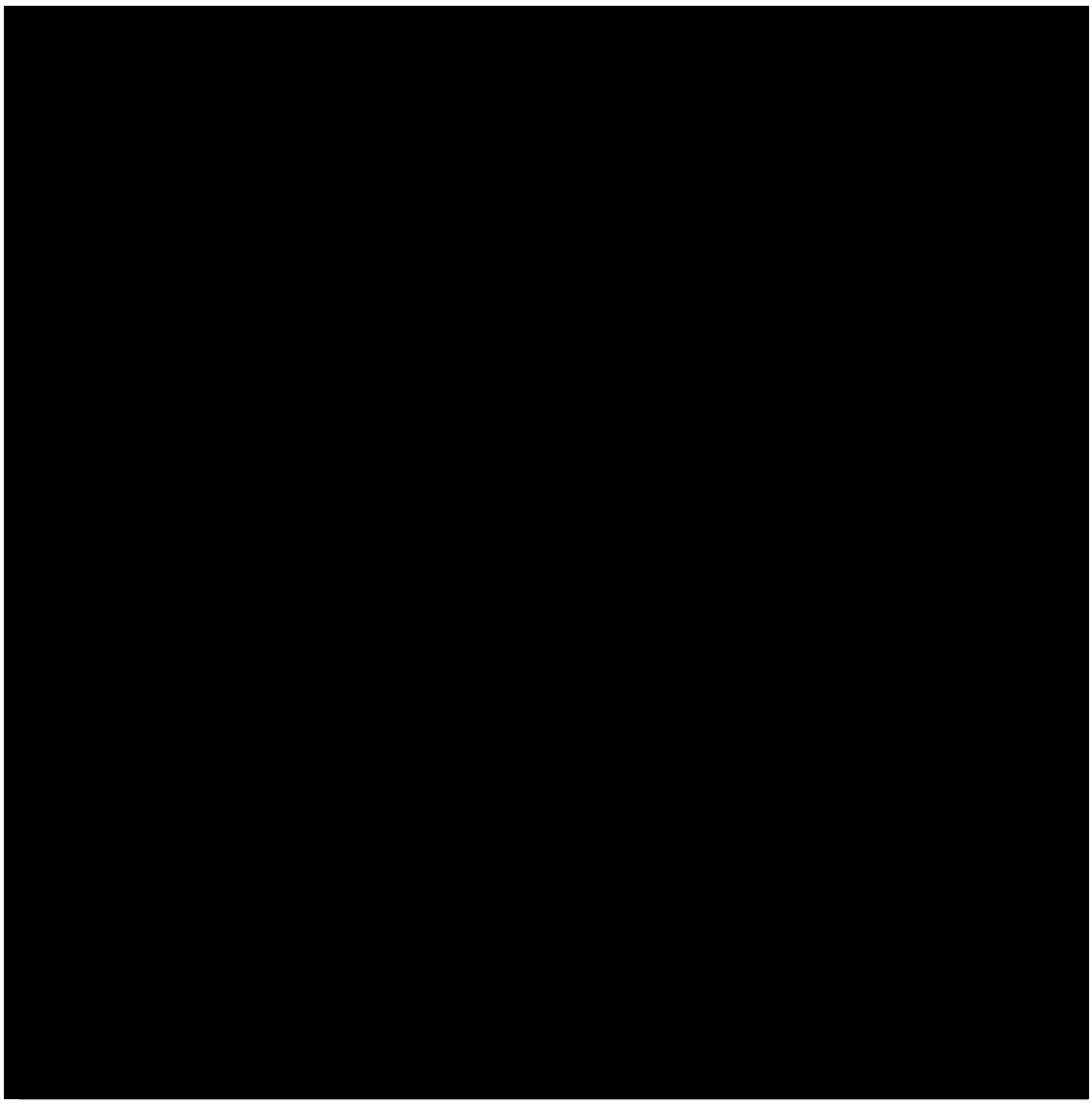
Skindex29
©MMChren,1996







10.10.7 Sample of Patient Global Impression of Change (PGIC) and Severity (PGIS) in cutaneous lupus erythematosus



10.10.8 Sample of Investigator's Global Assessment for Cutaneous Lupus Erythematosus Activity (IGA-CLE)

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.**

Cutaneous Lupus Activity Investigator's Global Assessment (IGA-CLE)	
Score	**Description**
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/follicular hyperkeratosis* in more than two quadrants of scalp **Secondary change** – marked erosion, crusting and/or vesicular change present

10.11 APPENDIX 11: ABBREVIATIONS

AE: adverse events
AESI: adverse event of special interest
ALT: alanine transaminase
ANA: antinuclear antibody
BID: twice a day
CCLE: chronic cutaneous lupus erythematosus
CLASI: Cutaneous Erythematosus Disease Area and Severity Index
CLASI-A: Cutaneous Erythematosus Disease Area and Severity Index - Activity
CLASI-D: Cutaneous Erythematosus Disease Area and Severity Index-skin damange
CLE: cutaneous lupus erythematosus
ClinRO: clinician reported outcome
CNS: central nervous system
DAMP: danger-associated molecular pattern
DLE: discoid lupus erythematosus
ECG: electrocardiogram
EOS: end of study
EOT: End of Treatment
EOT: end of treatment
FIH: first-in-human
GELP: Genital Erosive Lichen Planus
ID: interface dermatitis
IGA-CLE: Investigator's Global Assessment of CLE
IMP: Investigational medicinal product
INF: interferon
ISRC: internal safety review committee
itch-NRS: Peak Pruritus Numerical Rating Scale
LP: lichen planus
MAD: multiple ascending dose
NOAEL: no observed adverse effect level
NRS: numerical rating scale
OHIP-14: Oral Health Impact Profile
pain-NRS: Peak Pain Numerical Rating Scale
PBMC: peripheral blood mononuclear cell
PCSA: potentially clinically significant abnormality
PD: pharmacodynamics
PGAC: physician's global assessment of change in disease activity
PGIC: patient's global impression of change
PGIS: patient's global impression of disease severity
PhysGA-disease activity: physician's global assessment of disease activity
PK: pharmacokinetics
pMLKL: phosphorylated mixed lineage kinase domain-like protein
PRO: patient reported outcomes

QoL: quality of life
RIPK1: Receptor-Interacting serine-threonine Protein Kinase 1
SAE: serious adverse event
SCLE: subacute cutaneous lupus erythematosus
SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index
SGC: systemic glucocorticoid
SLE: systemic lupus erythematosus
TB: tuberculosis
TE: treatment-emergent
TEAE: treatment-emergent adverse event
TLR: toll-like receptor
TNF: tumor necrosis factor
ULN: upper limit of normal
UV: ultraviolet
WOCBP: woman of childbearing potential

10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY

The Protocol amendment summary of changes table for the current amended protocol 02 is located directly before Table of Contents.

10.12.1 Amended protocol 01 (10 DEC 2021)

This amended clinical trial protocol 01 (amendment 01) is considered to be not substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union. Because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

Overall Rationale for the Amendment

The main purpose of this amendment is to remove the 50% randomization cap for the discoid cutaneous lupus erythematosus (DLE) subtype.

Cutaneous Lupus erythematosus (CLE) is a heterogeneous skin disease with a wide spectrum of presenting cutaneous manifestations that have been subdivided into several subtypes. The present study is targeting the subacute cutaneous lupus erythematosus (SCLE) and discoid cutaneous lupus erythematosus (DLE) subtypes. While the pathophysiology of CLE is not fully understood, some publications suggest that the treatment response might be subtype dependent (40). DLE is known to be the most common subtype (9). To optimize the differential assessments of both subtypes, the original protocol included a cap at 50% for the DLE subtype. The sponsor now decided to remove the cap for the DLE subtype patients for a study population being more reflective of the natural distribution of the CLE population and to allow completion of the study within a reasonable time.

It is mentioned in the section 8 that "The clinician reported outcome (ClinRO) mentioned in the SoA will be used when copyright is obtained (if applicable)". Modified Oral Mucositis Index (MOMI) will not be used in the study as its full copyright has not been obtained. To improve the readability, the sponsor takes this opportunity to remove the text related to MOMI throughout the document. Other corrections of discrepancies, minor editorial errors identified during initial protocol submission and wording clarity have been made as well.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page	Added NCT number	Regulatory agency identifier number(s) is available
Section 1.1 Synopsis, Section 4.1 Overall Design, Section 6.3 Measures to minimize bias: randomization and blinding	Context related to "a cap of 50% for patients with histologically proven DLE will be implemented" was removed.	To be more reflective of the natural distribution of the CLE population and to allow completion of the study within a reasonable time.
Section 1.1 Synopsis, Section 3 Objectives and Endpoints Section 1.3 Schedule of Activities (SoA), Section 3.1 Appropriateness of Measurements, Section 8.1.6 Modified Oral Mucositis Index (MOMI), Section 10.9 Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency	Secondary Endpoint: "Change from baseline to Week 12 in Modified Oral Mucositis Index (MOMI) at Week 12 for patients with oral lesions at baseline" is deleted. Context related to MOMI was deleted.	To improve the readability as the MOMI will not be used in the study because copyright wasn't obtained (as per initial plan highlighted in Section 8: *The clinician reported outcome (ClinRO) mentioned in the SoA will be used when copyright is obtained (if applicable)*).
Section 2.3.1 Risk assessment: table 1	Reorganized table 1	To improve the clarity without content change
Section 6.3 Measures to minimize bias: randomization and blinding	Replaced "the Investigator should make every effort to contact the Sponsor" by "he/she may, at his/her discretion, contact the Sponsor to discuss the situation"	To improve the appropriateness of language related to the unblinding process as per a health authority's comment
Section 7.1.1.1 Handling of participants after permanent intervention discontinuation	Modified "skin biopsy and pharmacokinetics sample" to "skin biopsy, pharmacokinetic samples, and photography at Week 12". Foot note "u" was newly inserted in Section 1.3.	To improve the clarity

Section # and Name	Description of Change	Brief Rationale
Section 8.1.5 Investigator's Global Assessment for Cutaneous Lupus Erythematosus (IGA-CLE), Section 10.10.8 Sample of Investigator's Global Assessment for Cutaneous Lupus Erythematosus (IGA-CLE)	Added more detailed information on IGA-CLE assessment and provided an example in appendix.	To provide a more detailed description of IGA-CLE assessment in order to improve the clarity
Section 8.2.3 Electrocardiograms	Clarified "*QTcB or QTcF*" to "*QTcF*".	To provide more precision
Section 8.3.8 Adverse event of special interest	Added reference of calculation formula *(per QTcF)* to "*QTc ≥500 ms*".	
Section 8.6 Biomarkers	"Immunohistochemistry analysis" was replaced by "Immunohistochemistry and histology analysis".	To provide more precision
Section 9 Statistical Considerations	Aligned the names of the analysis populations with current Sponsor's standard. Removed a duplicated content in Section 9.3.5.3 (The same content is provided in Table 8) Added more detail description throughout the section	To improve precision and clarity
All sections throughout	Minor editorial and typographical error corrections.	To improve readability and overall quality of the document

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