ALE11

EVALUATION OF TOFACITINIB IN PREVENTION OF PHOTOSENSITIVITY IN CUTANEOUS LUPUS ERYTHEMATOSUS

VERSION 7.0/OCTOBER 25, 2023
IND-EXEMPT

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National Institute of Allergy and Infectious Diseases

SITE INVESTIGATOR SIGNATURE PAGE	
Protocol Number: ALE11	Version Number: 7.0/Date: October 25, 2023
Protocol Title: Evaluation of Tofacitinib in Prevention of Photosensitivity in Cutaneous Lupus Erythematosus	
Study Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)	
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I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, 312, and 812 and in the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) document titled *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2).* Further, I will conduct the study in keeping with local legal and regulatory requirements.

As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID.

**The site Principal Investigator should print, sign, and date at the indicated location below. A written Signature/date is acceptable (e.g., scanned and sent via email as a PDF version)., An electronic signature is acceptable (e.g., sent via email as a PDF version).*

_____

Site Principal Investigator (Print)

_____ _____

Site Principal Investigator (Signature) Date

Protocol Synopsis

Title	Evaluation of Tofacitinib in Prevention of Photosensitivity in Cutaneous Lupus Erythematosus
Clinical Phase	Phase I
Number of Sites	1-3
Sponsor/IND Number	DAIT/NIAID, NIH/IND #154164, IND-Exempt
Study Objectives	**Primary Objective** 1. To determine whether a 25-day regimen of tofacitinib impacts photosensitivity following UVB exposure in individuals with cutaneous lupus erythematosus (CLE). **Secondary Objectives** 1. To evaluate changes in cutaneous disease activity in individuals with CLE after a 25-day regimen of tofacitinib. 2. To evaluate changes in systemic lupus erythematosus (SLE) disease activity in individuals with CLE after a 25-day regimen of tofacitinib. 3. To evaluate safety and toxicity of a 25-day regimen of tofacitinib for individuals with CLE.
Study Design	This is a single-arm, multi-site, proof-of-concept study of 10 participants with CLE. Consenting individuals meeting all entry criteria will undergo 25 days of treatment with tofacitinib (11 mg orally (PO) daily) with evaluation of UVB-mediated cutaneous apoptosis and ancillary mechanistic studies before and after treatment. Post-screening study visits will be conducted on Days 0 (Visit 1), 1 (Visit 2), 14 (Visit 3), 25 (Visit 4), 26 (Visit 5), and 40 (Visit 6) to (1) evaluate adverse events, vital signs, hematology and chemistry, study drug compliance, medication use, and disease status, (2) conduct UVB phototesting, and (3) collect skin biopsies and blood samples for mechanistic studies. Tofacitinib will be distributed to eligible participants at Visit 2 (Day 1) and the first dose will be taken on Day 2. The last dose is the morning of Visit 5 (Day 26). Participants are allowed to continue on their stable background therapies for lupus according to Section 7.1.2, *Other Permitted Concomitant Medications*. Please refer to Section 8.1.1, *Exceptions to Visit Windows*, and Section 6.6, *Resumption of Investigational Product,* for more information regarding delays to visits 4 and 5.

Primary Endpoint	**Primary Endpoint** The change in percentage of UVB-induced apoptotic epidermal cells from Visit 2 (Day 1) (pre-treatment) to Visit 5 (Day 26) (post-treatment). Percentage of UVB-induced apoptotic cells at a visit is defined as the difference between the percentage of apoptotic epidermal cells in the UVB-exposed biopsy and percentage of apoptotic epidermal cells in the unexposed biopsy at the same visit. More information can be found in Section 8.5.5, *Research Assessments*.
Accrual Objective	10 participants completing two phototests at least 3 weeks apart.
Study Duration	This study is estimated to last 1 year.
Treatment Description	Participants will receive a 25-day regimen of tofacitinib 11 mg daily.
Inclusion Criteria	1. Cutaneous lupus erythematosus based upon all of the following: a. a clinical diagnosis made by a rheumatologist or dermatologist of one of the following: acute cutaneous lupus erythematosus, subacute cutaneous lupus, or chronic cutaneous lupus erythematosus; b. active skin disease within 5 years prior to screening. Participants may have concomitant SLE. 2. SLEDAI-2K score ≤4 (clinical criteria only, excludes all laboratory criteria) for all participants regardless of whether they have concomitant SLE. 3. If taking oral corticosteroids, the dose must be ≤ 10 mg daily of prednisone (or equivalent), stable dose for at least 4 weeks, and not anticipated to change over the course of the study. 4. If taking oral anti-malarial medications, the dose(s) must be ≤ 100 mg daily for quinacrine or/and ≤ 400 mg daily for hydroxychloroquine, stable for at least 6 months, and not anticipated to change over the course of the study. 5. If taking oral or subcutaneous methotrexate, the dose must be ≤ 25 mg weekly, stable for at least 4 weeks, and not anticipated to change over the course of the study. 6. If taking oral leflunomide, the dose must be ≤ 20 mg daily, stable for at least 4 weeks, and not anticipated to change over the course of the study. 7. If taking oral mycophenolate mofetil (MMF) or mycophenolic acid, the dose must be equivalent to ≤ 3000 mg of MMF daily, stable for at least 4 weeks, and not anticipated to change over the course of the study. 8. Adults 18 to 65 years of age at screening.

	9. All participants and/or their sexual partners who engage in sexual activity that could lead to pregnancy must be willing to use complete abstinence or an FDA-regulated form of contraception for the duration of the study and for at least one month after discontinuation of study drug to prevent pregnancy. Highly effective birth control methods include, but are not limited to, hormonal contraception, an intrauterine device, or surgical options. Periodic abstinence and withdrawal are not acceptable methods of birth control.
Exclusion Criteria	1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol. 2. Current or recent history, within the last year, of uncontrolled clinically significant renal, hepatic, hematologic, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, or neurologic disease or significant impairment that might negatively impact the participant's ability to participate or that may put a participant at increased risk. 3. Potential active nephritis and/or urinary tract infection at screening, defined as any one of the following determined at screening unless otherwise specified: a. >10 RBCs /hpf, b. >5 WBCs /hpf with either positive nitrites or greater than a trace leukocyte esterase, c. Signs or symptoms of a urinary tract infection, d. For individuals with no history of nephritis: Urine protein (mg/dL): creatinine (mg/dL) ratio (Pr/Cr)>0.5 at screening or a Pr/Cr level that has exceeded 1.0 in the prior 12 months, e. For individuals with a history of nephritis: A rise in Pr/Cr of >0.5 over the prior 3-6 months prior to screening. 4. History of severe gastrointestinal narrowing or strictures. 5. Medically confirmed history of diverticulitis or chronic, ulcerative lower gastrointestinal (GI) disease such as Crohn's disease, ulcerative colitis, or other symptomatic, lower GI conditions that might predispose a participant to perforations. 6. History of thrombosis, pulmonary embolism, or antiphospholipid syndrome. 7. History of any one of the following anti-phospholipid antibodies: a. Positive lupus anticoagulant test, or b. Anti-β2-glycoprotein I IgG ELISA titer ≥ 40 GPL, or c. Anti-cardiolipin IgG ELISA titer ≥ 40 GPL. 8. History of chronic pulmonary disease requiring supplemental oxygen including chronic obstructive pulmonary disease (COPD) requiring chronic treatment, interstitial lung disease (ILD) requiring

	immunosuppressive therapy, and asthma requiring chronic steroid (other than inhaled steroid) or biologic therapy. 9. History of moderate to severe atherosclerotic cardiovascular disease as evidenced by prior coronary artery bypass surgery, coronary artery stent placement, myocardial infarction, symptomatic carotid arterial disease, peripheral vascular disease, abdominal aortic aneurysm; or angina within the past 8 weeks prior to Visit 1 (Day 0). 10. History of keloid scarring. 11. History of any lymphoproliferative disorder or other malignancy with the exception of successfully treated or excised basal cell or squamous cell skin cancer or cervical cancer in situ. 12. Other autoimmune diseases likely to require immunosuppression. 13. Any of the following lab results at screening: a. Hemoglobin <9.5 g/dL b. White Blood Cell count <3.5 x 10^9/L c. Absolute Neutrophil count <1.2 x 10^9/L d. Platelet count <120 x 10^9/L e. Absolute Lymphocyte count <0.75 x 10^9/L f. Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) > 1.5 × the upper limit of normal (ULN) g. Total bilirubin > ULN h. Estimated glomerular filtration rate [GFR] <60mL/min/1.73 m^2 i. Triglycerides ≥ 300 mg/dL (fasting not required) j. Total Cholesterol ≥ 240 mg/dL (fasting not required). 14. Major surgery < 8 weeks prior to Visit 1 (Day 0). 15. Hospitalized for serious infection < 4 weeks prior to Visit 1 (Day 0). 16. Chronic infections other than chronic or intermittent uncomplicated urinary tract infections (including but not limited to tuberculosis, chronic pyelonephritis, osteomyelitis). 17. Presumed or documented COVID-19 infection within 30 days prior to Visit 1 (Day 0). 18. Recent (within one month prior to screening) close contact with a person who has active TB infection. 19. History of untreated active or latent TB infection. 20. History of incompletely treated active or latent TB infection unless at least one month of treatment has been completed prior to screening. 21. Positive Interferon-Gamma Release Assay (IGRA) or positive purified protein derivative tuberculin skin test (PPD) (> 5mm induration) at screening. 22. An indeterminate IGRA at screening unless followed by a subsequent negative IGRA or negative PPD. 23. History of human immunodeficiency virus (HIV).

	24. A positive test for HIV antigen/antibody or nucleic acid test (NAT) at screening. 25. History of a hepatitis B infection. 26. A positive test for hepatitis B surface antigen or hepatitis B core antibody at screening. 27. History of a hepatitis C infection. 28. A positive test for hepatitis C antibody (regardless of whether hepatitis C RNA levels are undetectable) at screening. 29. History of recurrent (more than one episode) herpes zoster, one or more episodes of any of the following: herpes zoster ophthalmicus, or disseminated herpes zoster, or disseminated herpes simplex. 30. Current, recent (< 4 weeks prior to Visit 1 (Day 0)) or chronic use of antibiotic medication, except for suppression of chronic/recurrent urinary tract infection, which is allowed. 31. Simultaneous use of more than one of the following: leflunomide, methotrexate and MMF. 32. Any of the following active medications (oral or parenteral): cyclosporine, voclosporin, cyclophosphamide, tacrolimus, rituximab or other anti-CD20s, or any other investigational or marketed biologic with immunomodulatory properties within a year prior to Visit 1 (Day 0). 33. Any of the following medications (oral or parenteral): azathioprine or belimumab within 3 months prior to Visit 1 (Day 0). 34. Any prior treatment with cell-depleting therapies other than anti-CD20s including but not limited to CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19 products. 35. Intravenous or intramuscular corticosteroids within 2 weeks prior to Visit 1 (Day 0). 36. Treatment with any investigational agent ≤ 4 weeks or ≤ 5 half-lives of the investigational drug prior to Visit 1 (Day 0), whichever is longer. 37. Treatment with more than one dose of ketoconazole within one week of screening. 38. Any prior treatment with chlorambucil, bone marrow transplantation, or total lymphoid irradiation. 39. Vaccinated or exposed by close contact, e.g., within a household, to a live/attenuated vaccine ≤ 6 weeks prior to Visit 1 (Day 0); or is expected to be vaccinated or to have household exposure to these vaccines during treatment or during the 6 weeks following discontinuation of study medication. 40. Received a non-live vaccine ≤ 2 weeks prior to initiation of study drug, or unwillingness of a participant to delay non-live vaccination until 1 month after completion of study therapy. 41. Pregnant or breastfeeding females.

	42. History of alcohol or substance abuse, unless in full remission for greater than 6 months prior to first dose of study drug. 43. Past or current medical or psychiatric conditions or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.
Study Stopping Rules	There are no pre-specified study stopping rules. An ad hoc comprehensive DSMB review will occur as a result of any of the following events: • Any death considered possibly or definitely related to study treatment or procedures. • The occurrence in 2 participants of Grade 3 or higher AEs or SAEs with the same MedDRA preferred terms considered at least possibly related to study treatment or procedures. • The occurrence in 2 participants of Grade 3 or higher infections. • Any grade 2 or higher thromboembolic event. After review of the data, the DSMB will make recommendations regarding the study conduct and/or continuation.

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Glossary of Abbreviations

ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APGAR	Appearance, Pulse, Grimace, Activity, and Respiration
AST	Aspartate Aminotransferase
CAPA	Corrective Action/Preventive Action
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLE	Cutaneous Lupus Erythematosus
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
DLE	Discoid Lupus Erythematosus
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
FFPE	Formalin Fixed Paraffin-Embedded
GCP	Good Clinical Practice
GI	Gastrointestinal
HDL	High-Density Lipoprotein
Hpf	High powered field
ICH	International Council for Harmonization
IGRA	Interferon-Gamma Release Assay
IND	Investigational New Drug
IFN_k	Interferon kappa
IRB	Institutional Review Board
JAK-1	Janus Kinase 1 Inhibitor
LDL	Low-Density Lipoprotein
MED	Minimal Erythema Dose
MMF	Mycophenolate mofetil

NAT	Nucleic Acid Test
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PBMCs	Peripheral Blood Mononuclear Cells
pcJIA	Polyarticular Course Juvenile Idiopathic Arthritis
PHI	Personal Health Identifiers
PI	[Site] Principal Investigator
PP1	Per Protocol 1
PP2	Per Protocol 2
PPD	Purified Protein Derivative
Pr/Cr	Urinary Protein (mg/dL):Creatinine (mg/dL) ratio
RA	Rheumatoid Arthritis
SACCC	Statistical and Clinical Coordinating Center
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SD	Standard Deviation
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SUSAR	Serious Unexpected Suspected Adverse Reaction
SLE	Systemic Lupus Erythematosus
SS	Safety Sample
TB	Tuberculosis
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
UV	Ultraviolet
UVB	Ultraviolet B

1. Background and Rationale

1.1. Background and Scientific Rationale

Disease Impact: Exposure to ultraviolet (UV) light can serve as a trigger for cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) disease flares[1] making it one of the few definitive known triggers for these diseases. Complicating our ability to treat UV light-induced cutaneous and systemic lupus disease flares is an incomplete understanding of the mechanisms which drive this phenomenon. Targeted systemic treatment to reduce the effect of UV light would be a novel and important mechanism for reduction in disease flare rate and potentially even treatment of these patients.

Scientific Rationale of Proposed Study: UV light is a known trigger of CLE lesions[2] and induces apoptosis through several pathways[3]. It has been reported that CLE lesions are characterized by increased apoptosis[4]. One hypothesis on the etiology of CLE lesions is that increased apoptosis following ultraviolet B (UVB) exposure of "normal skin" leads to autoantigen exposure in an environment where antigen clearance is impaired (as in lupus)[5]. This coupled with a robust keratinocyte-mediated inflammatory response promotes inflammatory cell recruitment to the skin where autoantigens are taken up, processed, and presented to autoreactive T cells. Interferon kappa (IFNκ) is overexpressed in non-lesional lupus skin and is a key regulator of apoptotic responses to UVB. Indeed, enhanced UVB-driven apoptosis can be induced by overexpressing IFNκ in N/TERT keratinocytes. Further, deletion of IFNκ is sufficient to significantly impair UVB-mediated apoptosis[6]. This suggests that the level of IFNκ present can serve as a rheostat for UVB-mediated apoptosis. Indeed, in non-lesional keratinocytes, enhanced apoptosis in SLE versus control can be abrogated by blocking type I IFN signaling via a Janus Kinase 1 (JAK1) inhibitor[6]. Patients with isolated CLE lesions and those with CLE as a manifestation of SLE exhibit high levels of IFNκ in their skin lesions, and both groups of patients have indistinguishable cutaneous IFN signatures [6, 7]. Thus, in CLE-prone skin, photosensitive reactions driven by keratinocyte apoptosis and increased cytokine production are primed for by IFNκ and are potentially inhibited through blockade of IFN signaling via JAK inhibition.

There is a gap in our knowledge regarding how non-lesional skin of individuals with CLE responds to UV light and whether blockade of IFN signaling will alleviate photosensitivity. Small trials and case reports have suggested that tofacitinib is beneficial in SLE and CLE patients, but none of these studies have evaluated photosensitivity as part of their studies[8] [9, 10]. This study will provide information on how JAK blockade impacts photosensitive responses and whether this strategy could be considered as a prophylactic measure to prevent cutaneous and systemic lupus flares. As CLE is a known manifestation of photosensitive reactions, we will study CLE patients for this trial.

1.2. Rationale for Selection of Investigational Product

What is the nature of the product to be tested? Tofacitinib is a Food and Drug Administration (FDA)-approved JAK3/JAK1 inhibitor that is used for treatment of rheumatoid arthritis, psoriatic arthritis, ulcerative colitis and polyarticular course Juvenile Idiopathic Arthritis (pcJIA). Despite its ability to block both JAK3 and JAK1 signaling, it is able to inhibit type I IFN signaling and IL-6 pathways with equal efficacy to baricitinib, where JAK1 is its primary target [11]. Based on published data, which shows blockade of JAK1 signaling *in vitro* normalizes SLE keratinocyte cell death after UVB [6], we hypothesize that treating individuals with CLE with tofacitinib will reduce UVB-mediated apoptosis and

consequently improve photosensitivity parameters. We thus propose to test this hypothesis by treating patients with tofacitinib 11 mg daily for 25 days and by performing photosensitivity testing and skin biopsies before and after treatment to investigate the impact on disease mechanisms.

Xeljanz®(tofacitinib) 5 mg BID and Xeljanz® XR (tofacitinib) 11 mg daily are approved for rheumatic conditions. Both have shown equivalent efficacy[12]. For this protocol, Xeljanz® XR 11 mg once daily was selected as the dosing regimen in order to reduce the number of pills the participants are required to take on a daily basis and thus increase compliance with dosing. Twenty-five days of dosing was chosen to provide for normalization of steady state levels with once daily dosing while limiting the overall exposure to the medication. Steady state of Xeljanz® XR 11 mg occurs within 5 days of dosing[13] to levels sufficient to inhibit peripheral immune signaling[14]. However, tissue penetration and signaling effects in the skin may require longer exposure, thus the 25-day dosing regimen prior to phototesting will be employed in this study.

Advantages of Using Tofacitinib

1. Once daily dosing
2. Has been tested in small Phase I/II study of SLE patients without safety signals[8].
3. FDA approved for other autoimmune conditions, i.e., rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and pcJIA, with extensive safety profile in these conditions.

1.3. Preclinical Experience

Murine studies support potential efficacy in lupus. In lupus-prone MRL/^{lpr} mice, treatment with tofacitinib results in improvement of cutaneous lesions as well as a decreased risk of developing nephritis[15]. Additional follow-up murine studies in the MRL/^{lpr} model have shown that tofacitinib impairs the survival and effector functions of pathogenic CD8+ T resident memory cells[16]. In an interferon-driven model of murine lupus, NZB/NZW F_1, tofacitinib also reduced interferon signatures and improvement in nephritis[17].

1.4. Clinical Studies

Tofacitinib is FDA approved for the treatment of rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and pcJIA, and dosed at 5 mg twice daily (BID) or 11 mg daily (extended release, XR). Tofacitinib is not currently approved for use in CLE or SLE patients. A Phase I/II study which enrolled 30 SLE patients with mild to moderate disease activity to assess safety in SLE patients (no skin measurements taken) with 56 days of active drug treatment of 5 mg BID, did not identify any serious adverse events (SAE) and there was no increase in adverse events over placebo[8]. A case series also reported partial to complete efficacy for skin and arthritis in 10 patients with SLE treated with tofacitinib 5 mg BID[18]. Currently, there are several additional small studies of tofacitinib: one with plans to enroll 12 adult discoid lupus erythematosus (DLE) patients in an open label pilot study to look at clinical changes[19]; one enrolling 20 young (18-30 years) patients with CLE for pharmacodynamics studies. Data from dose-ranging studies in SLE are not available. No long-term studies to evaluate toxicology or efficacy in lupus patients have yet been performed.

2. Study Hypotheses/Objectives

2.1. Hypotheses

In individuals with CLE, a 25-day regimen of tofacitinib will:

- reduce UVB-mediated cutaneous apoptosis,
- reduce UVB-mediated inflammatory gene transcription, and
- increase minimal erythema dose (MED) after UVB exposure.

2.2. Primary Objective

The primary objective is to determine whether a 25-day regimen of tofacitinib impacts photosensitivity following UVB exposure in individuals with CLE.

Photosensitivity parameters will be measured before and after tofacitinib treatment and will include: UVB-mediated cutaneous apoptosis, UVB-mediated inflammatory gene transcription, and MED in response to UVB exposure.

2.3. Secondary Objectives

The secondary objectives are as follows:

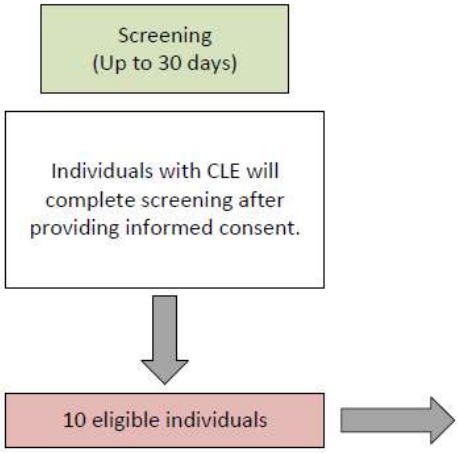
- To evaluate changes in cutaneous disease activity in individuals with CLE after a 25-day regimen of tofacitinib.
- To evaluate changes in SLE activity in individuals with CLE after a 25-day regimen of tofacitinib.
- To evaluate safety and toxicity of a 25-day regimen of tofacitinib for individuals with CLE.

3. Study Design

3.1. Description of Study Design

This is a single-arm, multi-site, proof-of-concept study of 10 participants with CLE. Consenting individuals meeting all entry criteria will undergo 25 days of treatment with tofacitinib (11 mg orally (PO) daily) with evaluation of UVB-mediated cutaneous apoptosis and ancillary mechanistic studies before and after treatment. Post-screening study visits will be conducted on Days 0 (Visit 1), 1 (Visit 2), 14 (Visit 3), 25 (Visit 4), 26 (Visit 5), and 40 (Visit 6) to (1) evaluate adverse events, vital signs, hematology and chemistry, study drug compliance, medication use, and disease status, (2) conduct UVB phototesting, and (3) collect skin biopsies and blood samples for mechanistic studies (See Figure 1). Tofacitinib will be distributed to eligible participants at Visit 2 (Day 1) and the first dose will be taken on Day 2. The last dose is the morning of Visit 5 (Day 26). Participants are allowed to continue on their stable background therapies for lupus according to Section 7.1.2, *Other Permitted Concomitant Medications*.

Please refer to Section 8.1.1, *Exceptions to Visit Windows*, and Section 6.6, *Resumption of Investigational Product,* for more information regarding delays to visits 4 and 5.



Study Visit	1	2	3	4	5	6
Target Day	0	1	14	25	26	40
Treatment		← Tofacitinib 11mg PO daily (Begins on Day 2) →				
UVB Exposure	X			X		
Erythema Assessment		X			X	
Biopsy		X			X	
Blood	X			X		
Clinical Evaluations	X			X		
Safety Follow-Up			X			X

Figure 1. Study Schematic

3.1.1. Considerations Regarding COVID-19

May 11, 2023, marked the end of the COVID-19 public health emergency (PHE) declaration in the US. The CDC states that many people in the United States now have some protection or immunity against COVID-19 due to vaccination, previous infection, or both. This immunity, combined with the availability of tests and treatments, has greatly reduced the risk of severe illness, hospitalization, and death from COVID-19 for many people (https://www.cdc.gov/coronavirus/2019-ncov/your-health/covid-by-county.html).

At the same time, some people—such as those who are older, are immunocompromised, have certain disabilities, or have certain underlying health conditions—continue to be at higher risk for serious illness. Mitigating risks of infections, including from endemic COVID-19, in immunocompromised populations remains important.

Participants are strongly recommended to be up to date with COVID-19 vaccinations per current CDC recommendations at the time of screening with last vaccine at least 14 days prior to Visit 1 (Day 0).

3.2. Primary Endpoint

The primary endpoint is the change in percentage of UVB-induced apoptotic epidermal cells from Visit 2 (Day 1) (pre-treatment) to Visit 5 (Day 26) (post-treatment). Percentage of UVB-induced apoptotic cells at a visit is defined as the difference between the percentage of apoptotic epidermal cells in the UVB-exposed biopsy and percentage of apoptotic epidermal cells in the unexposed biopsy at the same visit. More information can be found in Section 8.5.5, *Research Assessments*.

3.3. Secondary Endpoints

1. Change in MED due to UVB from Visit 2 (Day 1) to Visit 5 (Day 26)

2. Change in UVB-induced expression of inflammatory genes in skin from Visit 2 (Day 1) to Visit 5 (Day 26), based on enumeration of RNA transcripts. UVB-induced expression is defined as the difference in expression measured in the biopsy exposed at the Visit 2 (Day 1) 1x MED and that measured in the unexposed biopsy
3. Change in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score from Visit 1 (Day 0) to Visit 4 (Day 25)
4. Change in CLASI damage score from Visit 1 (Day 0) to Visit 4 (Day 25)
5. Change in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) total score from Visit 1 (Day 0) to Visit 4 (Day 25)
6. Changes in laboratory parameters
7. Incidence of adverse events

3.4. Stratification, Randomization, and Blinding/Masking

This is a single-arm open-label study. There are no plans for stratification, randomization, or masking.

4. Selection of Participants

4.1. Study Population

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol. For this Phase 1 study, conditions indicative of serious disease, such as CNS lupus or lupus nephritis, are excluded by limiting the total SLEDAI-2K score for clinical manifestations to ≤4 at entry.

4.2. Inclusion Criteria

Individuals must meet all of the following inclusion criteria to be eligible for enrollment in the study:

1. Cutaneous lupus erythematosus based upon all of the following:
    a. a clinical diagnosis made by a rheumatologist or dermatologist of one of the following: acute cutaneous lupus erythematosus, subacute cutaneous lupus, or chronic cutaneous lupus erythematosus;
    b. active skin disease within 5 years prior to screening.

    Participants may have concomitant SLE.
2. SLEDAI-2K score ≤4 (clinical criteria only, excludes all laboratory criteria) for all participants regardless of whether they have concomitant SLE.
3. If taking oral corticosteroids, the dose must be ≤ 10 mg daily of prednisone (or equivalent), stable dose for at least 4 weeks, and not anticipated to change over the course of the study.
4. If taking oral anti-malarial medications, the dose(s) must be ≤ 100 mg daily for quinacrine or/and ≤ 400 mg daily for hydroxychloroquine, stable for at least 6 months, and not anticipated to change over the course of the study.
5. If taking oral or subcutaneous methotrexate, the dose must be ≤ 25 mg weekly, stable for at least 4 weeks, and not anticipated to change over the course of the study.
6. If taking oral leflunomide, the dose must be ≤ 20 mg daily, stable for at least 4 weeks, and not anticipated to change over the course of the study.
7. If taking oral mycophenolate mofetil (MMF) or mycophenolic acid, the dose must be equivalent to ≤ 3000 mg of MMF daily, stable for at least 4 weeks, and not anticipated to change over the course of the study.
8. Adults 18 to 65 years of age at screening.

9. All participants and/or their sexual partners who engage in sexual activity that could lead to pregnancy must be willing to use complete abstinence or an FDA-regulated form of contraception for the duration of the study and for at least one month after discontinuation of study drug to prevent pregnancy. Highly effective birth control methods include, but are not limited to, hormonal contraception, an intrauterine device, or surgical options. Periodic abstinence and withdrawal are not acceptable methods of birth control.

4.3. Exclusion Criteria

Individuals who meet any of these criteria are not eligible for enrollment as study participants:

1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol.
2. Current or recent history, within the last year, of uncontrolled clinically significant renal, hepatic, hematologic, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, or neurologic disease or significant impairment that might negatively impact the participant's ability to participate or that may put a participant at increased risk.
3. Potential active nephritis and/or urinary tract infection at screening, defined as any one of the following determined at screening unless otherwise specified:
    a. >10 RBCs /hpf,
    b. >5 WBCs /hpf with either positive nitrites or greater than a trace leukocyte esterase,
    c. Signs or symptoms of a urinary tract infection,
    d. For individuals with no history of nephritis: Urine protein (mg/dL): creatinine (mg/dL) ratio (Pr/Cr)>0.5 at screening or a Pr/Cr level that has exceeded 1.0 in the prior 12 months,
    e. For individuals with a history of nephritis: A rise in Pr/Cr of >0.5 over the prior 3-6 months prior to screening.
4. History of severe gastrointestinal narrowing or strictures.
5. Medically confirmed history of diverticulitis or chronic, ulcerative lower gastrointestinal (GI) disease such as Crohn's disease, ulcerative colitis, or other symptomatic, lower GI conditions that might predispose a participant to perforations.
6. History of thrombosis, pulmonary embolism, or antiphospholipid syndrome.
7. History of any one of the following anti-phospholipid antibodies:
    a. Positive lupus anticoagulant test, or
    b. Anti-β2-glycoprotein I IgG ELISA titer ≥ 40 GPL, or
    c. Anti-cardiolipin IgG ELISA titer ≥ 40 GPL.
8. History of chronic pulmonary disease requiring supplemental oxygen including chronic obstructive pulmonary disease (COPD) requiring chronic treatment, interstitial lung disease (ILD) requiring immunosuppressive therapy, and asthma requiring chronic steroid (other than inhaled steroid) or biologic therapy.
9. History of moderate to severe atherosclerotic cardiovascular disease as evidenced by prior coronary artery bypass surgery, coronary artery stent placement, myocardial infarction, symptomatic carotid arterial disease, peripheral vascular disease, abdominal aortic aneurysm; or angina within the past 8 weeks prior to Visit 1 (Day 0).
10. History of keloid scarring.
11. History of any lymphoproliferative disorder or other malignancy with the exception of successfully treated or excised basal cell or squamous cell skin cancer or cervical cancer in situ.
12. Other autoimmune diseases likely to require immunosuppression.
13. Any of the following lab results at screening:
    a. Hemoglobin <9.5 g/dL
    b. White Blood Cell count <3.5 x 10^9/L

c. Absolute Neutrophil count <1.2 x 10^9/L
d. Platelet count <120 x 10^9/L
e. Absolute Lymphocyte count <0.75 x 10^9/L
f. Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) > 1.5 × the upper limit of normal (ULN)
g. Total bilirubin > ULN
h. Estimated glomerular filtration rate [GFR] <60mL/min/1.73 m^2
i. Triglycerides ≥ 300 mg/dL (fasting not required)
j. Total Cholesterol ≥ 240 mg/dL (fasting not required).

14. Major surgery < 8 weeks prior to Visit 1 (Day 0).
15. Hospitalized for serious infection < 4 weeks prior to Visit 1 (Day 0).
16. Chronic infections other than chronic or intermittent uncomplicated urinary tract infections (including but not limited to tuberculosis (TB), chronic pyelonephritis, osteomyelitis).
17. Presumed or documented COVID-19 infection within 30 days prior to Visit 1 (Day 0).
18. Recent (within one month prior to screening) close contact with a person who has active TB infection.
19. History of untreated active or latent TB infection.
20. History of incompletely treated active or latent TB infection unless at least one month of treatment has been completed prior to screening.
21. Positive Interferon-Gamma Release Assay (IGRA) or positive purified protein derivative tuberculin skin test (PPD) (> 5mm induration) at screening.
22. An indeterminate IGRA at screening unless followed by a subsequent negative IGRA or negative PPD.
23. History of human immunodeficiency virus (HIV).
24. A positive test for HIV antigen/antibody or nucleic acid test (NAT) at screening.
25. History of a hepatitis B infection.
26. A positive test for hepatitis B surface antigen or hepatitis B core antibody at screening.
27. History of a hepatitis C infection.
28. A positive test for hepatitis C antibody (regardless of whether hepatitis C RNA levels are undetectable) at screening.
29. History of recurrent (more than one episode) herpes zoster, one or more episodes of any of the following: herpes zoster ophthalmicus, or disseminated herpes zoster, or disseminated herpes simplex.
30. Current, recent (< 4 weeks prior to Visit 1 (Day 0)) or chronic use of antibiotic medication, except for suppression of chronic/recurrent urinary tract infection, which is allowed.
31. Simultaneous use of more than one of the following: leflunomide, methotrexate and MMF.
32. Any of the following active medications (oral or parenteral): cyclosporine, voclosporin, cyclophosphamide, tacrolimus, rituximab or other anti-CD20s, or any other investigational or marketed biologic with immunomodulatory properties within a year prior to Visit 1 (Day 0).
33. Any of the following medications (oral or parenteral): azathioprine or belimumab within 3 months prior to Visit 1 (Day 0).
34. Any prior treatment with cell-depleting therapies other than anti-CD20s including but not limited to CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19 products.
35. Intravenous or intramuscular corticosteroids within 2 weeks prior to Visit 1 (Day 0).
36. Treatment with any investigational agent ≤ 4 weeks or ≤ 5 half-lives of the investigational drug prior to Visit 1 (Day 0), whichever is longer.
37. Treatment with more than one dose of ketoconazole within one week of screening.

38. Any prior treatment with chlorambucil, bone marrow transplantation, or total lymphoid irradiation.
39. Vaccinated or exposed by close contact, e.g., within a household, to a live/attenuated vaccine ≤ 6 weeks prior to Visit 1 (Day 0); or is expected to be vaccinated or to have household exposure to these vaccines during treatment or during the 6 weeks following discontinuation of study medication.
40. Received a non-live vaccine ≤ 2 weeks prior to initiation of study drug, or unwillingness of a participant to delay non-live vaccination until 1 month after completion of study therapy.
41. Pregnant or breastfeeding females.
42. History of alcohol or substance abuse, unless in full remission for greater than 6 months prior to first dose of study drug.
43. Past or current medical or psychiatric conditions or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.

5. Known and Potential Risks and Benefits to Participants

5.1. Risks of Tofacitinib as cited in US Package Insert

The following are considered important risks or potential risks identified in the United States Prescribing Information (USPI) for XELJANZ®(tofacitinib) and XELJANZ® XR (tofacitinib)[20]:

1. **Serious infections:** Tofacitinib increases the risk of serious infections leading to hospitalization or death, including TB and bacterial, invasive fungal, viral, and other opportunistic infections. The most common serious infections reported include pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Among opportunistic infections, TB and other mycobacterial infections, cryptococcosis, histoplasmosis, esophageal candidiasis, pneumocystsis, multidermatomal herpes zoster, cytomegalovirus infections, BK virus infection, and listeriosis have been reported. In addition, disseminated infections have been reported, and were often associated with concurrent use of immunomodulating agents such as methotrexate or corticosteroids. Other serious infections that have not been reported in clinical studies may also occur.

2. **Mortality:** In rheumatoid arthritis (RA), individuals with at least one cardiovascular risk factor had a higher risk of all-cause mortality including sudden cardiovascular death.

3. **Malignancy and lymphoproliferative disorders:** In rheumatoid arthritis, higher rates of malignancies (excluding non-melanoma skin cancer) were observed, particularly among current and past smokers. Risks and benefits of treatment should be weighed prior to initiating therapy in individuals with a known malignancy other than a successfully treated non-melanoma skin cancer.

4. **Major Adverse Cardiovascular Events (MACE):** RA patients 50 years of age and older with at least one cardiovascular risk factor had a higher rate of MACE defined as cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke. Risks and benefits of treatment should be weighed prior to initiating or continuing therapy, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors.

5. **Thrombosis:** Thrombosis, including pulmonary embolism, deep venous thrombosis and arterial thrombosis have occurred. RA patients 50 years of age and older with at least one cardiovascular risk factor had an observed

increase in incidence of these events, many of which were serious and some resulting in death. Tofacitinib should be avoided in patients who may be at increased risk of thrombosis.

6. **Gastrointestinal perforations:** Gastrointestinal perforations have been reported. Caution is warranted in individuals who may be at increased risk for gastrointestinal perforation (e.g., those with a history of diverticulitis or taking Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

7. **Hypersensitivity**: Hypersensitivity reactions such as angioedema and urticaria that may reflect drug hypersensitivity have been observed including some serious events.

8. **Laboratory Abnormalities**:

   Lymphocyte abnormalities: Tofacitinib has been associated with a gradual decrease in mean absolute lymphocyte counts of approximately 10% over 12 months of therapy. Lymphocyte counts less than 500 cells/mm were associated with an increased incidence of treated and serious infections.

   Neutropenia: Tofacitinib has been associated with an increased incidence of neutropenia (less than 2000 cells/mm).

   Anemia: Avoid initiation of tofacitinib in individuals with low hemoglobin level (i.e., < 9 g/dL).

   Liver enzyme elevations: Tofacitinib has been associated with an increased incidence of liver enzyme elevation. Most of these abnormalities occurred in studies with background Disease-Modifying Anti-Rheumatic Drugs (DMARDs) (primarily methotrexate) therapy.

   Lipid elevations: Tofacitinib has been associated with dose-dependent increases in lipid parameters including total cholesterol, low density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. There were no clinically relevant changes in LDL/HDL cholesterol ratios. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

9. **Gastrointestinal obstruction**: As with any other non-deformable material, caution should be used when administering tofacitinib to individuals with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs utilizing a non-deformable extended-release formulation.

The following additional considerations are noted in the USPI:

1. Drug interactions:

- Strong CYP3A4 inhibitors increase exposure to tofacitinib. Participants taking ketoconazole are excluded from this study.

2. Co-administration with biologic DMARDs or potent immunosuppressive drugs such as azathioprine or cyclosporine is not recommended.

3. Pregnancy, Lactation, and Reproductive potential:

- Available data in pregnant women are insufficient to establish a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Feticidal and teratogenic effects were noted in animal reproduction studies.

- There are no data on the presence of tofacitinib in human milk, the effects on a breastfed infant, or the effects on milk production. Tofacitinib is present in the milk of lactating rats; it is likely that the drug will be present in human milk.

- Pregnancy planning and prevention is recommended for females of reproductive potential and is planned for this study.

4. **Vaccinations:** Avoid use of live vaccines concurrently with tofacitinib. The interval between live vaccinations and initiation of tofacitinib therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

5. **Hepatic impairment:** Tofacitinib has not been studied in individuals with severe hepatic impairment and its use is not recommended. In studies of individuals with moderate hepatic impairment, tofacitinib blood concentration than is higher than individuals with normal hepatic function. Higher blood concentrations may increase the risk of some adverse reactions. In addition, the safety and efficacy of tofacitinib have not been studied in patients with positive hepatitis B virus or hepatitis C virus serology.

6. **Renal impairment:** In individuals with moderate or severe renal impairment, tofacitinib blood concentrations are higher than in individuals with normal renal function.

5.2. Risks of Tofacitinib cited in Medical Literature and FDA Drug Safety Communications

As noted in Section 1.4, *Clinical Studies*, the clinical experience of using tofacitinib in lupus patients is limited. A recent report of 10 SLE patients with active skin disease who were treated with tofacitinib 5 mg twice daily for varying time points of 4 weeks to one year identified two adverse events. One patient had an outbreak of Herpes Zoster, the other experienced alopecia. It was not reported as to whether these events were considered related to tofacitinib as all patients in the study were on combination therapy with seven out of ten on concomitant corticosteroids and seven out of ten on concomitant immunosuppressive medications such as mycophenolate mofetil, tacrolimus, or methotrexate[21]. Case reports of successful treatment of patients with rheumatoid arthritis and lupus overlap made no mention of adverse events[22]. Preliminary reports of a 56-day active treatment phase 1b/2a safety study of tofacitinib 5 mg twice daily in patients with systemic lupus identified no severe adverse events or opportunistic infections. Total infections were reported in 55% of patients on tofacitinib and 40% of those on placebo[8], and most of these were reported as mild upper respiratory infections.

5.3. Risks of Other Protocol Specified Medications

Not applicable.

5.4. Risks of Study Procedures

1. **Storage of skin and blood samples:** Specimens will be identified with a participant-specific code number. Safeguards are used to protect the risk to participant's privacy as outlined in Section 17.3, *Privacy and Confidentiality.*

2. **Blood draw:** Drawing blood from a vein may cause some discomfort, bleeding, or bruising, and rarely, infection or fainting at puncture site. A total of 210mL (about 7 oz.) of blood will be collected over the course of the entire study. Blood will be drawn by trained persons and sterile technique will be used to minimize the risk of infection.

3. **Skin biopsy:** The risks include discomfort, e.g., pain, pruritus, and/or bruising at the site of biopsy during numbing of the skin or after the anesthetic has worn off, and allergic reactions to lidocaine. A small amount of bleeding may occur during the biopsy, and bleeding may be increased in participants taking blood thinners such as aspirin or coumadin. Rarely, biopsy sites may develop a skin infection. Biopsy sites may also result in small scars, and those with a history of scarring after skin trauma may be at increased risk of scarring.

4. **Ultraviolet Light Exposure:** Part of this study includes a brief exposure to different doses of UV light (up to 80 mJ/cm^2). The areas exposed are small (about 1 cm^2), but there is a risk of some burning sensation in the areas exposed. In addition, it is possible that skin inflammation following the UV light exposure could linger and cause a rash.

5.5. Summary of Potential Benefits

There is no direct benefit to participants. This is a proof-of-concept study with a short course of study drug.

Findings from the proposed studies will provide new information regarding the mechanisms of photosensitivity in lupus and the potential ways to treat it. The new information generated from this trial may lead to new therapies for CLE and SLE.

6. Investigational Agent /Device/Intervention

6.1. Investigational Agents

6.1.1. XELJANZ® XR (tofacitinib)

XELJANZ® XR (tofacitinib) extended-release tablets, for oral use are formulated with the citrate salt of tofacitinib, a JAK inhibitor. Tofacitinib citrate is a white to off-white powder with the following chemical name: (3R,4R)-4-methyl-3-(methyl-7H-pyrrolo [2,3-d]pyrimidin-4-ylamino)-ß-oxo-1-piperidinepropanenitrile, 2-hydroxy-1,2,3-propanetricarboxylate (1:1). The solubility of tofacitinib citrate in water is 2.9 mg/mL. Tofacitinib citrate has a molecular weight of 504.5 Daltons (or 312.4 Daltons as the tofacitinib free base) and a molecular formula of $C_{16}H_{20}N_{6O}\cdot C_6H_8O_7$ [20].

6.1.1.1. Formulation, Packaging, and Labeling

XELJANZ® XR (tofacitinib) will be purchased by the sponsor, DAIT NIAID, Investigational Products Procurement Center through DAIT Pharmacy Purchasing Program. DAIT's Clinical Product Center under contract (EMINENT Services Corporation) will distribute the investigational product and the labels to the study site. The site pharmacy will apply the study-specific flag drug label to the bottles before dispensing the IP.

XELJANZ® XR (tofacitinib) is available in 11mg tablets and will be supplied in bottles of 30 tablets. The tablets used for this study are pink, oval, extended-release film-coated tablets with a drilled hole at one end of the tablet band and "JKI 11" printed on one side of the tablet.

6.1.1.2. Dosage, Preparation, and Administration

Participants will take one 11 mg tablet by mouth every morning. XELJANZ® XR (tofacitinib) should be stored at room temperature, 20°C to 25°C (68°F to 77° F). It is recommended to take the drug with or without food. Tofacitinib tablets should be swallowed whole and intact, do not crush, split or chew[20] .

6.2. Drug Accountability

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator will maintain adequate records of the disposition of the investigational agent, including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting), and a detailed accounting of any drug accidentally or deliberately destroyed.

Records for receipt, storage, use, and disposition will be maintained by the study site. A drug-dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of drug dispensed.

All records regarding the disposition of the investigational product will be available for inspection.

6.3. Assessment of Participant Compliance with Investigational Agent

Participants will be asked to return to the clinic with their study drug pill bottles and drug accountability diary at Visit 3 (Day 14), Visit 4 (Day 25), and Visit 5 (Day 26). Compliance will be evaluated at Visit 4 (Day 25) before initiating phototesting (See Section 3.1, *Description of Study Design*). Participants will take their last dose of study medication on the morning of Visit 5 (Day 26). At Visit 5 (Day 26), bottles will be collected by site staff, and pills will be counted again. Participants who fail to return their pill bottles at Visit 5 will be asked to return the bottles at Visit 6 (Day 40).

6.4. Toxicity Prevention and Management

Prevention

- Entry criteria and laboratory testing are designed to exclude individuals with identifiable risk factors.
- Participants will be informed of the need to be up-to-date with respect to vaccinations per current immunization guidelines. They will be asked to confirm their vaccination status with their provider before enrolling in this study. Vaccination of participants with live components is prohibited within the 6 weeks prior to Visit 1 (Day 0), during treatment, or during the 6 weeks following discontinuation of study medication. Non-live vaccines should be administered at least 2 weeks prior to initiation of study drug and should not be administered during treatment or during the one month after completion of study drug.
- Concurrent use of drugs that are contradicted with tofacitinib 11 mg per day is prohibited while on study treatment (See Section 7.3, *Prohibited Medications*).
- Safety monitoring will serve to monitor for adverse events that require further evaluation and/or treatment.

Management

- Participants will be seen in clinic on Day 14, approximately 2 weeks after starting study drug, to evaluate signs and symptoms and screen for possible adverse events.
- Participants will be instructed to call the study coordinator if signs or symptoms of an infection occur during the course of the study.

- Prior to biopsies, participants will be asked about allergies to local anesthetics and solutions used to prepare the biopsy site. A stitch will be used to close the skin biopsy site to minimize the risk of infection and scar formation. Biopsies will be performed using sterile techniques by trained staff, and participants will be provided with wound care instructions to minimize the risk of infection.

6.5. Discontinuation/Suspension of Investigational Agent

6.5.1. Permanent Discontinuation of Investigational Agent

Participants MUST permanently discontinue tofacitinib for any of the following reasons:

1. The participant elects to withdraw consent for study treatment.
2. The participant loses the ability to freely provide consent through imprisonment or involuntary commitment for treatment of a psychiatric condition.
3. The participant becomes pregnant.
4. The participant experiences anaphylaxis or a Grade 3 or higher allergic reaction.
5. The participant develops a malignancy excluding basal cell or squamous cell skin cancer or cervical cancer in situ.
6. The participant experiences a grade 2 or higher thromboembolic event.
7. A participant is found to have ALT or AST > 3X ULN and total bilirubin > 2X ULN (Hy's Law).

If a participant prematurely discontinues study therapy, all subsequent study visits will be cancelled with the exception of Visit 6 (Day 40). The participant will be asked to return for an in-person safety follow-up Visit 6 (Day 40) if the safety event that led to the permanent discontinuation of study treatment was related to study participation. The participant will be asked to participate in a virtual or telephone safety follow-up Visit 6 (Day 40) if the discontinuation of study treatment was not due to an adverse event related to study participation. See Table 8.2, *Schedule of Events*, for more detail.

6.5.2. Temporary Suspension of Investigational Agent

Participants MUST temporarily suspend tofacitinib for any of the following reasons:

1. The participant experiences a clinical adverse event, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued treatment with study drug is not in the best interest of the participant.
2. The participant develops a SAE as defined in Section 12.2.4, *Serious Adverse Events*.
3. The participant develops any grade 2 or higher infection.
4. The participant is diagnosed with an active SARS-CoV-2 (COVID-19) infection, confirmed by PCR or alternative viral test according to CDC guidance, independent of symptoms or grade of infection.
5. The participant develops a fever >101^{o}F.
6. The participant requires an increase in dose of a permitted background lupus medication as defined in Section 7.1.2, *Other Permitted Concomitant Medications*.
7. If a participant is found to have any of the following lab values (from either unscheduled clinic visits or evaluations outside this study):

    - Lymphocyte count <0.50 x 10^{9}/L

- Absolute neutrophil count (ANC) <1.0 x 10^9/L
- Hemoglobin < 8.0 g/dL or a decrease > 2 g/dL from Visit 1 (Day 0).

6.6. Resumption of Investigational Product

Tofacitinib should be taken as prescribed, unless a participant has an event that requires premature discontinuation or temporary suspension, as outlined in Section 6.5, *Discontinuation/Suspension of Investigational Agent*. If a participant inadvertently misses one to seven consecutive doses, the participant should resume tofacitinib as soon as possible. If a participant is required to temporarily suspend tofacitinib as outlined in 6.5.2, *Temporary Suspension of Investigational Agent,* the participant may resume tofacitinib once the event leading to dose suspension resolves and/or stabilizes, provided visits 4 and 5 will occur within 12 weeks after the participant's Visit 1 (Day 0) and the investigator feels resumption of tofacitinib is appropriate.

In order to achieve the study drug compliance criteria, as described in Section 8.5.5, *Research Assessments*, one additional bottle of tofacitinib may be dispensed. If it is necessary to start a new 25-day course of tofacitinib (e.g. substantial study therapy non-adherence or suspension of study therapy for 8 or more consecutive days), the participant must undergo a Restart Visit and meet all entry criteria listed in Sections 4.2 *Inclusion Criteria* and 4.3 *Exclusion Criteria,* prior to starting the new course of tofacitinib. Visits 4 (Day 25) and 5 (Day 26) must occur within 12 weeks after the participant's Visit 1 (Day 0). A participant may only start a new 25-day course of tofacitinib once. For more information, see Table 8.2, *Schedule of Events.*

If resumption of tofacitinib is not appropriate, the procedures outlined in 6.5.1, *Permanent Discontinuation of Investigational Agent*, should be followed.

7. Other Medications

7.1. Concomitant Medications

All concomitant medication taken during the study must be recorded with generic name of the medication, indication, daily dose, and start and stop dates of administration. A participant who is receiving an allowed concomitant medication for any reason must be on a dose that is considered standard-of-care for the treated indication. Medications taken after informed consent is obtained but before the first dose of study medication will be documented as prior medications. Medications taken after the first dose of study drug has been administered will be documented as concomitant medications.

7.1.1. Protocol-mandated

There are no protocol-mandated concomitant therapies for participants in this study.

7.1.2. Other Permitted Concomitant Medications

Participants are allowed to continue on the following background lupus therapies at permitted doses (as indicated) that have been stable for at least 4 weeks prior to Visit 1 (Day 0). Stopping or decreasing doses of these background lupus therapies is allowed during the study. Increasing doses of these background lupus therapies (other than PRN NSAIDs) is not permitted. See Section 6.5.2, *Temporary Suspension of Investigational Agent*, for more details.

Permitted Lupus Medications[1]	Permitted doses
Non-steroidal anti-inflammatory drugs (NSAIDs including COX 2 inhibitors)	Daily Dose[2] and PRN Usage[3]
Corticosteroids	≤ 10 mg daily of prednisone (or equivalent) orally
Quinacrine	≤ 100 mg daily orally
Hydroxychloroquine	≤ 400 mg daily orally
Methotrexate	≤ 25 mg weekly orally or subcutaneously
Leflunomide	≤ 20 mg daily orally
Mycophenolate mofetil (MMF) (or equivalent dose of mycophenolic acid)	≤ 3000 mg daily orally

[1]Topical agents including corticosteroids and tacrolimus are permitted for use except on the area of the skin exposed to UVB. Inhaled corticosteroids are also permitted.

[2]Daily doses must remain stable for 1 week prior to UV Treatment and Biopsy.

[3]PRN doses are not allowed for 1 week prior to UV treatment and biopsy.

7.2. Prophylactic Medications

There are no protocol-mandated prophylactic medications for this study.

7.3. Prohibited Medications

Use of tofacitinib in combination with biologic DMARDs or potent immunosuppressants not listed in Section 7.1.2, such as azathioprine, voclosporin, and cyclosporine is not allowed. Oral corticosteroids, other than specified in Section 7.1.2, and parenteral corticosteroids are prohibited. Methotrexate, leflunomide, or MMF may be continued at stable doses indicated in Section 7.1.2, but they may not be used simultaneously with each other.

No topical therapies of any kind can be used on the area exposed to UVB from the time of the UVB exposure assessment until the skin biopsy has been taken the next day. Chemical sunscreens should not be used on the region that will be exposed to UVB for at least 12 hours prior to the UVB exposure assessment. Zinc and titanium-based sunscreens may be used, but will need to be removed prior to UVB treatment.

7.4. Rescue Medications

There are no protocol-mandated rescue medications for this study.

8. Study Procedures

8.1. Visit Windows

With one exception, described below, study visits should take place within the time limits specified in Table 8.1, *Visit Windows*. The designated visit windows for each scheduled visit are also indicated in Table 8.2, *Schedule of Events*. Whenever possible, a rescheduled visit should remain within the designated visit window. The coordinating center should be notified if the study procedures for any scheduled visit cannot be performed within the designated window.

Table 8.1. Visit Windows

VISIT	Target Day (window)
Screening Period	(Days -30 to -1)
Visit 1	Day 0
Visit 2	Day 1, 24 hours after Visit 1 UVB exposure (within 20-28 hours of Visit 1 UVB exposure)
Visit 3	Day 14 (Days 10 to 15)
Visit 4	Day 25 (Days 21 to 29)
Visit 5	Day 26, 24 hours after Visit 4 UVB exposure (within 20-28 hours of Visit 4 UVB exposure)
Visit 6	Day 40 (Days 36 to 41)

8.1.1. Exception to Visit Window Rules

For participants who complete phototesting and the biopsy at Visit 1 (Day 0) and Visit 2 (Day 1), Visit 4 (Day 25) may be delayed up to 12 weeks after Visit 1 (Day 0), if necessary. This may occur if study therapy compliance criteria, as described in *Section 8.5.5, Research Assessments*, have not been met.

If it is necessary to start a new 25-day course of tofacitinib as described in Section 6.6, *Resumption of Investigational Product*, the participant will have a virtual visit 14 days after reinitiating tofacitinib to assess adverse events.

8.2. Screening and Enrollment

The study will be explained in lay terms to each potential research participant. The potential participant will sign an informed consent form before undergoing any study procedures. Once informed consent is obtained, all screening procedures, assessments, and laboratory measures to determine participant eligibility will be conducted within a 30-day screening window. Eligible participants who meet all entry criteria will proceed with treatment, visits, and assessments according to Table 8.2, *Schedule of Events*. See Section 8.5, *Study Procedures and Assessments* for more information on individual clinical and research assessments. Participants who do not meet eligibility criteria will be permitted to rescreen once. In addition, participants who cannot complete visits 4 (Day 25) and 5 (Day 26) within 12 weeks after the participant's Visit 1 (Day 0) may rescreen and start the study over, if deemed appropriate by the investigator. The participant must be off tofacitinib for at least one month prior to the new baseline phototesting and biopsy.

8.3. Unscheduled Visits

The investigator may schedule visits in addition to those listed in Table 8.2, *Schedule of Events* in order to conduct evaluations or assessments required to protect the well-being of the participant. If disease activity increases or other concerns arise between regularly scheduled visits, participants should be instructed to contact study personnel and may be asked to return to the study site for an "unscheduled" visit.

8.4. Early Termination Visits

An Early Termination Visit should be requested for participants who withdraw from the study prior to Visit 4 (Day 25). See Table 8.2, *Schedule of Events,* for more information about the assessments that should be conducted at an Early Termination Visit.

8.5. Study Procedures and Assessments

8.5.1. Study Drug

- Study drug will be dispensed to eligible participants at Visit 2 (Day 1). Dosing will begin on day 2 and end on day 26 prior to the erythema assessment and biopsy at Visit 5 (Day 26).
- Study drug compliance will be evaluated at Visit 3 (Day 14).
- Study drug compliance will be evaluated at Visit 4 (Day 25) prior to phototesting.
- Pill bottles will be collected, and remaining pills will be counted at Visit 5 (Day 26).

8.5.2. General Assessments

- **Informed Consent**
- **Demographics:** Participants should provide demographic information. In particular, race and ethnicity should be self-identified.
- **Medical History:** Medical history will be performed as part of screening activities and standard medical care. The medical history assessment will include current illnesses/conditions and past medical history.
- **Concomitant Medications:** A current list of prescription and over-the-counter medications, supplements, and treatments for CLE and SLE will be obtained. Assessment of eligibility should include a review of permitted and prohibited medications. The medication, dose, frequency, route, start date, stop date, and indication will be captured in the electronic case report form (eCRF). Medications taken 30 days prior to screening through study completion or termination should be reported.
- **Eligibility Review:** All entry criteria should be reviewed, and eligibility confirmed prior to scheduling Visit 1 (Day 0) and again at Visit 1 (Day 0) before drawing blood or phototesting (UVB exposure).

8.5.3. Clinical Assessments

- **EULAR/ACR Lupus 2019 [23]:** Screening only.
- **CLASI [24]:** This is a validated instrument for evaluating skin inflammation and damage.
- **SLEDAI-2K:** This is a validated instrument for evaluating SLE disease activity. Each component has a weighted point value which can sum up to 105. Conditions that are ongoing, recurrent, or new should be assessed consistently in relation to a participant's lupus disease activity. A score ≥ 6 is indicative of active disease.
- **Physical Examination:** A comprehensive physical examination will be performed at each clinic visit where the CLASI and/or SLEDAI 2K are indicated. See Table 8.2, *Schedule of Events*, for more detail.
- **Height, Weight, and Vital signs:** Height and weight will only be collected at Screening. Vital signs will include pulse, blood pressure, and temperature (C^o). Vital signs should be obtained with the participant in a seated position prior to taking samples for laboratory testing at applicable study visits.
- **Fitzpatrick Scale Assessment[25]**
- **Adverse Event Monitoring**

8.5.4. Clinical Laboratory Assessments

Blood and urine for the clinical laboratory assessments listed below will be collected per Table 8.2, *Schedule of Events*. The results will be evaluated for safety by the site investigator. Abnormal tests that meet grading and reporting criteria will be reported as adverse events (See Section 12.3.1, *Grading Criteria*).

- **Hematology**: complete blood count (CBC) including hemoglobin, hematocrit, white cell count, absolute neutrophil count, absolute lymphocyte count, and platelet count; and erythrocyte sedimentation rate (ESR).
- **Blood Chemistry**: including lipids (triglycerides and cholesterol), ALT, AST, bilirubin, creatinine, eGFR, C3, C4.
- **Urinalysis**: including protein: creatinine ratio, RBCs, and WBCs.
- **Serum immunoglobulins**: including anti-ds DNA.
- **Infectious Disease Testing** (Screening only): including HIV antigen/antibody or NAT, IGRA or PPD, hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C virus (HCV) antibody with HCV RNA (PCR) if antibody positive
- **Pregnancy Testing**: serum pregnancy test (Screening), urine pregnancy test (Visit 4 (Day 25) or Early Termination Visit).

8.5.5. Research Assessments

- **Blood for Serum Biomarkers** will be drawn at Visit 1 (Day 0) and Visit 4 (Day 25).
- **Blood for Cellular and Proteomic studies** will be drawn at Visit 1 (Day 0) and Visit 4 (Day 25).
- **UVB Exposure**:
    - A UV Lamp (Ultralite Enterprises Model 36P10A 10-UNV or equivalent device) will be identified by model name and number, and manufacturer at each site. The same device will be used for all phototesting at each site. The UVB dose, based upon the distance from the UV lamp to the participant, will be determined using dedicated photometer and probe prior to each use.

Phototesting will occur at the study site. A photo-barrier template will be placed on non-lesional skin of the participant's exposed lower back/buttock. The template will be placed on the right lower back/buttock for the phototest on Visit 1 (Day 0) and on the left lower back/buttock for the Visit 4 (Day 25) test. UV irradiation will be applied to the template area via a UV Lamp (Ultralite Enterprises Model 36P10A 10-UNV or equivalent device), and every 40 seconds a single template square of the barrier will be covered until all 8 template squares have been covered (i.e., total exposure ranges from 10-80 mJ/cm^2).

Before initiating phototesting at Visit 4 (Day 25), the participant should meet all the following criteria:

- The participant must have completed at least 21 days of IP dosing.
    - For individuals whose Visit 4 (Day 25) has been delayed (See Section 8.1.1, *Exception to Visit Windows*), the 21 days starts from the day IP dosing is resumed.
- The participant must confirm that no IP doses have been missed in the prior 7 days. Dosing will be tracked on a paper patient diary and in the EDC (Electronic Data Capture) system.
- The participant must have taken at least 84% of expected daily doses from the day of the first IP dose. Compliance is based on a pill count conducted at Visit 4 (Day 25).

- For individuals whose Visit 4 (Day 25) has been delayed (See Section 8.1.1, *Exception to Visit Window Rules*), compliance should be computed from the day IP dosing is resumed.

If a participant fails to bring the IP pill bottle(s) back at Visit 4 (Day 25), UVB exposure may proceed during this visit. However, site personnel must confirm at least 84% compliance via a visual pill count prior to the erythema assessment and biopsy at Visit 5 (Day 26). If 84% compliance is not achieved, participant may resume IP dosing. Once the participant has completed appropriate IP dosing, the UVB exposure will be conducted on a site on the lower back, above the original. If the participant does not take the final dose of IP the morning of Visit 5 (Day 26), the erythema assessment and biopsy will still take place, as long as the participant is compliant with their IP dose the 7 days prior to Day 26.

- **Erythema Assessment**:

  At Visit 2 (Day 1) and Visit 5 (Day 26), erythema levels for unexposed skin and each template square of the UVB-exposed skin will be quantified using a Chroma Meter (Minolta Model CR-400 or equivalent device). To determine the MED, first compute the average of all the unexposed skin's a* (redness) readings and add 2.5. The lowest exposure with the site's average a* (redness) readings at or above this value is the MED. All skin types (except for Fitzpatrick VI) can be expected to show a response within the planned exposure range[26].

- **Skin Biopsy**: At the indicated time points, 6mm-diameter punch biopsies of nonlesional skin are planned at 3 sites as follows:

  1. On Visit 2 (Day 1), 3 biopsy sites on the right buttock include (1) unexposed skin, (2) skin exposed to the 1x MED, and (3) skin exposed to the UVB dose that is 1 step higher than the 1x MED.
  2. On Visit 5 (Day 26), 3 biopsy sites on the left buttock will be comparable to those taken on Visit 2 (Day 1), including (1) unexposed skin, (2) skin exposed to the same UVB Dose as the 1x MED from the Visit 2 (Day 1) assessment, and (3) skin exposed to the UVB dose that is 1 step higher than the 1x MED from the Visit 2 (Day 1) assessment. If the 1x MED from the Visit 2 (Day 1) assessment is at the highest UVB dose (80mJ/cm2) or if no erythema is detectable on exposed skin at any dose, then two 4mm biopsies of skin exposed the highest UVB dose will be taken at both Visit 2 (Day 1) and Visit 5 (Day 26).
  3. Stitch removal is planned for Visit 3 (Day 14) and Visit 6 (Day 40).

Table 8.2. Schedule of Events

			Treatment							
Time Point	**Screening**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**			
Visit Windows (Days)	**(-30 to -1)**	**Day 0**	**Day 1** *(20-28hrs after UVB exposure)*	**Day 14**[A] (Day 10-15)	**Day 25** (Day 21-29)	**Day 26** *(20-28hrs after UVB exposure)*	**Day 40** (Day 36 - 41)[B]	**Early Termination Visit**	**Restart Visit**[H]	**Unscheduled Visit**
Clinical Blood Draw (mL)	20	0	0	0	20	0	0	20	20	20
Research Blood Draw (mL)	0	Up to 50	0	0	Up to 50	0	0	0	0	0
Visit Draw Total (mL)[C]	20	Up to 50	0	0	Up to 70	0	0	20	20	20
Informed Consent	X									
Demographics	X									
Medical History	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Eligibility Review	X	X							X	
Dispense tofacitinib[D]			X						X	X
Tofacitinib Collection						X		X		
Tofacitinib Count/Confirm Compliance; Review Patient Diary				X	X[E]	X		X		
EULAR/ACR Lupus 2019	X									
SLEDAI-2K	X	X			X			X	X	X
CLASI		X			X			X	X	X
Comprehensive Physical Examination	X	X			X			X	X	X
Fitzpatrick Scale Assessment	X									
Height, Weight, Vital Signs	X	X	X		X	X		X	X	X
Adverse Event monitoring		X	X	X	X	X	X	X	X	X
UVB Exposure		X			X					
Erythema Assessment			X			X				
Skin Biopsy			X			X				
Stitch Removal				X			X	X[F]		

			Treatment							
Time Point	**Screening**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Early Termination Visit**	**Restart Visit[H]**	**Unscheduled Visit**
Visit Windows (Days)	**(-30 to -1)**	**Day 0**	**Day 1** (20-28hrs after UVB exposure)	**Day 14[A]** (Day 10-15)	**Day 25** (Day 21-29)	**Day 26** *(20-28hrs after UVB exposure)*	**Day 40** (Day 36 - 41)[B]			
Complete Blood Count (CBC)	X				X			X	X	X[G]
Erythrocyte sedimentation rate (ESR)	X				X			X	X	X[G]
Lipids	X				X			X	X	X[G]
Chemistries: Liver Enzymes, Bilirubin, Creatinine, eGFR	X				X			X	X	X[G]
C3, C4	X				X			X	X	X[G]
anti-ds DNA	X				X			X	X	X[G]
Urinalysis: Urine Protein/Creatinine	X				X			X	X	X[G]
IGRA or PPD	X									
Hepatitis B surface antigen and core antibody	X									
Hepatitis C antibodies with HCV RNA (PCR) if antibody positive	X									
HIV antigen/antibody or NAT	X									
Serum Pregnancy	X									
Urine Pregnancy					X			X	X	
Blood draw for Biomarkers (Serum)- 10mL		X			X					
Whole blood Proteomic Studies- (40mL at University of Michigan; 10mL at all other study sites)		X			X					

A. Participants who start a new 25-day course of tofacitinib will have a virtual or telephone visit at Day 14 to assess adverse events and concomitant medications.

B. See Section 6.5.1, *Permanent Discontinuation of Investigational Agent*, for more information regarding the Visit 6 (day 40) visit for participants who prematurely discontinue study drug.

C. Lab volumes to not exceed 450 cc every 3 months.

D. See Section 3.1, *Description of Study Design,* for information regarding the timing of IP dosing.

E. See Section 8.5.5, *Research Assessments*, regarding the compliance requirements for phototesting, erythema assessment and biopsy.

F. As needed.

G. Laboratory assessments as relevant to the reason for the Unscheduled visit. These labs must be drawn prior to reinitiating study drug if the participant has had a pause or interruption in IP dosing.

H. In order to reassess entry criteria, all labs will be performed STAT. Once eligibility has been reconfirmed, tofacitinib will be dispensed. The first dose of the new course of tofacitinib will be taken the following day.

9. Mechanistic Assays

Studies on skin biopsies

1. RNA sequencing to identify changes in inflammatory gene expression before and after UV exposure before and after tofacitinib.
2. TUNEL, 8-hydroxyguanosine, and caspase-3 staining to evaluate for cell death before and after UV exposure before and after tofacitinib.
3. Spatial sequencing to evaluate the inflammatory cell populations before and after UV exposure before and after tofacitinib.
4. Vgll3 localization in biopsies before and after UV exposure before and after tofacitinib to understand how this regulator of female bias in autoimmunity is modulated in lupus.

Studies on blood

1. Activation of neutrophil NETosis before and after tofacitinib.

10. Biospecimen Storage

1. Formalin Fixed, paraffin-embedded (FFPE) skin biopsies collected as part of this study will be retained for up to 15 years.
2. Plasma from treated participants will be stored for contribution to approved other collaborative projects.
3. Peripheral blood mononuclear cells (PBMCs) from studies left over from neutrophil isolation will be frozen and stored in LN_2 for additional analysis.

11. Criteria for Participant and Study Completion and Premature Study Termination

11.1. Participant Completion

Participants must complete Visits 1 (Day 0), 2 (Day 1), 4 (Day 25), and 5 (Day 26) for inclusion in the final analysis of photosensitivity endpoints.

11.2. Participant Withdrawal Criteria

Participants may be prematurely withdrawn from the study for the following reasons:

1. The participant elects to withdraw consent from all future study activities, including follow-up.
2. The participant is “lost to follow-up” under the following conditions:
    - An eligible participant who could not be contacted to schedule Visit 1 (Day 0) within the screening period. Alternatively, this participant may be re-screened.
    - A participant who attended Visit 2 (Day 1) but, at some point during follow-up, attempts to reestablish contact with the participant fail. Attempts to reconnect should continue until Day 25 at which point “lost to follow-up” may be declared.
    - A participant who attended Visit 1 (Day 0), but misses Visit 2 (Day 1) is allowed to re-screen if contact can be reestablished. Otherwise, “lost to follow-up” may be declared.
3. The participant dies.
4. The investigator no longer believes participation is in the best interest of the participant.

If a participant withdraws from the study, the participant will be asked to return for a final visit where the assessments outlined in the early termination visit in Table 8.2, *Schedule of Events*, will be performed. No additional follow-up will be requested from participants after early study withdrawal.

11.3. Participant Replacement

Participants who fail to complete the Visit 4 (Day 25) and Visit 5 (Day 26) photosensitivity and biopsy assessments may be replaced according to the following rules, which depend on the reason for withdrawal from the study:

- No more than three individuals withdrawn for reasons due to concerns over safety or tolerability of tofacitinib may be replaced.
- No more than 18 individuals withdrawn for reasons other than safety or tolerability concerns, including "external" reasons unrelated to the individual (e.g., study site closed due to COVID-19), may be replaced.

11.4. Follow-up after Early Study Withdrawal

Participants who withdraw from the study for any reason will be asked to consent to a final Early Termination Visit to complete clinical and safety assessments. See Protocol Section 8.4 *Early Termination Visits* for more information.

11.5. Study Stopping Rules

There are no pre-specified study stopping rules.

If any of the events described in Section 12.8.2.2, *Ad hoc DSMB Reviews* occur, an ad hoc DSMB review will occur. After review of the data, the Data Safety Motoring Board (DSMB) will make recommendations regarding the study conduct and/or continuation.

12. Safety Monitoring and Reporting

12.1. Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per Section 12.5, *Reporting of Serious Adverse Events and Adverse Events*) to the sponsor, DAIT/NIAID. Appropriate notifications will also be made to site principal investigators, Institutional Review Boards (IRBs).

Information in this section complies with International Council for Harmonization (ICH) Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice, the principles of 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 : Common Terminology Criteria for Adverse Events PDF.

12.2. Definitions

12.2.1. Adverse Event (AE)

Any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP

"Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2)

12.2.2. Suspected Adverse Reaction

Any adverse event for which there is a reasonable possibility that the investigational drug [or investigational study therapy regimen] caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction (SAR) implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

For this study, a SAR will include any untoward or unfavorable medical occurrence associated with:

- Study therapy: tofacitinib
- Skin biopsy
- UVB exposure

12.2.3. Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the package insert or is not listed at the specificity, severity or rate of occurrence that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the Investigational New Drug (IND).

12.2.4. Serious Adverse Event

An adverse event or SAR is considered "serious" if, in the view of either the investigator or DAIT/NIAID, it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death.
2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or DAIT/NIAID, its occurrence places the participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Elective hospitalizations or hospital admissions for the purpose of conduct of protocol mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

12.3. Grading and Attribution of Adverse Events

12.3.1. Grading Criteria

The study site will grade the severity of adverse events experienced by the study participants according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) 5.0. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to

analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the Protocol Chair and has been deemed appropriate for the population to be studied in this protocol.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event.
Grade 2 = moderate adverse event.
Grade 3 = severe or medically significant.
Grade 4 = life-threatening consequences; urgent intervention indicated.
Grade 5 = death.

Events of Grade 2 or higher and all Grade 1 or higher COVID-19 events will be recorded on the appropriate AE eCRF for this study according to 12.4, *Collection and Recording of Adverse Events*.

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram etc.), a treatment-emergent adverse event is defined as an increase in grade from the last assessment prior to a participant starting treatment, or from the last post-baseline value that doesn't meet grading criteria. Changes in grade from screening to Day 0, Day 1, and treatment initiation (Day 2) will also be recorded as adverse events, but are not treatment-emergent. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

Liver function abnormalities will be graded using criteria from NCI-CTCAE version 4.0, defined relative to the ULN as follows:

- Aspartate aminotransferase [AST] increased
  - Grade 1: > ULN – 3.0x ULN
  - Grade 2: > 3.0x ULN - 5.0x ULN
  - Grade 3: > 5.0x ULN - 20.0x ULN
  - Grade 4: > 20.0x ULN
- Alanine aminotransferase [ALT] increased
  - Grade 1: > ULN – 3.0x ULN
  - Grade 2: > 3.0x ULN - 5.0x ULN
  - Grade 3: > 5.0x ULN - 20.0x ULN
  - Grade 4: > 20.0x ULN
- Alkaline phosphatase [ALP] increased
  - Grade 1: > ULN – 2.5x ULN
  - Grade 2: > 2.5x ULN - 5.0x ULN
  - Grade 3: > 5.0x ULN - 20.0x ULN
  - Grade 4: > 20.0x ULN
- Blood bilirubin increased
  - Grade 1: > ULN – 1.5x ULN
  - Grade 2: > 1.5x ULN - 3.0x ULN
  - Grade 3: > 3.0x ULN - 10.0x ULN
  - Grade 4: > 10.0x ULN

12.3.2. Attribution Definitions

The relationship, or attribution, of an adverse event to the study therapy regimen or study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE/SAE eCRF. Final determination of attribution for safety reporting will be determined by DAIT/NIAID. The relationship of an adverse event to study therapy regimen or procedures will be determined using the descriptors and definitions provided in Table 12.1.

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: http://ctep.cancer.gov/reporting/ctc.html.

Table 12.1 Attribution of Adverse Events

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure)
Unrelated Category		
1	Not Related	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
Related Categories		
2	Possibly Related	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Related	The adverse event is clearly related.

12.4. Collection and Recording of Adverse Events

12.4.1. Collection Period

Adverse events will be collected and recorded in EDC from Visit 1 (Day 0), until a participant completes study participation or until 30 days after he/she prematurely withdraws or is withdrawn from the study (without withdrawing consent). Serious Adverse Events, as defined in Section 12.2.4 *Serious Adverse Events*, Suspected Adverse Reactions, as defined in Section 12.2.2, *Suspected Adverse Reactions,* and adverse events related to study procedures will be collected and recorded in EDC from the time of consent until a participant completes study participation or until 30 days after he/she prematurely withdraws or is withdrawn from the study (without withdrawing consent).

12.4.2. Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the participant.
- Interviewing the participant [e.g., using a checklist, structured questioning, diary, etc.].
- Receiving an unsolicited complaint from the participant.

In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 12.3, *Grading and Attribution of Adverse Events.*

12.4.3. Recording Adverse Events

Throughout the study, the investigator will record all adverse events and SAEs as described previously (Section 12.2, *Definitions)* on the appropriate AE/SAE eCRF regardless of the relationship to study therapy regimen or study procedure.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the participant prematurely withdraws or is withdrawn from the study, whichever occurs first (without withdrawing consent).

12.5. Reporting of Serious Adverse Events and Adverse Events

12.5.1. Reporting of Adverse Events

This section describes the responsibilities of the site investigator to report AEs to the study sponsor via the DAIT-SACCC (Division of Allergy, Immunology, and Transplantation Statistical and Clinical Coordinating Center).

Timely reporting of AEs of NCI-CTCAE Grade 2 and higher and Grade 1 or higher COVID-19 event is required. Unless otherwise noted below in Section 12.5.2 for SAEs, AEs must be recorded on the AE/SAE eCRF within five (5) days of discovery of the event. Whenever possible, a diagnosis should be provided, rather than compilation of signs/symptoms, with grade of the event dictated by highest grade of the sign/symptom component.

12.5.2. Reporting of Serious Adverse Events to DAIT/NIAID (Sponsor)

This section describes the responsibilities of the site investigator to report SAEs to the Study Sponsor (NIAID/DAIT) via the AE/SAE eCRF. Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines.

When a site investigator identifies a SAEs, he or she must notify DAIT/NIAID via the DAIT-SACCC within 24 hours regardless of the relationship or expectedness. Site investigators are to report these events on the SAE eCRF in Electronic Data Capture (EDC). Should EDC become unavailable/ inaccessible, the site investigator should notify DAIT/NIAID via the DAIT-SACCC email at Rho_productsafety@rhoworld.com. This email can serve as the initial notification; however, within the next business day the SAE eCRF must be completed.

All requested information on the SAE eCRF should be provided. Unavailable details of the event at time of initial report should not delay submission of known information. The initial report should include at a minimum: AE term, relationship to tofacitinib, and reason why event is serious (per definitions). Supplementary Case Report Form (CRF) pages including medical history, concomitant medications, demographics, study drug administration, and death must be provided. As additional details become available, the SAE eCRF should be updated and submitted. With each iteration of the form, the investigator (or designated sub-investigator) must sign the form electronically.

For additional information regarding SAE reporting, contact Rho Product Safety (DAIT-SACCC):

Rho Product Safety
2635 E. NC Hwy. 54
Durham, NC 27713
[redacted]

12.5.3. Reporting to FDA

This clinical study has been granted exemption from investigational new drug application (IND) regulations by the FDA in accordance with 21 CFR 312.2(b) of the regulations, therefore, AEs will not be reported to the FDA by the study sponsor (NIAID).

12.5.4. Reporting of Adverse Events to IRBs/IECs

In this multi-site study, the investigators shall report adverse events, including expedited reports, in a timely fashion to their respective IRB/IEC in accordance with applicable regulations and guidelines.

12.6. Pregnancy Reporting

The investigator shall be informed immediately of any pregnancy in a study participant or a partner of a study participant. A pregnant study participant shall be instructed to stop taking study medication immediately. A study participant whose partner is pregnant shall be advised to inform the partner's obstetrician about the trial. The investigator shall counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant participant shall continue until the conclusion of the pregnancy. Additionally, pregnant participants and partners should be given information about Mother to Baby. The current patient information fact sheet on tofacitinib can be found at the following link: https://mothertobaby.org/fact-sheets/tofacitinib-pregnancy/

The investigator shall report to DAIT/NIAID via the DAIT-Statistical and Clinical Coordinating Center (SACCC) within 1 business day of becoming aware of the event using the Pregnancy eCRF. All pregnancies in study participants identified during the study shall be followed to conclusion and the outcome of each must be reported. Pregnancies in the partners of study participants do not have to be followed to conclusion; however, the status of the partner should be reported at the last study visit, if known. The Pregnancy eCRF shall be updated and submitted to the DAIT-SACCC when details about the outcome are available. When possible, similar information shall be obtained for a pregnancy occurring in a partner of a study participant.

Information requested about the delivery shall include:

- Gestational age at delivery.
- Birth weight, length, and head circumference.
- Gender.
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available.
- Any abnormalities.

All pregnancy complications that result in a congenital abnormality, birth defect, miscarriage, and medically indicated abortion - an SAE shall be submitted to the DAIT-SACCC using the SAE reporting procedure described above (Section 12.5.1, *Reporting of Serious Adverse Events to DAIT/NIAID*).

12.7. Reporting of Other Safety Information

An investigator shall promptly notify DAIT/NIAID via the DAIT-SACCC when an "unanticipated problem involving risks to participants or others" is identified, which is not otherwise reportable as an adverse event.

12.8. Review of Safety Information

12.8.1. Medical Monitor Review

The DAIT/NIAID Medical Monitor shall receive monthly reports from the DAIT-SACCC compiling new and accumulating information on AEs, SAEs, and pregnancies recorded by the study site on appropriate eCRFs.

In addition, the Medical Monitor shall review and make decisions on the disposition of the SAE and pregnancy reports received by the DAIT-SACCC (See Sections 12.5.1, *Reporting of Serious Adverse Events to DAIT/NIAID*, and 12.6, *Pregnancy Reporting*).

12.8.2. Data Safety and Monitoring Board Review

12.8.2.1. Planned DSMB Reviews

The progress of the study will be monitored by the NIAID Data and Safety Monitoring Board (DSMB). The DSMB shall review safety data at least yearly during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs. The DSMB will also be informed of any Expedited Safety Reports during planned safety reviews.

In addition, the DSMB will be notified of any notable impacts on the study due to COVID-19 (See Section 3.1.1, *Considerations Regarding COVID-19*.)

12.8.2.2. Ad hoc DSMB Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for *ad hoc* reviews. The DSMB will review any event that potentially impacts safety at the request of the protocol chair or DAIT/NIAID. In addition, the following events will trigger an *ad hoc* comprehensive DSMB Safety Review:

- Any death considered possibly or definitely related to study treatment or procedures.
- The occurrence in 2 participants of Grade 3 or higher AEs or SAEs with the same MedDRA preferred terms considered at least possibly related to study treatment or procedures.
- The occurrence in 2 participants of Grade 3 or higher infections.
- Any grade 2 or higher thromboembolic event.

After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

12.8.2.2.1. Temporary Suspension of Tofacitinib Dosing for ad hoc DSMB Safety Review

If a triggering event occurs and an ad hoc DSMB Safety Review is required (Section 12.8.2.2, *Ad hoc DSMB Reviews*), then a temporary halt in initiating dosage for new enrollees will be implemented. Participants on study treatment will continue as planned. If two weeks has elapsed and the ad-hoc DSMB has not met, then no new participants will be consented or enrolled until after the DSMB completes review of the safety data.

13. Statistical Considerations and Analytical Plan

13.1. Overview

This is a single-arm multi-site proof-of-concept study in which participants with CLE will undergo 25 days of treatment with tofacitinib (11 mg daily PO). The primary objective is to determine the impact of tofacitinib on photosensitivity parameters, including UVB-mediated cutaneous apoptosis, UVB-mediated inflammatory gene transcription, and MED in response to UVB exposure. The study will also evaluate changes in clinical endpoints and safety.

13.2. Endpoints

Primary and secondary endpoints are listed in Sections 3.2, *Primary Endpoint* and 3.3, *Secondary Endpoints*.

13.3. Measures to Minimize Bias

This study includes well-defined entry criteria to ensure the target population is correctly identified. Although the study has a single open-label arm, the photosensitivity parameters, which are key to evaluating the primary objective, are all objectively measured and not subject to participant or investigator bias. To minimize the potential threat to study integrity by loss of participants between the first and second phototests/biopsies, assessments are kept to minimum, and attention will be paid to participant well-being during and after procedures.

13.4. Analysis Plan

13.4.1. Analysis Populations

The **Safety Sample (SS)** population includes all participants who receive any amount of tofacitinib.

The **Per Protocol 1 (PP1)** population includes all participants who receive any amount of tofacitinib and who complete phototests and skin biopsies at both baseline (Visits 1 and 2) and post-treatment (Visits 4 and 5) time points. Only individuals who complete at least 21 days of IP dosing will have the post-treatment phototest. The primary objective of this proof-of-concept study cannot be evaluated in individuals who do not have data at both pre- and post-treatment time points.

The **Per Protocol 2 (PP2)** population includes all PP1 participants with no protocol deviations that would impact photo sensitivity assessments. The reported major deviations will be reviewed during a masked data review to determine which participants should be excluded from the PP2 population.

13.4.2. Primary Analysis of Primary Endpoint

The primary endpoint is change in percentage of UVB-induced apoptotic epidermal cells from Visit 2 (Day 1) (pre-treatment) to Visit 5 (Day 26) (post-treatment). Percentage of UVB-induced apoptotic cells (A^{UVB}) is defined as the number of TUNEL positive cells in the epidermis divided by the number of nuclei in that high powered field. The percentage of UVB-induced apoptotic cells at a visit is defined as the difference between the percentage of apoptotic epidermal cells in the biopsy exposed at the MED ($A^{Day1MED}$) and percentage of apoptotic epidermal cells in the unexposed biopsy ($A^{unexposed}$), for both biopsies taken at the same visit. The change in percentage of UVB-induced apoptotic epidermal cells will be computed as follows for each individual in the study:

$$\mathrm{A}^{\mathrm{UVB}}_{\mathrm{Day\ 1}} = \mathrm{A}^{\mathrm{Day1MED}}_{\mathrm{Day\ 1}} - \mathrm{A}^{\mathrm{Day\ 1\ unexposed}}_{\mathrm{Day\ 1}}$$

$$\mathrm{A}^{\mathrm{UVB}}_{\mathrm{Day\ 26}} = \mathrm{A}^{\mathrm{Day1MED}}_{\mathrm{Day\ 26}} - \mathrm{A}^{\mathrm{Day\ 26\ unexposed}}_{\mathrm{Day\ 26}}$$

$$\text{change in } \mathrm{A}^{\mathrm{UVB}} = \mathrm{A}^{\mathrm{UVB}}_{\mathrm{Day\ 26}} - \mathrm{A}^{\mathrm{UVB}}_{\mathrm{Day\ 1}}$$

The null and alternative hypotheses for the primary analysis of the primary endpoint are:

H_0: Mean change in $A^{UVB} = 0$

H_A: Mean change in $A^{UVB} \neq 0$

The statistical hypotheses outlined above for the mean change in A^{UVB} will be evaluated in the PP1 population using a two-sided Wilcoxon signed-rank test at a Type 1 error rate of 0.05.

13.4.3. Supportive Analyses of the Primary Endpoint

The primary hypothesis will also be evaluated in the PP2 population. In addition, depending on findings, exploratory analyses may be considered post hoc.

13.4.4. Analyses of Secondary Endpoints

The PP1 population will be used for evaluation of photosensitivity and disease activity measures. For each secondary endpoint, the null hypothesis is that there is no change in the parameter of interest from pre- to post-treatment time points. All secondary inferential analyses are considered supportive; p-values will be presented without adjustment for multiple comparisons.

Analysis of secondary safety endpoints will be conducted using the safety population.

13.4.4.1. Photosensitivity parameters

The following analyses of these secondary endpoints will support the primary objective to evaluate the impact of tofacitinib on photosensitivity parameters.

- **Change in MED due to UVB from Visit 2 (Day 1) to Visit 5 (Day 26)**: MED is an ordinal endpoint. Shifts in MED levels from pre- to post-treatment will be evaluated using the McNemar-Bowker test for symmetry.

- **Change in UVB-induced expression of inflammatory genes in skin from Visit 2 (Day 1) to Visit 5 (Day 26), based on enumeration of RNA transcripts**: The mean change will be evaluated using a two-sided Wilcoxon signed-rank test.

13.4.4.2. Disease activity

- **Changes in CLASI activity score, CLASI damage scores, and SLEDAI-2K total scores from Visit 1 (Day 0) to Visit 4 (Day 25)**: For each endpoint, the mean change will be evaluated using a two-sided Wilcoxon signed-rank test.

13.4.4.3. Safety

- Clinical laboratory values will be summarized using descriptive statistics. In addition, individuals with a laboratory value that increases during the study by 1 or more severity grades per NCI-CTCAE will be identified and tabulated.
- Treatment-emergent AEs and SAEs will be summarized by severity, by relationship to study drug, and by MedDRA Organ Class and Preferred Term.

13.4.5. Descriptive Analyses

Descriptive statistics will be provided for participant disposition, baseline and demographic characteristics, study drug compliance, and use of concomitant medications. Continuous measures will be summarized using n, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using counts and percentages.

13.5. Interim Analyses

Other than interim looks by the DSMB to review data on safety and study conduct, no interim analyses are planned for either efficacy or futility.

13.6. Statistical Hypothesis

See Section 13.4.2, *Primary Analysis of Primary Endpoint*.

13.7. Sample Size Considerations

Preliminary data for the sample size computations are derived from a study that examined UVB-induced apoptosis of keratinocytes derived from individuals with cutaneous lupus before and after exposure to baricitinib, a Jak inhibitor like tofacitinib[6]. Although this study examined in vitro exposure of cultured keratinocytes, apoptotic percentages are expected to be similar to skin since UVB is penetrant to the basal keratinocyte layer in vivo. Estimates for means and SDs are presented in Table 13.1.

Table 13.1: Estimates for mean (SD) for Percentage of apoptotic keratinocytes that were unexposed, UVB-exposed with no drug, and UVB-exposed with baricitinib

	Percentage of apoptotic keratinocytes			
	unexposed [1]	UVB only [2]*	UVB + drug [3]*	[3]*
	$A^{\text{unexposed}}$	$A_{\text{pre}}^{\text{exposed}}$	$A_{\text{post}}^{\text{exposed}}$	$A_{\text{post}}^{\text{exposed}} - A_{\text{pre}}^{\text{exposed}}$
n	6	11	5	5
Mean	6%	50%	16%	-37%
SD	6%	14%	9%	15%
80% CI for SD	(4.4%, 11%)	(11%, 20%)	(6.5%, 17%)	(11%, 30%)

[1] Data points derived from Fig 6B of Sarkar et al (2018) [6].

[2] Data points derived from Fig 6B and Fig 6E of Sarkar et al (2018) [6].

[3] Data points derived from Fig 6E of Sarkar et al (2018) [6].

*5 of these samples were paired.

Since $A^{\text{unexposed}}$ is expected to be similar at pre and post-treatment time points, the change in $A^{\text{UVB}} = A_{\text{post}}^{\text{UVB}} - A_{\text{pre}}^{\text{UVB}}$ is approximately equal to $A_{\text{post}}^{\text{exposed}} - A_{\text{pre}}^{\text{exposed}}$. As such, the SD for $A_{\text{post}}^{\text{exposed}} - A_{\text{pre}}^{\text{exposed}}$ for the preliminary data, 15% (Table 13.1), is used as starting point for power calculations. Power estimates for a design with 10 participants were computed over a range of possible means for change in A^{UVB}, and for different distribution assumptions (normal, logistic, double exponential and uniform; Figure 2). For this study, an improvement (decrease) from pre- to post-treatment of at least 20 percentage points is considered relevant for demonstrating proof-of-concept. For the best estimate of SD, 15%,

power is ≥93% for a mean change in A^{UVB} of at least 20 percentage points under all four distributions (α=0.05, two-sided, Wilcoxon signed-rank test). Power is ≥80% under all 4 distributions for a mean change in A^{UVB} of at least 21.4 percentage points as long as the SD≤ 20%. If the underlying SD is 30%, the upper 80% confidence limit from Table 13.1, the design has at least 80% power to detect a change of at least 30 percentage points under the uniform, logistic, and double exponential distributions, and 32.1 percentage points under the normal distribution. Power was computed using PASS version 15.

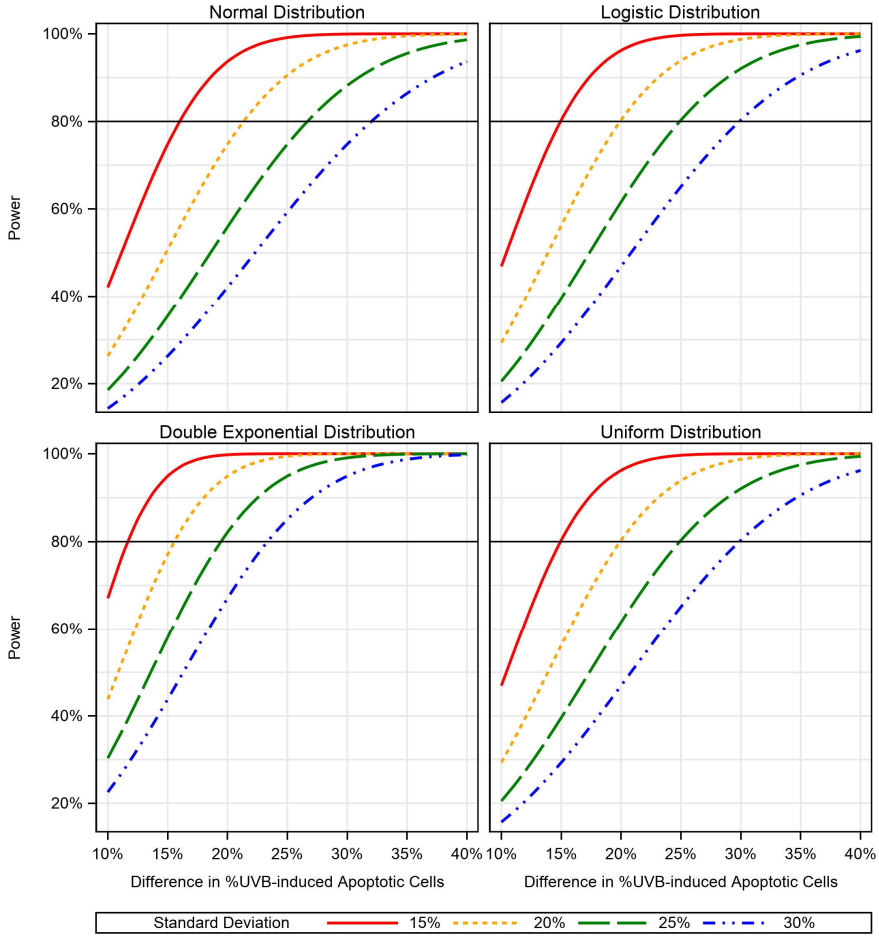


Figure 2. Power for 10 paired samples (pre and post treatment) under different distribution assumptions

All participants completing Visit 5 (Day 26) skin biopsy will be included in the primary analysis of the primary endpoint. For the primary analysis, there will be no missing data; participants who cannot complete the second biopsy will be replaced. As such, missing data does not impact the power/sample size considerations, but attrition will be considered when evaluating generalizability of the results.

14. Identification and Access to Source Data

14.1. Source Data

Source documents and source data are considered to be the original documentation where participant information, visits consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation, and validation of clinical findings, observations, and other activities during a clinical trial.

14.2. Access to Source Data

The site investigators and site staff will make all source data available to the DAIT/NIAID, NIAID representatives, agents, employees, contractors, and other persons assisting in conducting, monitoring, or analyzing the study, as well as to relevant health authorities. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

15. Quality Assurance and Quality Control

The principal investigator is required to keep accurate records to ensure that the conduct of the study is fully documented. The principal investigator is required to ensure that all eCRFs are completed for every participant entered in the trial. The period of record retention should be consistent with the record retention policies of the sponsoring agency or applicable regulatory agencies. However, in certain instances, documents should be retained for a longer period if required by the applicable regulatory agency or by the National Institutes of Health.

Data will be obtained from a variety of sources including, but not limited to laboratory notebooks, automated instrument output files, and clinical participant charts. Data from these source materials will be transmitted to the DAIT data center via one of two mechanisms. Data collected electronically at central laboratories will be transferred electronically directly from the laboratory to the DAIT data center using standard secure data transfer procedures. Data collected at the clinical site will be transmitted to the DAIT data center using an internet-based remote data entry system. Clinical site personnel use an internet browser to key data into eCRFs; each CRF page is submitted to the clinical database electronically as the page is completed. Univariate data validation tests are performed as the data are keyed. The clinical database is backed up nightly; backup tapes are saved in a secure, off-site location. At any time, authorized site personnel may log in to the remote data entry system, review and correct previously entered data, or key additional data. The data will be further validated per the study data validation plan via a series of computerized and manual edit checks, and all relevant data queries will be raised and resolved on an ongoing basis. Complete, clean data will be frozen to prevent further inadvertent modifications. All discrepancies will be reviewed, and any resulting queries will be resolved with the investigators and amended in the database. All elements of data entry (i.e., time, date, verbatim text, and the person performing the data entry) will be recorded in an electronic audit trail to allow all data changes in the database to be monitored and maintained in accordance with federal regulations.

Monitors are responsible for regular inspection of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data.

Monitors will periodically visit the participating clinical site and audit the source documents in order to validate the data in the central database. Data will be provided using the participant's screening or enrollment number, the DAIT data center will not collect personally identifying information such as the participant's name or social security number. Participants will provide demographic information such as race, ethnicity, and birth date.

Data collected by the DAIT data center will be held in the strictest confidence and are protected from access that could reveal personally identifying information about any participant in the trial.

16. Protocol Deviations

16.1. Protocol Deviation Definitions

Protocol Deviation – The investigators and site staff will conduct the study in accordance with the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.

Major Protocol Deviation (Protocol Violation) – A Protocol Violation is a deviation from the IRB approved protocol that may affect the participant's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

Non-Major Protocol Deviation – A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the participant's rights, safety or well-being, or the completeness, accuracy, and reliability of the study data.

16.2. Reporting and Managing Protocol Deviations

The study site principal investigator has the responsibility to identify, document and report protocol deviations as directed by the DAIT/NIAID. However, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review.

When a deviation occurs, corrective actions may be necessary depending on the nature of the deviation. The Principal Investigator (PI) and NIAID/DAIT conduct a risk assessment. The PI is responsible for the timely correction and documentation of problems identified by study personnel, outside monitors or auditors, or other parties involved in the conduct of a study. The depth of Corrective Action/Preventive Action (CAPA) required should match the risk and impact on safety of participants and/or the quality of the data.

Upon determination that a protocol deviation has occurred, the PI/designated study staff will report the deviation according to the processes outlined for the study. A major deviation is to be reported within 3 business days and reported by the PI to the IRB per IRB reporting requirements. NIAID/DAIT will determine if the deviation is reportable to the DSMB, as applicable.

17. Ethical Considerations and Compliance with Good Clinical Practice

17.1. Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the IRB. Any amendments to the protocol or to the consent materials will also be approved by the IRB before they are implemented.

17.2. Informed Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or their designee listed on the Investigator of Record Agreement will review the consent and answer questions. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant.

The consent process will be ongoing. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

17.3. Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. The code linking the participant's identity to the unique identification number will be securely stored a password protected, HIPPA compliant shared drive managed by University of Michigan Health Information Technology. The only the protocol chair and approved study team members who have completed appropriate human subjects research training have access to the drive. Site personnel will not transmit documents containing personal health identifiers (PHI) to the NIAID/DAIT or their representatives.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of NIAID/DAIT.

The study Monitor or other authorized representatives of the NIAID/DAIT may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

18. Publication Policy

The Autoimmunity Centers of Excellence's policy on the publication of study results will apply to this trial. Authorized participants may find details regarding the policy statement on the ADCT internet website at http://www.rhoworld.com.

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