Autoimmunity Centers of Excellence

ALE10

A Phase 2, Double-Blind, Placebo-Controlled Trial of Mycophenolate Mofetil alone or with Voclosporin for Systemic Lupus: Examining Distinct Immunophenotypes to Validate and Enhance Rational Treatment

The DIVERT Trial

VERSION 4.0/October 26, 2023

Investigational New Drug (IND) Exempt

Study Sponsor	*The National Institute of Allergy and Infectious Diseases (NIAID)*
NIAID Funding Mechanism	*Autoimmunity Centers of Excellence*
Study Drug Manufacturer/Provider	*Mycophenolate Mofetil/Sandoz; Voclosporin/Aurinia Pharmaceuticals*

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INVESTIGATOR SIGNATURE PAGE	
Protocol: ALE10 (DIVERT)	Version Number: 4.0/Date: 26Oct2023
Site Principal Investigator:	
Title: A Phase 2, Double-Blind, Placebo-Controlled Trial of Mycophenolate Mofetil alone or with Voclosporin for Systemic Lupus: Examining **D**istinct **I**mmunophenotypes to **V**alidate and **E**nhance **R**ational **T**reatment	
Study Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)	
Return Signed Form to: *The original signature page must be kept for your records. Return an electronic PDF copy of the signed signature page (*as described below) to the DAIT Regulatory Management Center (RMC) via email to DAITRegulatory_SiteRegistration (SM) at DAITReg@ppd.com.*	
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 on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) document entitled *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 is acceptable (e.g., scanned and sent via email as a PDF version). An electronic signature is also acceptable (e.g., sent via email as a PDF version).* _____ **Site Principal Investigator** (Print) _____ _____ **Site Principal Investigator** (Signature) **Date**	

Protocol Synopsis

Title	A Phase 2, Double-Blind, Placebo-Controlled Trial of Mycophenolate Mofetil alone or with Voclosporin for Systemic Lupus: Examining **D**istinct **I**mmunophenotypes to **V**alidate and **E**nhance **R**ational **T**reatment
Short Title	**The DIVERT trial**
Clinical Phase	II
Number of Sites	Approximately 15 sites in the United States
Sponsor/IND Number	The National Institute of Allergy and Infectious Diseases (NIAID)/IND Exempt
Study Objectives	Primary Objective Assuming that mycophenolate mofetil (MMF) is an effective treatment in some, but not all, systemic lupus erythematosus (SLE) patients, the primary objective of this study is to evaluate the potential effectiveness of 24 weeks of MMF within previously discovered immunologically defined subsets of SLE patients [1]. This objective will be most effectively supported within the context of a successful demonstration of superiority of MMF over placebo, pooled over all clusters. To this end, individuals with lupus who are without organ-threatening disease will be randomized to 24 weeks of MMF or placebo. The primary objective is to compare the cumulative incidence of treatment failure with 24 weeks of MMF or placebo by treatment arm. Subsequently, treatment effects will be evaluated within the individual immunologically-homogenous subsets defined at screening. Secondary Objectives • To describe the effects of long-acting corticosteroid injections, MMF, MMF plus voclosporin, and placebo on measures of safety and toxicity. • To describe the effects of MMF, MMF plus voclosporin, and placebo on exploratory clinical response measures and disease flare indices. • To describe the effects of MMF, MMF plus voclosporin, and placebo on patient-reported quality of life indices. Mechanistic Objectives • To explore and compare pre-randomization gene expression patterns among responders and non-responders to MMF and MMF plus voclosporin.

	• To use comprehensive immunophenotyping to study the immunologic changes that accompany treatment-induced disease improvement to better understand key checkpoints in SLE pathophysiology. • To use comprehensive immunophenotyping to better understand immunologic changes associated with the loss of clinical response.
Study Design	This will be a multicenter, double blind, placebo-controlled Phase 2 trial of 120 participants with SLE who will enter with significant symptoms, but no organ-threatening disease. The study will be conducted in 3 stages. **Stage 1: Treatment Withdrawal**: During Stage 1, which may last up to 4 weeks, consenting participants will receive an intramuscular (IM) injection of a long-acting corticosteroid, which may be repeated if needed to achieve amelioration of symptoms. A total of 3 corticosteroid injections may be given during Stage 1 with the first injection given as early as the Screening Visit after the mechanistic blood draw is completed and the last injection given as late as the Stage 2 Randomization Visit after the mechanistic blood draw is completed. Dose will be dependent on the available formulation. In addition, participants will withdraw from all other treatments for lupus with the following exceptions: (i) as needed (PRN) nonsteroidal anti-inflammatory treatments may be started or continued, (ii) PRN topicals may be continued, (iii) hydroxychloroquine, chloroquine, or quinacrine may be continued at any stable dose, and (iv) prednisone, if ≤ 10 mg/day, may be continued at stable doses but not started. Participants may screen if taking up to 20 mg/day prednisone (or equivalent) but both the participant and the investigator must be willing and able to taper to 10 mg/day (under cover of corticosteroid injections) by the Stage 2 Randomization Visit. Withdrawal of background lupus medications can start any time after the first corticosteroid injection is given but must be completed by the Stage 2 Randomization Visit. **Stage 2: Randomization**: One hundred and twenty qualifying participants who withdraw from treatment as described in protocol Section 3.1.1, *Stage 1: Treatment Withdrawal,* and meet improvement criteria for randomization as outlined in Section 4.2.2, *Inclusion criteria required prior to randomization,* will be randomized (1:1) to receive up to 48 weeks of either MMF or corresponding MMF placebo. For the first 2 weeks, a scheduled “taper-up” of MMF will take place. Participants will receive 500mg MMF (or corresponding MMF placebo) twice a day (BID) for 7 days, followed by 500mg and 1,000mg MMF (or corresponding MMF placebo) in divided doses for 7 days. They will then continue at a stable dose of 1,000mg MMF (or corresponding MMF placebo) BID. Visits to evaluate adverse events (AE), vital signs, hematology and chemistry, study medication compliance, medication use, disease status, participant reported outcomes, and to obtain biomarker samples will occur every 4 weeks after randomization.

	Participants will be followed for a maximum of 48 weeks on study-provided medication in Stage 2. If a participant experiences an increase in SLE symptoms at any scheduled or unscheduled visit at or before the Stage 2 Week 24 visit, they will proceed in the study as follows: • If the participant is deemed a Stage 2 treatment failure as defined in protocol Section 3.2, *Primary Endpoint*, and a corticosteroid injection is deemed sufficient for treatment without new or increased lupus medication, then a blood sample for mechanistic studies will be drawn, the injection will be administered, and the participant will immediately proceed to Stage 3: Re-randomization. (See Section 3.1.3, *Stage 3 Re-Randomization*). • If the participant is deemed a Stage 2 treatment failure as defined in protocol Section 3.2, *Primary Endpoint*, and a corticosteroid injection is deemed sufficient for treatment without new or increased lupus medication, but the participant refuses the corticosteroid injection, then a blood sample for mechanistic studies will be drawn, and the participant will still immediately proceed to Stage 3: Re-randomization without the corticosteroid injection. (See Section 3.1.3, *Stage 3 Re-Randomization*). • If the participant is deemed a Stage 2 treatment failure as defined in protocol Section 3.2, *Primary Endpoint*, and a corticosteroid injection is deemed insufficient and a new or increased lupus medication is required, then a blood sample for mechanistic studies will be drawn, Stage 2 study-provided medication will be stopped, and the new or increased lupus medication will be started outside of the study. The participant will <u>not</u> be eligible for Stage 3 but will be followed to Stage 2 Week 24 or 4 weeks ± 10 days after the last dose of study-provided medication, whichever is later, before exiting the study. Participants who exit the study at Stage 2 Week 24 should complete all End of Study/Safety Follow-Up visit assessments at this time. Participants who have not failed Stage 2 on or before the Stage 2 Week 24 visit will continue on Stage 2 study-provided medication through Stage 2 Week 48 or until treatment failure, whichever occurs first. • If the participant is deemed a Stage 2 treatment failure after Stage 2 Week 24, then study-provided medication will be stopped. Prior to treatment with a corticosteroid injection or a new or increased lupus medication outside of the study, a blood sample for mechanistic studies will be drawn. The participant will return for an End of Study/Safety Follow-Up Visit 4 weeks ± 10 days after the final dose of study-provided medication. • Participants who have not failed Stage 2 on or before the Stage 2 Week 48 visit will return for an End of Study/Safety Follow-Up Visit 4 weeks ± 10 days after the final dose of study-provided medication.

	Severe lupus manifestations that are life-threatening or organ-threatening should prompt consideration for withdrawal from the study in order to enable maximal therapy with corticosteroids and other lupus medications. The ultimate decision on withdrawal should be left up to the clinical judgment of the investigator. **Stage 3: Re-Randomization:** Participants moving into Stage 3 will be re-randomized (1:1) to receive up to 24 weeks of either MMF plus voclosporin (23.7 mg BID) or MMF plus placebo for voclosporin. Individuals who previously received MMF placebo in Stage 2 will receive a 2-week taper-up of MMF (see taper details for Stage 2, Section 3.1.2, *Stage 2: Randomization*). During the first 2 weeks of treatment, a single IM injection of a long-acting corticosteroid may be administered if needed to achieve amelioration of symptoms without meeting the definition of treatment failure in Stage 3 and without a requirement to stop Stage 3 study-provided medication. This single IM corticosteroid injection within the first 2 weeks of Stage 3 treatment may be administered regardless of whether or not one was given at the time of Stage 2 treatment failure for a total of 2 corticosteroid injections (dose will be dependent on the available formulation) with the first injection given as early as the visit where participants have a Stage 2 treatment failure after the mechanistic blood draw and the second injection given as late as the Stage 3 Week 2 Visit. Visits to evaluate AEs, vital signs, hematology and chemistry, study medication compliance, medication use, disease status, participant reported outcomes, and to obtain biomarker samples will occur every 4 weeks after re-randomization. In Stage 3, participants will be on treatment for a maximum of 24 weeks or until treatment failure, whichever occurs first. • If the participant is deemed a Stage 3 treatment failure, study-provided medication will be stopped. Prior to treatment with a corticosteroid injection or a new or increased lupus medication outside of the study, a blood sample for mechanistic studies will be drawn. The participant will return for an End of Study/Safety Follow-Up Visit 4 weeks ± 10 days after the final dose of study-provided medication. • Participants who have not failed Stage 3 on or before the Stage 3 Week 24 visit will return for an End of Study/Safety Follow-Up Visit 4 weeks ± 10 days after the final dose of study-provided medication. As in Stage 2, severe lupus manifestations that are life-threatening or organ-threatening should prompt consideration for withdrawal from the study in order to enable maximal therapy with corticosteroids and other lupus medications. The ultimate decision on withdrawal should be left up to the clinical judgment of the investigator.
Primary Endpoint	The primary endpoint is the cumulative incidence of participants who experience a Stage 2 treatment failure at or before the Stage 2 Week 24 visit. The criteria for treatment failure are defined in Section 3.5.1, *Treatment Failure*.

Secondary Endpoint(s)	Efficacy • Clinical response in Stage 2, defined by the BILAG-based combined Lupus Assessment (BICLA) (see Section 3.5.3, *BILAG-based Combined Lupus Assessment (BICLA)*) at Stage 2 Week 24. • The cumulative incidence of participants who experience a Stage 3 treatment failure, defined as the occurrence of any criteria in Section 3.5.1, *Treatment Failure* after re-randomization and on or before completing Stage 3. • Time to treatment failure in Stage 3, defined as the interval from the day of Stage 3 randomization until the day of treatment failure. • Clinical response in Stage 3, defined by the BICLA (see Section 3.5.3, *BILAG-based Combined Lupus Assessment (BICLA)*) at Stage 3 Week 24. Safety The following specific events will be evaluated separately for each stage of the study: • The incidence of Grade 3 or higher related AEs. • The incidence of Grade 3 or higher infections. • The incidence of renal dysfunction, defined as Grade 3 or higher chronic kidney disease with estimated glomerular filtration rate (eGFR) < 30 ml/min per 1.73 m^2. • The incidence of Grade 3 or higher hypertension (HTN), defined as a systolic blood pressure ≥ 160 mm Hg or a diastolic blood pressure of ≥ 100 mm Hg. Exploratory Endpoints Clinical Endpoints: The following will be evaluated in Stage 2 and Stage 3: • Proportions of participants in each arm who achieve responder status as assessed by Systemic Lupus Erythematosus Responder Index (SRI)-4, SRI-6, and SRI-7 (as defined in Section 3.5.2, *Systemic Lupus Erythematosus Responder Index (SRI)*) every 4 weeks through Week 24. • Incidence rates for Mild/Moderate and Severe flares accumulated during the treatment period. Three flare assessments will be evaluated independently: a. Thanou modified Safety of Estrogen in Lupus: National Assessment Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) Flare Index (See Section 19.3.5, *Thanou Modified SFI)* [2]. b. BILAG (British Isles Lupus Assessment Group) flare, defined as a new A or 2 new Bs. c. BILAG flare, defined as any item marked new or worse that could support a BILAG A (severe flare) or 2 organs with items marked new or worse that could support a BILAG B (moderate flare). • Incidence rates for Mild, Moderate and Severe disease activity. Assessments across multiple organs/systems are rated using:

	a. Lupus Foundation of America Rapid Evaluation of Activity in Lupus (LFA-REAL) clinician assessment b. LFA-REAL participant assessment • Longitudinal profiles of the Physical Component Summary, Mental Component Summary, and individual domains of the SF-36 patient-reported outcome that are observed over the treatment period. Mechanistic Endpoints: The following pharmacodynamic markers will be evaluated in Stage 2 and Stage 3: • Differential expression, at the module or single gene level, between participants within immunologically-homogenous clusters who do and do not obtain a clinical response. • Identification of complex immunophenotypes characterizing clinical response or non-response to study treatment. • Longitudinal profiles of Tumor Necrosis Factor-Like Weak Inducer of Apoptosis (TWEAK), CR3, FYN, Interleukin-16 (IL16), Interleukin 17 Receptor A (IL17RA), and Interleukin-2 receptor Subunit Beta (IL2RB) over 24-week treatment periods.
Accrual Objective	120 randomized (1:1) to MMF or placebo MMF Randomization will be stratified by screening gene expression signature: • Group 1: high interferon and high inflammation • Group 2: low inflammation and high B Cells (interferon can be high or low) • Group 3: other profiles not included in groups 1 or 2 • Group 4: gene expression signature results unavailable (e.g. due to shipping or laboratory error)
Study Duration	Participants will be engaged in the study for a maximum of 56 Weeks. We anticipate 2.5 years to achieve the target number of randomizations at Stage 2. Overall study duration is expected to be 3.5 years.
Treatment Description	Stage 1 (Treatment Withdrawal), up to 4 weeks: • Long-acting corticosteroid IM injection, may be repeated twice for a total of 3 corticosteroid injections prior to Stage 2 randomization. Dose will be dependent on the available formulation. • Lupus medications are withdrawn. Stage 2 (Randomization): • After a 2-week taper-up, 1000 mg MMF BID or corresponding MMF placebo BID for up to 48 weeks. Stage 3 (Re-Randomization): • Optional long-acting corticosteroid IM injection, one may also be given within the first 2 weeks of Stage 3 regardless of whether or not one was

	given at the time of Stage 2 treatment failure for a total of 2 corticosteroid injections. Dose will be dependent on the available formulation. • 1000 mg MMF BID plus either voclosporin (23.7 mg) or corresponding placebo for voclosporin BID for up to 24 weeks. o Those on MMF placebo during Stage 2 will taper up to the full MMF dose over 2 weeks.

Inclusion Criteria	**Inclusion Criteria**
	Participants must meet all of the following criteria to be eligible for randomization as study participants.
	
	1. Aged ≥ 18 and ≤ 60 years at the time of informed consent.
	
	2. Meets European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) 2019 criteria for SLE [3].
	
	3. Moderately severe, active, but non-organ threatening disease. Specifically, signs or symptoms meeting criteria for a minimum of:
	  a. 1 BILAG A (severe) score in the constitutional, musculoskeletal or mucocutaneous system at the time of screening. See Section 4.3, *Exclusion Criteria* number 2 for additional detail.
	  b. 2 BILAG B (moderate) activity scores in any organ systems; or
	  c. 1 BILAG B (moderate) activity score in any organ systems **and** a SELENA-SLEDAI score of ≥ 6.
	  • If there is only 1 BILAG B score:
	  ▪ If a musculoskeletal BILAG B is scored due to moderate arthritis, where some loss off functional range of movements was present on several days over the last 4 weeks, there must also be a minimum of at least 3 joints that are both tender and swollen due to lupus disease activity in wrists, MCPs or PIPs for the participant to qualify.
	  ▪ If a mucocutaneous BILAG B is scored due to acute or subacute cutaneous skin eruption, the rash must cover at least 4% of the body surface area for the participant to qualify. Any active discoid lesion or other form of chronic cutaneous lupus would be qualifying.
	
	4. Approval, by an adjudication committee, of a brief entry packet describing the type, severity and duration of symptoms meeting the minimal criteria for entry. The participant will meet this criterion if the committee is confident of all of the following:

	a. Convincing diagnosis of SLE, b. Active disease, due to SLE, warranting the potential of dual therapy with potent immune modulators, c. No medical or other condition to contraindicate participation in a placebo-controlled, outpatient study of this design. 5. Women of childbearing potential must have a negative serum pregnancy test at screening. 6. Able or willing to use reliable methods of contraception, as outlined in the Mycophenolate Risk Evaluation and Mitigation Strategy (REMS) brochure for health care providers, from 4 weeks prior to first randomization to 6 weeks after completion of the study. This criterion applies to females of reproductive potential. Mycophenolate REMS Program acceptable contraceptive methods are outlined in Appendix 1, see Section 19.1. **Inclusion Criteria Required Prior to Randomization** Participants who meet the following criterion at the Stage 2 Randomization Visit may proceed to randomization in Stage 2: 7. After completion of corticosteroid injection(s) and prior to randomization in Stage 2, the participant and his/her physician must agree that disease activity has improved sufficiently from screening such that randomization is acceptable. a. The physician must score the Clinical Global Impression of Change [4] (CGI-C) as “moderately better” or “much better” prior to randomization. • The reference value for the CGI-C should be the investigator’s determination of the participant’s condition at the Screening Visit. b. The participant must agree that his/her symptoms have improved (yes/no).
Exclusion Criteria	**Exclusion Criteria** Participants who meet any of the following criteria are not eligible for randomization as study participants: 1. Inability or unwillingness of a participant to understand and provide written informed consent or comply with the study protocol. 2. BILAG A (severe) disease in the Cardiorespiratory, Neuropsychiatric, Gastrointestinal, Ophthalmic, Renal, or Hematological Systems. 3. Severe or unstable nephritis defined as any of the following: a. History of confirmed Class 3-5 nephritis within the last 2 years,

	b. History of confirmed Class 3-5 nephritis > 2 years ago in the absence of documented treatment including both induction and maintenance therapy, c. Urine protein: creatinine ratio (UPCR) > 1 g/g at screening, • If UPCR is > 0.5 g/g and ≤ 1 g/g at screening, then a second assessment must be completed with at least 1 week between assessments. If the second assessment is > 1 g/g or has increased by ≥ 0.3 g/g, then the participant is excluded. 4. Evidence of chronic kidney disease defined as eGFR < 45 mL/min per 1.73 m^2 at screening, where 175 x (Creatinine/88.4)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if of African descent) [5]. 5. History of cirrhosis or chronic liver disease unrelated to SLE other than fatty liver disease. 6. History, within 1 year of the Screening Visit, of uncontrolled SLE that would have warranted a BILAG A (except mucocutaneous, constitutional, musculoskeletal) including, but not limited to, hemolytic anemia, neuropsychiatric lupus, or interstitial lung disease. 7. Uncontrolled HTN at the Screening or Randomization Visits defined as blood pressure > 150/100 with or without treatment, not to exceed 3 complementary antihypertensive treatments. 8. Any of the following laboratory values during screening: a. Hemoglobin (Hg) < 8.0 g/dL, b. White blood cell count (WBC) < 2.0 x 10^9 cells/L, c. Absolute neutrophil count (ANC) < 1.0 x 10^9 cells/L, d. Platelets < 60 x 10^9 cells/L at screening, • If platelets < 70 x 10^9 cells/L at screening, platelet count should be retested 2 weeks later. If platelets are < 60 x 10^9 cells/L at retest, participant will be excluded. e. Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) > 2.5 times the upper limit of normal (ULN), f. Serum IgG levels < 5 g/L 9. Use of ≥ 40 mg/day of prednisone within 4 weeks prior to the Screening Visit, or use of ≥ 20 mg/day of prednisone at screening. 10. Unwilling or unable to taper to ≤ 10 mg/day of prednisone or equivalent by the day of randomization.

	11. Use of hydroxychloroquine, chloroquine or quinacrine, if taking, at a prescribed dose that has not been stable for at least 2 months prior to randomization. 12. Use of MMF within 1 year of randomization. 13. Use of calcineurin inhibitors (CNI) within 3 months of randomization. Topical formulations applied stably for at least one month are allowed. 14. Use of rituximab, obinutuzumab, ocrelizumab, or long-acting B cell depletion agents within 1 year of randomization. Use of agents ≥ 6 months and within 1 year of randomization is permitted if there is evidence of B cell reconstitution as defined as CD19+ counts of ≥ 50 cells/μL. 15. History of intolerance or allergy to MMF, voclosporin or long-acting corticosteroid preparations. 16. Individuals with a known hypersensitivity to Polysorbate 80 (Tween). 17. A woman who is pregnant, breastfeeding, or planning pregnancy from the time of consent until 6 weeks after completion of the study. 18. Any participant with plans for major surgery during the time of the trial. 19. Active infections requiring hospitalization or intravenous antibiotics within 1 month prior to the Screening Visit. 20. Any grade 2 infection or higher from 14 days prior to the Screening Visit and through the screening period that has not resolved by randomization. 21. Acute herpes zoster within 4 months of the Screening Visit. 22. Positive results from a SARS-CoV-2 antigen test administered 2 days prior to and on the day of first randomization. 23. Positive Quantiferon Gold (or equivalent) assay. Indeterminate Quantiferon Gold (or equivalent) assays must be repeated (with same or other interferon gamma release assay per local policy) and shown to be negative. Alternatively, if the Quantiferon Gold (or equivalent) assay remains indeterminate, a participant must have a negative purified protein derivative (PPD). Finally, if the participant has had the Bacille Calmette-Guerin (BCG) vaccine or has some other condition complicating the interpretation of tuberculosis (TB) testing, consultation with infectious disease specialist must be obtained.

	• Participants diagnosed with latent TB are eligible but must have received appropriate prophylaxis for 30 days prior to initiation of Stage 2 treatment. 24. Serologic evidence at screening of chronic infections including: a. Human immunodeficiency virus (HIV) infection. b. Hepatitis B as indicated by surface antigen or hepatitis B core antibody positivity; if a participant has an isolated positive hepatitis B core antibody, they will be eligible to participate in the study if they are negative for reflex viral load at Screening. c. Hepatitis C as indicated by anti-hepatitis C antibody positivity; if a participant is Hepatitis C antibody positive, they will be eligible to participate in the study if they are negative for viral load at Screening. 25. Current, diagnosed, or self-reported drug or alcohol abuse within the last 6 months that, in the opinion of the investigator, would interfere with the ability to comply with study protocol. 26. Recipient of live attenuated vaccine(s) within 8 weeks of the Screening Visit. 27. Use of investigational drugs (excluding SARS-CoV-2 vaccinations or SARS-CoV-2 therapeutics) within 8 weeks of the Screening Visit or 5 half-lives, whichever is longer. 28. Past or current mental or physical problems 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 may impact the quality or interpretation of the data obtained from the study.
Study Stopping Guidance	There are no pre-specified criteria that will stop the study, but the Data and Safety Monitoring Board (DSMB) will be convened for an ad hoc meeting should any of the following events occur: • Any death that occurs during the study. • BILAG A flares in Cardiorespiratory, Neuropsychiatric, Gastrointestinal, Ophthalmic, Renal, or Hematological Systems occurring in o 3 or more of the first 10 randomized participants or o 30% or more of randomized participants at any time point after the 11th participant is randomized. • Infections requiring hospitalization or > 1 dose of intravenous antibiotics occurring in o 3 or more of the first 10 randomized participants or

	○ 30% or more of randomized participants at any time point after the 11th participant is randomized.

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Glossary of Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
Anti-dsDNA	Antibodies to double stranded DNA
AST	Aspartate Aminotransferase
BCG	Bacille Calmette-Guerin
BICLA	BILAG-based Combines Lupus Assessment
BID	Twice a day
BILAG	British Isles Lupus Assessment Group
BOLD	Biomarkers of Lupus Disease
CGI-C	Clinical Global Impression of Change
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CFR	Code of Federal Regulations
ClinRO	Clinical Reported Outcome
CMV	Cytomegalovirus
CNI	Calcineurin Inhibitor
CNS	Central Nervous System
CPC	Clinical Product Center
CR3	Complement receptor 3
CRR	Complete Renal Remission
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
DAIT	Division of Allergy, Immunology, and Transplantation
DDI	Drug-Drug Interactions
DSMB	Data Safety Monitoring Board
EBV	Epstein Barr Virus
eCRF	Electronic Case Report Form

eGFR	Estimated Glomerular Filtration Rate
EUA	Emergency Use Authorization
EULAR/ACR	European League Against Rheumatism/American College of Rheumatology
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HTN	Hypertension
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IORA	Investigator of Record Agreement
H-SLEDAI	Hybrid Systemic Lupus Erythematosus Disease Activity Index
ICF	Informed Consent Form
IL16	Interleukin-16
IL17RA	Interleukin 17 Receptor A
IL2RB	Interleukin-2 receptor Subunit Beta
IM	Intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
LN	Lupus Nephritis
LFA-REAL	Lupus Foundation of America Rapid Evaluation of Activity in Lupus
mITT	Modified Intent-to-Treat Population
mITT3	Stage 3 Modified Intent-to-Treat Population
MMF	Mycophenolate Mofetil
MPA	Mycophenolic Acid
NIAID	National Institute of Allergy and Infectious Diseases
NSAIDS	Non-steroidal Anti-inflammatory Drugs
PGA	Physician Global Assessment
PGI-C	Patient Global Impression of Change
PGI-I	Patient Global Impression of Improvement

PGI-S	Patient Global Impression of Severity
PRO	Patient-Reported Outcome
P-GP	Permeability Glycoprotein
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
PPD	Purified Protein Derivative
PRCA	Pure Red Cell Aplasia
PRN	As Needed
PRR	Partial Renal Response
PTLD	Post-Transplant Lymphoproliferative Disorder
REMS	Risk Evaluation and Mitigation Strategy
RR	Renal Response
SCCC	Statistical and Clinical Coordinating Center
SADR	Serious Adverse Drug Reactions
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SELENA-SLEDAI	Safety of Estrogen in Lupus: National Assessment Systemic Lupus Erythematosus Disease Activity Index
SLE	Systemic Lupus Erythematosus
SRI	Systemic Lupus Erythematosus Responder Index
TB	Tuberculosis
TWEAK	Tumor Necrosis Factor-Like Weak Inducer of Apoptosis
ULN	Upper limit of Normal
UPCR	Urine Protein: Creatinine Ratio
USPI	United States Prescribing Information
WBC	White Blood Cell Count

1 Rationale and Background

1.1 Background and Scientific Rationale

1.1.1 Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE or lupus) is a chronic, waxing and waning autoimmune disorder [6] which usually affects women in their childbearing years but may arise in people of any age and gender. Clinical manifestations range from mild to moderate flares of mucocutaneous and musculoskeletal features to severe manifestations of the hematologic, constitutional, renal, cardiopulmonary, neurologic, or central nervous systems (CNS). The onset, timing, severity, and type of symptom that a patient can expect to develop is unpredictable. Patients are known to be heterogeneous in both clinical manifestations and in their underlying immune abnormalities.

1.1.1.1 Subsets of Disease

Clinical manifestations do not predict response to treatment. Most SLE patients share arthritis and mucocutaneous involvement [7, 8]. Other clinical signs and symptoms occur sporadically, and do not sort patients into stable subsets [6, 7, 9]. Although autoantibody profiles may predict prognosis, they are not helpful in choosing treatment. Although antinuclear antibodies are seen in almost all SLE patients, certain patterns of less ubiquitous autoantibodies are a long-known way to distinguish subsets at risk for discrete clinical manifestations [1]. Antibodies to double stranded DNA (anti dsDNA) are strongly associated with renal involvement and risk for other more serious organ disease. Anti-SSA (RO) antibodies correlate with subacute cutaneous rashes, lymphopenia, secondary Sjogren's Syndrome and neonatal lupus symptoms; and antiphospholipid antibodies are harbingers for thrombotic complications. Lupus signs and symptoms appear to represent an overlapping spectrum disorder and cannot be used to subset patients for optimal treatment.

Given longstanding confusion of conflicting pathways in SLE immune pathology [10], failure of past subsetting methods to improve current treatment choices [11], and disappointing results of 40 investigational agents for lupus [12], there is a mandate for better stratification of patients into subsets likely to respond to specific treatments. Recently, several investigators have utilized multi-omic approaches to define clusters of SLE patients that manifest unique and reproducible patterns of altered gene and protein expression. In a longitudinal cohort of pediatric SLE patients, Banchereau and colleagues [13] identified patterns of transcriptional modules that change with disease activity and clarified clinically relevant subsets of pediatric patients. A similar approach was utilized by Guthridge and colleagues to define 7 clusters of adult lupus patients based on Random Forest modeling of gene co-expression pathways [1]. This group also identified cytokines, chemokines, adhesion molecules, and soluble receptors associated with risk of disease flare [14, 15].

These findings demonstrate the value of high-dimensional data for understanding the range of pathogenic mechanisms in SLE and suggested a method for more rational testing of targeted treatments. In one study, insights into the impact of MMF have been obtained [13] and in an exploratory analysis of a Phase 2 abatacept trial, a preliminary identification of responsive immunophenotypes [16] were identified. We used similar methodology to study samples from a Phase 2 trial of an agonist to Fc gamma RIIb and identified 2 clusters of SLE patients with overlapping immunologic features where the treatment effect was far greater than in the overall population [17]. The current project focuses on utilizing these methods for immunophenotying to investigate which individuals might benefit from a single agent or combination therapy.

1.1.2 **Current Therapeutic Landscape of SLE**

1.1.2.1 **Licensed Therapies**

A few medications have been approved for the treatment of SLE without undergoing the rigorous approval process that is required today, including corticosteroids, hydroxychloroquine, and aspirin. Corticosteroids and hydroxychloroquine are staples of care despite their limitations and long-term risks with sustained use. In 2011, belimumab was approved for treating the signs and symptoms of general lupus with approval specifically for lupus nephritis (LN) in 2020 [18]. This agent has repeatedly been demonstrated to be safe and well tolerated in many large studies [19] but it has never been evaluated as a single agent, and is generally used in combination with other medications. Efficacy rates have ranged from 35-60% underscoring the unmet need for new treatments and/or a better understanding of how we combine different treatments together. Similarly, anifrolumab was approved for SLE in 2021 with similar efficacy considerations and unresolved issues about optimal use [20]. Voclosporin, a relatively new CNI, was recently approved for LN [21]. In other diseases it has been considered safer than other drugs in its class. Data on its efficacy and safety in SLE is discussed below.

1.1.3 **Unlicensed Drugs**

Despite these few recently approved licensed therapies, the standard of care in lupus is to empirically prescribe immune modulating treatments marketed for use in other diseases. These most commonly include azathioprine (or 6 mercapto-purine), methotrexate, MMF (or mycophenolic acid (MPA)), leflunomide, or CNIs such as tacrolimus. The efficacy and pharmacodynamics of these medications on heterogeneous SLE populations are not completely understood.

Many novel treatments currently in development are being used (or tested) in the context of “background” therapy, with little to no knowledge of whether these combinations are optimal for patients or whether efficacy might vary among different pathophysiologic subsets of lupus patients. The combination of MMF and CNI is a recent development in the treatment of SLE. This project focuses on addressing several questions: What is the clinical and immunologic impact of MMF on different subsets of patients and does this depend on baseline immune phenotype? What changes when those who did not respond to MMF receive the addition of a CNI?

1.2 Rationale for Selection of Study Design

1.2.1 **The BOLD Design**

This protocol design is based on the Biomarkers of Lupus Disease (BOLD) study. The trial is limited to participants without organ-threatening disease and mandates withdrawal of all lupus medications except for low dose steroids, antimalarials and/or Non-steroidal Anti-inflammatory Drugs (NSAIDs). The BOLD protocol was designed to test the hypothesis that if patients with active but not organ threatening SLE are given temporary relief by steroid injections, withdrawal of background immunosuppressants can be accomplished safely. Improvement from the initial steroid injection will wane, ensuring low response rates in the absence of additional effective treatment. In a clinical trial designed on the BOLD principle, participants can be designated as non-responders once steroid response starts to wane and then they may be immediately treated with reasonable safety. Furthermore, responses to the test medication can be more cleanly evaluated without excessive interaction or interference from other medications. A total of 41 participants with moderate disease underwent the BOLD procedure; all but 1 lost their steroid response within 6 months. The protocol was safe and well tolerated and all subsequent flares resolved with treatment within 6 weeks [22].

The BOLD design has been employed in the assessment of several investigational agents, including small investigator-initiated trials of MMF and abatacept, a pilot study of AMG 557, and a Phase 2 study of obexelimab (Xmab5871) [17, 23-25]. The latter was the most successful in that in a small trial of 102 patients, a subset analysis of patient baseline phenotypes identified 2 clusters of lupus patients with overlapping features that exhibited a large treatment effect, whereas there was no difference at all between treatment and placebo in all other clusters. No safety concerns were identified. The BOLD study approach will be utilized in the current study to lessen placebo response rates so differences can be observed in this smaller study, and to better define phenotypic subsets that may benefit from MMF alone or MMF combined with voclosporin.

1.2.2 **Rationale for Withdrawal of Background Medication**

Since participants will be receiving a proven effective treatment for their immediate symptoms through steroid injections, this mitigates concerns that reduction of background treatments as early as the Screening Visit might precipitate a flare. Indeed, since all patients will be entered with active disease, the treatments being withdrawn will not be effective at that time point by definition. Safety is improved by allowing a washout of potentially interacting immune suppressants prior to starting the investigational treatment. Furthermore, simplification of background treatment early in the study will improve interpretability of both clinical and biomarker data, providing a valuable clarity for evaluation of the study treatment(s). In particular, the evaluation of MMF as a single agent will be facilitated by allowing it to exert its effects as a single agent from the start of administration.

Substitution of an ineffective treatment with a known, almost universally effective treatment (corticosteroid) is consistent with standard of care. The actual withdrawal of background treatment per se begins as a gradual decline in steroid levels over time. The earliest flares may start within a month, indicating that sufficient steroid dose was likely not given during the withdrawal phase. In the rare situations this does not ameliorate disease activity sufficiently for a participant to safely enter the trial, the participant will be taken off study, and they will be treated with whatever is appropriate at that time. Most flares in studies of this design occur after 2 or 3 months. This allows time to distinguish an effective treatment from placebo. As a flare becomes apparent, the participant becomes a non-responder in that part of the protocol and will also be immediately treated. Because of this, the trial design is in some ways easier to tolerate than some alternative protocols where participants who do not feel well must drop out or wait many weeks for treatment.

1.2.3 **Rationale for the Current Two-Part Protocol Design**

The two parts of this protocol are designed to:

- Test the clinical and immunologic effects of MMF, compared to placebo in phenotypic clusters of participants with SLE. This first part of the trial (Stage 2) is expected to identify molecular clusters associated with clinical success or failure of MMF treatment.
- Test the clinical and immunologic effects of adding voclosporin (or not) for those participants who do not respond to MMF alone. Compare MMF vs MMF + voclosporin in a subset of non-responders who received placebo in the first part (Stage 2) of the trial. If one or more clusters of participants who have not responded to MMF alone can be identified by immunophenotypes, either at baseline or after receiving MMF, the question of whether all of these or only certain subsets are candidates for voclosporin can be addressed in an exploratory way. The study is likely underpowered to fully confirm cluster association with response (non-response) in this second part of the trial (Stage 3). The observations obtained may provide important hypotheses for further testing.

1.3 Rationale for Selection of Investigational Products

Data from the AURA and AURORA trials [26, 27] suggests a potent additive efficacy for LN when voclosporin is added to MMF, which is the most commonly used, first line treatment for nephritis. In 2021, the FDA approved the use of voclosporin in combination with MMF for the treatment of LN [28]. Other data have also confirmed a particularly strong effect when CNIs are used with MMF. Recently, a 24-week, multicenter randomized trial of induction therapy for LNat 26 centers in China reported superiority of MMF plus tacrolimus (45.9% complete remission) to cyclophosphamide (25.6% complete remission) ($p < 0.001$) [29]. At least 1 meta-analysis concluded that these agents are effective at about the same rates when used singly [30] and an open label, randomized study of 150 LN patients from C.C. Mok's group in Hong Kong prospectively confirmed equal efficacy between tacrolimus and MMF [31]. Taken together, these data suggest the possibility of a potential synergy between MMF and T cell modulators such as voclosporin, or at least complementary mechanisms.

A fundamental concept underlying this study is that, in at least some patients, MMF alone is effective. For example, it was equally effective as cyclophosphamide or tacrolimus in head to head nephritis studies [30, 31], at least somewhat effective as a background treatment in many studies [12, 32-47] superior to azathioprine in a maintenance study [48], superior to placebo in a small trial at Oklahoma Medical Research Foundation (OMRF) [49] and superior to other standard of care treatments in a summary analysis of several clinical trials [50]. This substantial evidence suggests the importance of determining which patients benefit from MMF alone as opposed to those who would require the addition of a CNI to obtain clinical improvement and whether identifiable immune phenotypes can help predict response.

These considerations justify a study to investigate how the effects of MMF, alone and in combination with a CNI, play out in identifiable immune phenotypes of lupus. To facilitate the safety and interpretability of such study, the BOLD approach will be taken in patients without nephritis or any other organ-threatening disease and background medications will be limited. Our work has already demonstrated that patients with non-nephritis fall into the same immune-phenotypes as patients with nephritis [1]. Therefore, we hypothesize that the immune components of the additive effects of MMF and a CNI are unlikely to differ in non-nephritis lupus [1]. Finally, the controlled circumstance of studying patients without organ-threatening disease, which will increase the safety of treatment withdrawal, is unlikely to mean that the findings will be completely inapplicable to nephritis patients who share the same phenotypes.

1.4 Experience with MMF

One of the investigational products to be studied in this protocol is MMF. MMF is indicated for the prophylaxis of organ rejection in recipients of allogenic kidney, heart, or liver transplants and should be used in combination with other immunosuppressants. MMF is widely used in clinical practice around the world for SLE [28].

1.4.1 Preclinical Experience with MMF

At least two models have confirmed efficacy of MMF in murine nephritis [51-56]. In the (NZB x NZW) F1 model, MMF had a dose-dependent effect in autoantibodies [51] and disease severity [51, 52]. In the MRL *lpr* model, beneficial effects on proteinuria, survival and histologic severity of glomerulonephritis have been reported [53], with confirmation of efficacy in several other reports [54, 55]. MMF has also been compared to cyclophosphamide in murine lupus and found to be more effective than cyclophosphamide in preventing renal fibrosis, associated with decreased expression of TGF-β1, fibronectin and collagen I [57]. In a mouse with SLE disease accompanied by accelerated atherosclerosis (the gld apoE model), MMF treatment was associated with decreased autoantibodies, improved nephritis, and also decreased accumulation of atherosclerotic lesions [58] . In a recent study using the (NZB

x NZW) F1 model, MMF treatment was associated with decreased glomerular deposits and proteinuria, and decrease of the podocyte urokinase receptor, which conducts signals associated with foot process effacement and proteinuria [59].

1.4.2 **Clinical Experience with MMF**

MMF has been used as a background therapy in many clinical trials of SLE [12, 32-47, 60]. Most of these trials were either unable to find differences between treatment and placebo groups (added to standard of care) or, at best, revealed disappointing results, with placebo group response rates as high as 35-40%. MMF has performed very well in LN trials when it was directly compared to cyclophosphamide [61-64] and with little or no difference in efficacy rates in the induction phase, and in general a better safety profile for MMF. Voclosporin has now been tested in combination with MMF in two pivotal trials [26, 27] in LN, demonstrating greater efficacy than MMF alone. The summary of clinical trials data below focuses mostly on safety.

The most complete summary of AEs in lupus patients with MMF comes from the international ALMS trial [23] The treatments were equally effective. The most common AEs in the MMF group were infections and diarrhea. There were more deaths in the MMF group, in contrast to data from previous trials. Most of the participants who died had severe renal disease at baseline. Details are shown in the following table:

Parameter	MMF (N=184) n (%)	CYC (N=180) N (%)
Deaths	9 (4.9)	5 (2.8)
Withdrawals as a result of	24 (13.0)	13 (7.2)
All AEs	177 (96.2)	171 (95.0)
Diarrhea	52 (28.3)	23 (12.8)
Headache	38 (20.7)	47 (26.1)
Peripheral	35 (19.0)	30 (16.7)
Arthralgia	29 (15.8)	43 (23.9)
Nausea	27 (14.7)	82 (45.6)
Hypertension	26 (14.1)	25 (13.9)
Nasopharyngitis	25 (13.6)	29 (16.1)
Vomiting	25 (13.6)	68 (37.8)
Cough	24 (13.0)	16 (8.9)
Anemia	23 (12.5)	12 (6.7)
Alopecia	20 (10.9)	64 (35.6)
Abdominal Pain	19 (10.3)	16 (8.9)
Back Pain	19 (10.3)	17 (9.4)
Muscle Spasms	19 (10.3)	21 (11.7)
Urinary Tract	19 (10.3)	17 (9.4)

1.5 Experience with Voclosporin

One of the investigational products to be studied in this protocol is voclosporin, and the preclinical experience and clinical studies in LN are reported in the Investigator's Brochure for voclosporin (version 2.0 dated 15 October 2021) and is summarized below [65].

1.5.1 Preclinical Experience with Voclosporin

Preclinical studies suggest CNIs are associated with T cell inhibition. The MRL/l*pr* model was recently used for a "post-human" study in mice, reported only after the combination of MMF and tacrolimus were studied in a human trial [66]. Mice were treated with prednisone, MMF, or tacrolimus, or with the combination, and renal outcomes were significantly improved in the mice that received combination treatment. Transcriptome analysis of kidney samples demonstrated that the combination treatment inhibited expression of TLR7, stabilized podocyte actin and suppressed the IL-6/Stat3 pathway [66]. In vitro studies of voclosporin using human cells support similar action to other CNIs in T cell inhibition [67] but with more potency [68]. In non-human primates, voclosporin prolonged renal graft survival [69]. It has also been found to suppress lymphocyte proliferation, and cytokine production more or equally than cyclosporine despite lower peak and trough concentrations [70], confirming similar mechanistic impact with a greater potency. Calcineurin inhibition at trough blood levels was also found to by higher with the voclosporin construct [69].

1.5.2 Clinical Studies with Voclosporin

1.5.2.1 Pharmacokinetic (PK) Studies

Administration of voclosporin oral solution with meals decreased both the rate and extent of absorption, which seemed related to the fat content of the meal. This suggests that the drug should be taken on an empty stomach. In *in vitro* assays, none of the major metabolites seem to cause much calcineurin inhibition. In the Phase 1 studies, inhibition of calcineurin by voclosporin appeared to be dose-related up to a maximum of approximately 90% after either a 1.5 mg/kg single dose or a 1 mg/kg BIDdose for 10 days. The degree of calcineurin inhibition is related to both dose and whole blood concentration of voclosporin.

1.5.2.2 Drug-Drug Interactions

Three clinical drug-drug interactions (DDI) studies have confirmed that voclosporin is a substrate for the Cytochrome P450 3A4 (CYP3A4)/5, which is primarily responsible for its metabolism. Interaction with other substrates of CYP3A4/5 have not been observed. However, use of voclosporin with ketoconazole a strong CYP3A4/5 inhibitor or rifampin, an enhancer, will affect voclosporin levels. Voclosporin has also been found to be both a substrate for and an inhibitor of P-gp (permeability glycoprotein or multidrug resistance protein 1). Verapamil, a known inhibitor of P-gp, was observed to increase voclosporin levels. Concomitant administration of voclosporin with digoxin, which is a P-gp substrate, was associated with a 25% increase in digoxin levels and a decrease in renal clearance.

1.5.2.3 Clinical Efficacy and Safety of Voclosporin in Lupus Nephritis

Voclosporin has been demonstrated to be efficacious in two pivotal LN studies [26, 27, 65]. The AURA-LV study tested the novel CNI voclosporin for efficacy and safety in active LN. AURA-LV was a Phase 2, multicenter, randomized, double-blind, placebo-controlled trial of two doses of voclosporin (23.7 mg or 39.5 mg, each BID) versus placebo in combination with MMF (2 g/d) and rapidly tapered low-dose oral corticosteroids for induction of remission in LN. Two hundred sixty-five participants from 79 centers in 20 countries were recruited and randomized to treatment for 48 weeks. Complete renal remission (CRR) at week 24 was achieved by 29 (32.6%) participants in the low-dose voclosporin

group, 24 (27.3%) participants in the high-dose voclosporin group, and 17 (19.3%) participants in the placebo group (OR=2.03 for low-dose voclosporin versus placebo). The significantly greater CRR rate in the low-dose voclosporin group persisted at 48 weeks, and CRRs were also significantly more common in the high-dose voclosporin group compared to placebo at 48 weeks. The overall incidence of AEs and treatment-related AEs appeared to increase with increasing dose of voclosporin, with AEs attributed as treatment-related in 17.0% of participants in the placebo group compared to 50.6% and 62.5% of participants in the low-dose and high-dose voclosporin groups, respectively. The majority of AEs were mild or moderate in severity. There were more serious adverse events (SAE) in both voclosporin groups, and 13 participants died during the study with more deaths observed in the low-dose group compared to placebo and high-dose voclosporin groups (11.2%, 1.1%, and 2.3%, respectively). These results suggested that the addition of low-dose voclosporin to MMF and corticosteroids for induction therapy of active LN results in a superior renal response compared to MMF and corticosteroids alone but higher rates of AEs including death were observed in the Phase II study. A combined safety analysis of Phase II and III studies will be discussed in more detail below.

AURORA 1 was a Phase III multicenter, randomized, double-blind, placebo-controlled 52-week study of active LN patients. Participants were randomized 1:1 to voclosporin (23.7 mg BID) or placebo in combination with MMF (1 g BID) and rapidly tapered oral steroids. Three hundred fifty-seven participants were enrolled, 88% female, median age of 31 and 33% of Hispanic/Latino ethnicity. Renal response (RR) by intention to treat analysis at 52 weeks was 40.8% for the voclosporin arm and 22.5% for the control arm (OR: 2.65; 95% CI: 1.64, 4.27; p< 0.001). Ethnicity subgroup analysis of RR at 52 weeks noted benefit of voclosporin in both Hispanic/Latino (voclosporin 38.6% and control 18.6%, p=0.0062, OR 3.45) and non-Hispanic/Latino participants (voclosporin 41.8% and control 24.6%, p=0.0045, OR 2.29). The benefits of voclosporin were also seen for all pre-specified hierarchical secondary endpoints: RR at 24 weeks, partial renal response (PRR) at 24 and 52 weeks, time to achieve UPCR ≤ 0.5, and time to 50% reduction in UPCR. Furthermore, all pre-specified subgroup analyses (age, sex, race, biopsy class, region, and prior MMF use) favored voclosporin. Voclosporin was well tolerated with no unexpected safety signals, as summarized below. Participants who completed 52 weeks of study treatment (voclosporin or placebo) in the AURORA 1 study were eligible to continue with their randomized treatment for up to a further 24 months in the AURORA 2 continuation study. A total of 216 participants entered the AURORA 2 study: 116 participants from the voclosporin arm and 100 participants from the placebo arm. The AURORA 2 study is ongoing with final analyses planned to evaluate long term efficacy, including programmed renal response, PRR and changes in UPCR.

In a combined safety analysis of the three clinical trials (AURORA 1, AURA-LV and AURION) and the ongoing continuation study AURORA 2, the most common AEs were in Infections and Infestations, reported by 66% and 59% of participants respectively [26, 27, 65], in the voclosporin/MMF and placebo/MMF groups. The majority were mild or moderate. Gastrointestinal disorders were also common in both voclosporin/MMF and placebo/MMF groups (49% and 38%, respectively), predominantly diarrhea and nausea. The most common individual AEs in voclosporin-treated participants were glomerular filtration rate (GFR) decreased (voclosporin: 29%, placebo 11%) and hypertension (voclosporin 21%, placebo 11%), both known effects of CNIs. The majority of GFR decreases were of mild to moderate intensity and resolved following temporary interruption or modification of dose per protocol guidance based on theeGFR. SAEs occurred in a similar proportion of participants in the voclosporin/MMF and placebo/MMF groups (28% and 25%, respectively). Infections and infestations were the most common SAEs reported in both groups (12% and 13%, respectively). Serious opportunistic infections were uncommon (<1%) in both treatment groups. Seventeen participants (2.5%) died due to AEs occurring on or within 30 days of the last dose of study treatment (10 (2.7%) voclosporin/MMF, 7

(2.6%) placebo/MMF). None of the AEs leading to death were considered by the investigator, sponsor or the DSMB to be related to study treatment. The reasons for death were consistent with the types of comorbid conditions and complications that would be expected in a population with LN.

2 Study Hypotheses/Objectives

2.1 Hypotheses and Research Questions

2.1.1 **MMF versus placebo**

Hypothesis 1: Long-acting corticosteroid-induced improvement in lupus disease activity achieved prior to randomization will be lost more rapidly in the placebo arm compared to the MMF arm.

Research Question 1: Are there immunologically definable subsets of SLE patients [1] for whom MMF is an effective treatment?

Hypothesis 2: Expression of TWEAK, complement receptor 3 (CR3), FYN, IL16, IL17RA, and/or IL2RB will decline over 24 weeks for those participants on MMF who do not develop treatment failure compared to those who do fail on or prior to week 24.

2.1.2 **MMF versus MMF plus Voclosporin**

Research Question 2: Do baseline gene expression patterns characterizing response (or non-response) to MMF and MMF plus voclosporin differ?

2.2 Primary Objective

Assuming that MMF is an effective treatment in some, but not all, SLE patients, the primary objective of this study is to evaluate the potential effectiveness of 24 weeks of MMF within previously discovered immunologically defined subsets of SLE patients [1].

This objective will be most effectively supported within the context of a successful demonstration of superiority of MMF over placebo, pooled over all clusters. To this end, individuals with lupus who are without organ-threatening disease will be randomized to 24 weeks of MMF or placebo. The primary objective is to compare the cumulative incidence of treatment failure with 24 weeks of MMF or placebo by treatment arm. Subsequently, treatment effects will be evaluated within the individual immunologically-homogenous subsets defined at screening.

2.3 Secondary Objectives

- To describe the effects of long-acting corticosteroid injections, MMF, MMF plus voclosporin, and placebo on measures of safety and toxicity.
- To describe the effects of MMF, MMF plus voclosporin, and placebo on exploratory clinical response measures and disease flare indices.
- To describe the effects of MMF, MMF plus voclosporin, and placebo on patient-reported quality of life indices.

2.4 Mechanistic Objectives

- To explore and compare pre-randomization gene expression patterns among responders and non-responders to MMF and MMF plus voclosporin.
- To use comprehensive immunophenotyping to study the immunologic changes that accompany treatment-induced disease improvement to better understand key checkpoints in SLE pathophysiology.
- To use comprehensive immunophenotyping to better understand immunologic changes associated with the loss of clinical response.

3 Study Design

3.1 Description of Study Design

This will be a multicenter, double blind, placebo-controlled Phase 2 trial of 120 participants with SLE who will enter with significant symptoms, but no organ-threatening disease. The study will be conducted in 3 stages.

3.1.1 **Stage 1: Treatment Withdrawal:**

During Stage 1, which may last up to 4 weeks, consenting participants will receive an IM injection of a long-acting corticosteroid, which may be repeated if needed to achieve amelioration of symptoms. A total of 3 corticosteroid injections may be given during Stage 1 with the first injection given as early as the Screening Visit after the mechanistic blood draw is completed and the last injection given as late as the Stage 2 Randomization Visit after the mechanistic blood draw is completed. Dose will be dependent on the available formulation.

In addition, participants will withdraw from all other treatments for lupus with the following exceptions: (i) PRN nonsteroidal anti-inflammatory treatments may be started or continued, (ii) PRN topicals may be continued, (iii) hydroxychloroquine, chloroquine, or quinacrine may be continued at any stable dose, and (iv) prednisone, if ≤ 10 mg/day, may be continued at stable doses but not started. Participants may screen if taking up to 20 mg/day prednisone (or equivalent) but both the participant and the investigator must be willing and able to taper to 10 mg/day (under cover of long-acting corticosteroids) by the Stage 2 Randomization Visit. Withdrawal of background lupus medications can start any time after the first corticosteroid injection is given but must be completed by the Stage 2 Randomization Visit.

3.1.2 **Stage 2: Randomization**

One hundred and twenty qualifying participants who withdraw from treatment as described in protocol Section 3.1.1, *Stage 1: Treatment Withdrawal*, and meet improvement criteria for randomization as outlined in Section 4.2.2, *Inclusion criteria required prior to randomization*, will be randomized (1:1) to receive up to 48 weeks of either MMF or corresponding MMF placebo. For the first 2 weeks, a scheduled “taper-up” of MMF will take place. Participants will receive 500 mg MMF (or corresponding MMF placebo) BID for 7 days, followed by 500mg and 1,000mg MMF (or corresponding MMF placebo) in divided doses for 7 days. They will then continue at a stable dose of 1,000mg MMF (or corresponding MMF placebo) BID. Visits to evaluate AEs, vital signs, hematology and chemistry, study medication compliance, medication use, disease status, participant reported outcomes, and to obtain biomarker samples will occur every 4 weeks after randomization.

Participants will be followed for a maximum of 48 weeks on study-provided medication in Stage 2. If a participant experiences an increase in SLE symptoms at any scheduled or unscheduled visit at or before the Stage 2 Week 24 visit, they will proceed in the study as follows:

- If the participant is deemed a Stage 2 treatment failure as defined in protocol Section 3.2, *Primary Endpoint*, and a corticosteroid injection is deemed sufficient for treatment without new or increased lupus medication, then a blood sample for mechanistic studies will be drawn, the injection will be administered, and the participant will immediately proceed to Stage 3: Re-randomization. (See Section 3.1.3, *Stage 3 Re-Randomization*).
- If the participant is deemed a Stage 2 treatment failure as defined in protocol Section 3.2, *Primary Endpoint*, and a corticosteroid injection is deemed sufficient for treatment without new or increased lupus medication, but the participant refuses the corticosteroid injection, then a blood sample for mechanistic studies will be drawn, and the participant will still immediately proceed to Stage 3: Re-randomization without the corticosteroid injection. (See Section 3.1.3, *Stage 3: Re-Randomization*).
- If the participant is deemed a Stage 2 treatment failure as defined in protocol Section 3.2, *Primary Endpoint*, and a corticosteroid injection is deemed insufficient and a new or increased lupus medication is required, then a blood sample for mechanistic studies will be drawn, Stage 2 study-provided medication will be stopped, and the new or increased lupus medication will be started outside of the study. The participant will not be eligible for Stage 3 but will be followed to Stage 2 Week 24 or 4 weeks ± 10 days after the last dose of study-provided medication, whichever is later, before exiting the study. Participants who exit the study at Stage 2 Week 24 should complete all End of Study/Safety Follow-Up visit assessments at this time.

Participants who have not failed Stage 2 on or before the Stage 2 Week 24 visit will continue on Stage 2 study-provided medication through Stage 2 Week 48 or until treatment failure, whichever occurs first.

- If the participant is deemed a Stage 2 treatment failure after Stage 2 Week 24, then study-provided medication will be stopped. Prior to treatment with a corticosteroid injection or a new or increased lupus medication outside of the study, a blood sample for mechanistic studies will be drawn. The participant will return for an End of Study/Safety Follow-Up Visit 4 weeks ± 10 days after the final dose of study-provided medication.
- Participants who have not failed Stage 2 on or before the Stage 2 Week 48 visit will return for an End of Study/Safety Follow-Up Visit 4 weeks ± 10 days after the final dose of study-provided medication.

Severe lupus manifestations that are life-threatening or organ-threatening should prompt consideration for withdrawal from the study in order to enable maximal therapy with corticosteroids and other lupus medications. The ultimate decision on withdrawal should be left up to the clinical judgment of the investigator.

3.1.3 **Stage 3: Re-Randomization**

Participants moving into Stage 3 will be re-randomized (1:1) to receive up to 24 weeks of either MMF plus voclosporin (23.7 mg BID) or MMF plus placebo for voclosporin. Individuals who previously received MMF placebo in Stage 2 will receive a 2-week taper-up of MMF (see taper details for Stage 2, Section 3.1.2 *Stage 2: Randomization).*During the first 2 weeks of treatment, a single IM injection of a long-acting corticosteroid may be administered if needed to achieve amelioration of symptoms without meeting the definition of treatment failure in Stage 3 and without a requirement to stop Stage 3 study-provided medication. This single IM corticosteroid injection

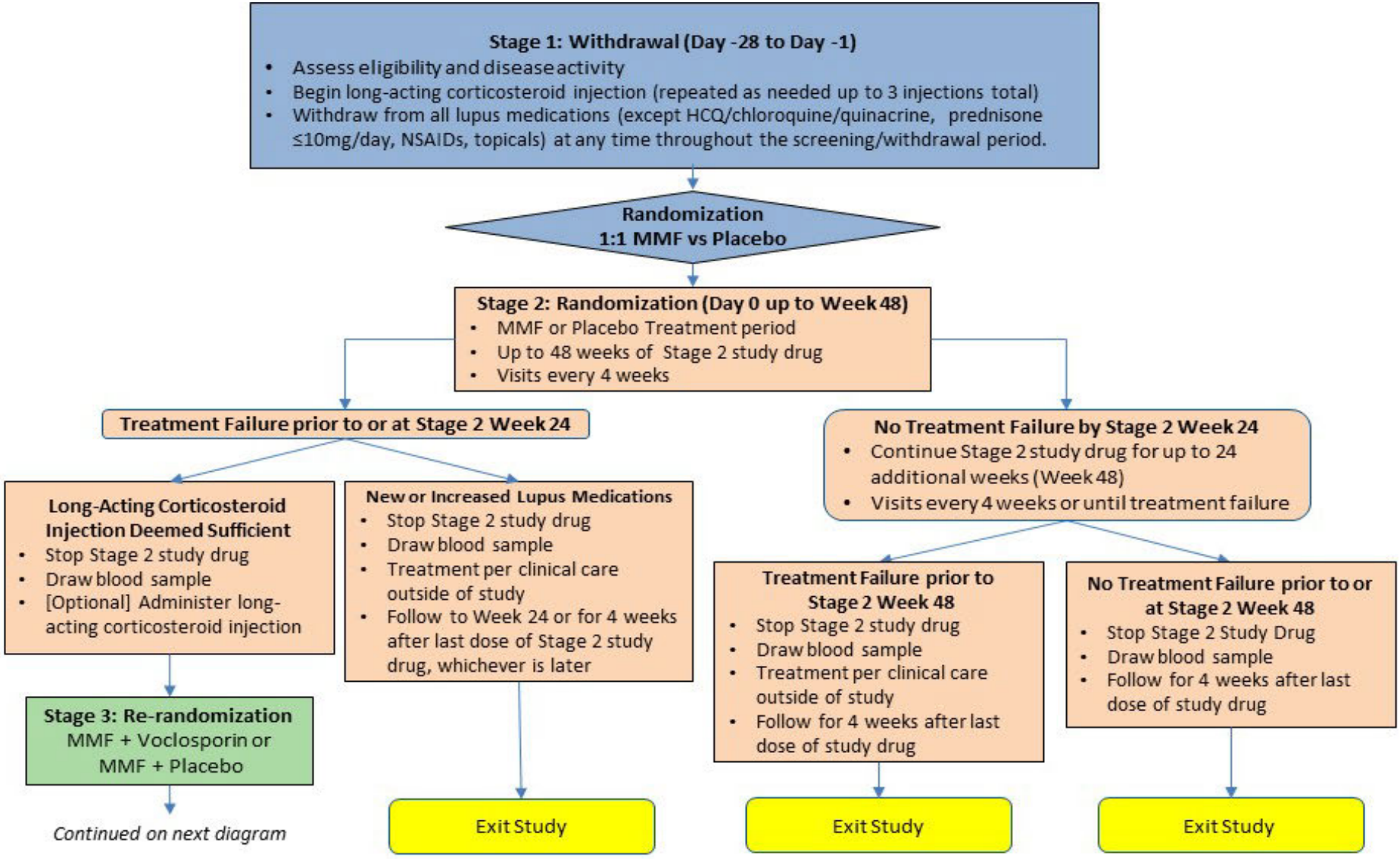
within the first 2 weeks of Stage 3 treatment may be administered regardless of whether or not one was given at the time of Stage 2 treatment failure for a total of 2 corticosteroid injections (dose will be dependent on the available formulation) with the first injection given as early as the visit where participants have a Stage 2 treatment failure after the mechanistic blood draw and the second injection given as late as the Stage 3 Week 2 Visit. Visits to evaluate AEs, vital signs, hematology and chemistry, study medication compliance, medication use, disease status, participant reported outcomes, and to obtain biomarker samples will occur every 4 weeks after re-randomization.

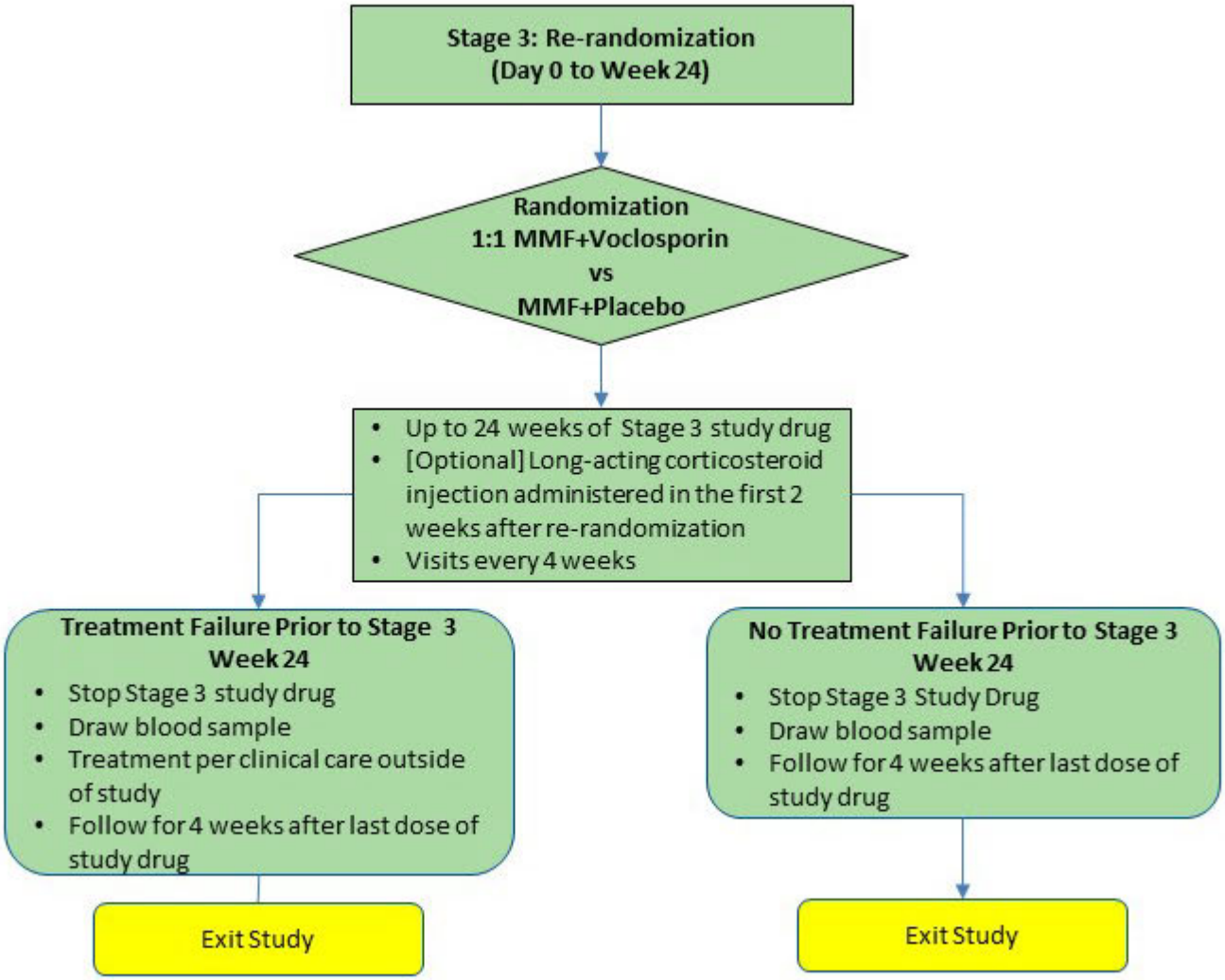
In Stage 3, participants will be on treatment for a maximum of 24 weeks or until treatment failure, whichever occurs first.

- If the participant is deemed a Stage 3 treatment failure, study-provided medication will be stopped. Prior to treatment with a corticosteroid injection or a new or increased lupus medication outside of the study, a blood sample for mechanistic studies will be drawn. The participant will return for an End of Study/Safety Follow-Up Visit 4 weeks ± 10 days after the final dose of study-provided medication.
- Participants who have not failed Stage 3 on or before the Stage 3 Week 24 visit will return for an End of Study/Safety Follow-Up Visit 4 weeks ± 10 days after the final dose of study-provided medication.

As in Stage 2, severe lupus manifestations that are life-threatening or organ-threatening should prompt consideration for withdrawal from the study in order to enable maximal therapy with corticosteroids and other lupus medications. The ultimate decision on withdrawal should be left up to the clinical judgment of the investigator.

Figure 1. Study Flow Diagram




Stage 3: Re-randomization
(Day 0 to Week 24)
Randomization
1:1 MMF+Voclosporin
vs
MMF+Placebo
• Up to 24 weeks of Stage 3 study drug
• [Optional] Long-acting corticosteroid injection administered in the first 2 weeks after re-randomization
• Visits every 4 weeks
Treatment Failure Prior to Stage 3 Week 24
• Stop Stage 3 study drug
• Draw blood sample
• Treatment per clinical care outside of study
• Follow for 4 weeks after last dose of study drug
Exit Study
No Treatment Failure Prior to Stage 3 Week 24
• Stop Stage 3 Study Drug
• Draw blood sample
• Follow for 4 weeks after last dose of study drug
Exit Study

3.2 Primary Endpoint

The primary endpoint is the cumulative incidence of participants who experience a Stage 2 treatment failure at or before the Stage 2 Week 24 visit. The criteria for treatment failure are defined in Section 3.5.1, *Treatment Failure*.

3.3 Secondary Endpoints

3.3.1 Efficacy Endpoints

- Clinical response in Stage 2, defined by the BICLA (see Section 3.5.3, *BILAG-based Combined Lupus Assessment (BICLA)*) at Stage 2 Week 24.
- The cumulative incidence of participants who experience a Stage 3 treatment failure, defined as the occurrence of any criteria in Section 3.5.1, *Treatment Failure* after re-randomization and on or before completing Stage 3.
- Time to treatment failure in Stage 3, defined as the interval from the day of Stage 3 randomization until the day of treatment failure.
- Clinical response in Stage 3, defined by the BICLA (see Section 3.5.3, *BILAG-based Combined Lupus Assessment (BICLA)*) at Stage 3 Week 24.

3.3.2 Safety Endpoints

The following specific events will be evaluated separately for each stage of the study:

- The incidence of Grade 3 or higher related AEs.
- The incidence of Grade 3 or higher infections.
- The incidence of renal dysfunction, defined as Grade 3 or higher chronic kidney disease with eGFR < 30 ml/min per 1.73 m^2.
- The incidence of Grade 3 or higher hypertension, defined as a systolic blood pressure ≥ 160 mm Hg or a diastolic blood pressure of ≥ 100 mm Hg.

3.4 Exploratory Endpoints

3.4.1 Clinical Endpoints

The following will be evaluated in Stage 2 and Stage 3:

- Proportions of participants in each arm who achieve responder status as assessed by SRI-4, SRI-6, and SRI-7 (as defined in Section 3.5.2, *Systemic Lupus Erythematosus Responder Index)* every 4 weeks through Week 24.
- Incidence rates for Mild/Moderate and Severe flares accumulated during the treatment period. Three flare assessments will be evaluated independently:
    a. Thanou modified SELENA-SLEDAI Flare Index (see Section 19.3.5, *Thanou Modified SFI*)[2].
    b. BILAG flare, defined as a new A or 2 new Bs.
    c. BILAG flare, defined as any item marked new or worse that could support a BILAG A (severe flare) or 2 organs with items marked new or worse that could support a BILAG B (moderate flare).
- Incidence rates for Mild, Moderate and Severe disease activity. Assessments across multiple organ/systems are rated using:
    a. LFA-REAL clinician assessment
    b. LFA-REAL participant assessment

- Longitudinal profiles of the Physical Component Summary, Mental Component Summary, and individual domains of the SF-36 patient-reported outcome (PRO) that are observed over the treatment period.

3.4.2 **Mechanistic Endpoints**

The following pharmacodynamic markers will be evaluated in Stage 2 and Stage 3:

- Differential expression, at the module or single gene level, between participants within immunologically-homogenous clusters who do and do not obtain a clinical response.
- Identification of complex immunophenotypes characterizing clinical response or non-response to study treatment.
- Longitudinal profiles of TWEAK, CR3, FYN, IL16, IL17RA, and IL2RB over 24-week treatment periods.

3.5 Definitions

3.5.1 **Treatment Failure**

Treatment failure is defined as the first occurrence after randomization (Stage 2) or as the first occurrence after re-randomization (Stage 3) of any of the following events:

- Corticosteroid injections or treatment with a new or increased lupus medication, except the occasional use of corticosteroids for reasons not associated with SLE flare (see Section 7.1.2.2, *Prednisone (or equivalent)* for additional information); or
- BILAG flare, defined as any item marked new or worse that could support a BILAG A (severe flare) or 2 organs with items marked new or worse that could support a BILAG B (moderate flare), and if the participant's condition is deemed by the investigator to be "moderately worse" or "much worse" compared to the day of randomization, as assessed by the CGI-C; or
- Premature permanent discontinuation of study-assigned treatment for any reason.

For Stage 2, the reference values for the CGI-C should be the investigators determination of the participant's condition at the Stage 2 Day 0 Randomization Visit. For Stage 3, the reference values for the CGI-C should be the investigator's determination of the participant's condition at the most recent assessment before the Stage 3 Re-randomization Visit.

3.5.2 **Systemic Lupus Erythematosus Responder Index (SRI)**

A response for the SRI-4, SRI-6 and SRI-7 is defined as meeting the following four criteria at the time of the SRI assessment:

- For SRI-4, SRI-6, and SRI-7, a decrease in the Hybrid Systemic Lupus Erythematosus Disease Activity Index (H-SLEDAI) total score of ≥ 4, 6, or 7 points from the reference visit.
- No new BILAG A scores among organs scored as B, C, D, or E at the reference visit, and
- ≤ 1 new BILAG B scores among organs scored as C, D, or E at the reference visit, and
- No worsening (≤ 0.3 point increase) in Physician Global Assessment (PGA) compared to the reference visit.

For Stage 2 and Stage 3, the reference value for SRI-4, SRI-6, and SRI-7 will be the H-SLEDAI total score, BILAG scores, and PGA obtained at the Screening Visit. For Stage 3, additional supportive analyses will use the most recent assessment before the Stage 3 Re-Randomization Visit as the reference value for the H-SLEDAI total score, BILAG scores, and PGA.

3.5.3 **BILAG-based Combined Lupus Assessment (BICLA)**

Clinical response at Week 24, defined by the BICLA [71] as follows:

- All BILAG A scores must improve to B, C, or D, and
- All BILAG B scores must improve to C or D, and
- No new BILAG A scores among organs scored as B, C, D, or E, and
- ≤ 1 new BILAG B scores among organs scored as C, D, or E , and
- No worsening of H-SLEDAI total score, and
- Less than a 10% increase (worsening) in the Physician's Global Assessment (visual analogue scale).

For Stage 2 and Stage 3, the reference values for BILAG, H-SLEDAI total score and PGA are the assessments obtained at the Screening Visit. For Stage 3, additional supportive analyses will use the most recent assessment before the Stage 3 Re-Randomization Visit as the reference value for H-SLEDAI total score, BILAG scores, and PGA.

3.6 Stratification, Randomization, and Blinding

For Stage 2 randomization, participants will be stratified by screening gene expression signature:

- Group 1: high interferon and high inflammation
- Group 2: low inflammation and high B Cells (interferon can be high or low)
- Group 3: other profiles not included in groups 1 or 2
- Group 4: gene expression signature results unavailable (e.g. due to shipping or laboratory error)

For Stage 3 re-randomization, participants will be stratified by the Stage 2 treatment assignment: MMF vs Placebo MMF along with whether or not a long-acting corticosteroid injection was given at the time of Stage 2 treatment failure.

The randomization will be performed by the Division of Allergy, Immunology, and Transplantation (DAIT) Statistical and Clinical Coordinating Center (SCCC). Blinding will be maintained for all study participants and trial personnel throughout the study, except for the study site pharmacist. Treatment assignments will be centrally randomized and communicated to the unblinded study site pharmacist. The investigators, clinic personnel, and participants will not be informed regarding the intervention assignment until the study is unblinded. Laboratories performing assays for this protocol will be blinded to the identity and group assignment of biological materials to be studied.

3.6.1 **Procedure for Unblinding**

Unblinding must be approved by the study NIAID Medical Monitor unless an immediate life-threatening condition has developed and the Medical Monitor is not accessible. The site investigator will notify the NIAID Medical Monitor, Protocol Chair and the SCCC of the unblinding event on the next business day. The emergency unblinding will also be reported to the DSMB by the NIAID Medical Monitor.

A full account of the event will be recorded, including the date and time of the unblinding, the reason for the decision to unblind, and the name of the individual who made the decision and the names of the Medical Monitor and others who were notified. The reasons for unblinding of a participant's treatment will be included in the final study report.

Unblinding the study due to an approved interim analysis, final analysis, or study termination will require written approval from NIAID.

4 Selection of Participants

4.1 Rationale for Study Population

SLE affects all races, all genders, and all ages, but is more prevalent in women in their childbearing years who are of African, Asian or Native American Ancestry. This will be a trial of individuals between the ages of 18 and 60 with no restrictions for race or gender. These criteria are inclusive of most people with SLE, with restrictions for those who are medically vulnerable or who cannot complete all of the procedures. Children are not included since they usually have more severe disease, and this is unlikely to be a safe protocol for them. The current treatments for SLE are inadequate to prevent recurrent flares, progressive disability, and early mortality, often from accelerated atherosclerosis or infection. The population of SLE patients selected for this trial is an underserved community with chronic, sometimes life-long symptoms that significantly affect their work productivity, family relationships and overall quality of life. However, flares tend to be moderate in severity and primarily affect the musculoskeletal and mucocutaneous systems, without life-threatening or organ-threatening components. Our qualification criteria, adjudication process, and pre-testing for early flare markers have all evolved from our past experience with (and test development from) the BOLD study [22].

The BOLD study was conducted safely [22] (clinicaltrials.gov # ***NCT00987831),*** as was our past pilot study of MMF ***NCT00594932,*** which used a BOLD design, and since then two industry-sponsored trials have utilized the same design - ***NCT00774943, NCT02725515*** - one of which is completed and recently published[23]. We are also in the process of completing three Investigator-initiated trials in Oklahoma using the BOLD design: ***NCT02270957, NCT03355482, NCT02270970.*** All of the unpublished SLE trials using the BOLD design are a short time from completion and there has been no unacceptable safety signal to date. However, selection of the appropriate participant population for a trial of this structure is critical, both to its success in obtaining interpretable results and for participant well-being and safety. Our Inclusion and Exclusion Criteria address the selection and verification of this very population.

4.2 Inclusion Criteria

4.2.1 **Inclusion Criteria**

Participants must meet all of the following criteria to be eligible for randomization as study participants.

1. Aged ≥ 18 and ≤ 60 years at the time of informed consent.
2. Meets EULAR/ACR 2019 criteria for SLE [3].
3. Moderately severe, active, but non-organ threatening disease. Specifically, signs or symptoms meeting criteria for a minimum of:
    a. 1 BILAG A (severe) score in the constitutional, musculoskeletal or mucocutaneous system at the time of screening. See Section 4.3, *Exclusion Criteria* number 2 for additional detail.
    b. 2 BILAG B (moderate) activity scores in any organ systems; or
    c. 1 BILAG B (moderate) activity score in any organ systems **and** a SELENA-SLEDAI score of ≥ 6.
        - If there is only 1 BILAG B score:
            - If a musculoskeletal BILAG B is scored due to moderate arthritis, where some loss off functional range of movements was present on several days over the last 4 weeks, there must also be a minimum of at least 3 joints that are both tender and

swollen due to lupus disease activity in wrists, MCPs or PIPs for the participant to qualify.

- If a mucocutaneous BILAG B is scored due to acute or subacute cutaneous skin eruption, the rash must cover at least 4% of the body surface area for the participant to qualify. Any active discoid lesion or other form of chronic cutaneous lupus would be qualifying.

4. Approval, by an adjudication committee of a brief entry packet describing the type, severity and duration of symptoms meeting the minimal criteria for entry. The participant will meet this criterion if the committee is confident of all of the following:
    a. Convincing diagnosis of SLE,
    b. Active disease, due to SLE, warranting the potential of dual therapy with potent immune modulators,
    c. No medical or other condition to contraindicate participation in a placebo-controlled, outpatient study of this design.

5. Women of childbearing potential must have a negative serum pregnancy test at screening.

6. Able or willing to use reliable methods of contraception, as outlined in the Mycophenolate REMS brochure for health care providers, from 4 weeks prior to first randomization to 6 weeks after completion of the study. This criterion applies to females of reproductive potential. Mycophenolate REMS Program acceptable contraceptive methods are outlined in Appendix 1, see Section 19.1.

4.2.2 **Inclusion Criteria Required Prior to Randomization**

Participants who meet the following criterion at the Stage 2 Randomization Visit may proceed to randomization in Stage 2:

7. After completion of corticosteroid injection(s) and prior to randomization in Stage 2, the participant and his/her physician must agree that disease activity has improved sufficiently from screening such that randomization is acceptable.
    a. The physician must score the CGI-C [4] as “moderately better” or “much better” prior to randomization.
        - The reference value for the CGI-C should be the investigator’s determination of the participant’s condition at the Screening Visit.
    b. The participant must agree that his/her symptoms have improved (yes/no).

4.3 Exclusion Criteria

Participants who meet any of the following criteria are not eligible for randomization as study participants:

1. Inability or unwillingness of a participant to understand and provide written informed consent or comply with the study protocol.

2. BILAG A (severe) disease in the Cardiorespiratory, Neuropsychiatric, Gastrointestinal, Ophthalmic, Renal, or Hematological Systems.

3. Severe or unstable nephritis defined as any of the following:
    a. History of confirmed Class 3-5 nephritis within the last 2 years,

b. History of confirmed Class 3-5 nephritis > 2 years ago in the absence of documented treatment including both induction and maintenance therapy,
c. UPCR > 1 g/g at screening,
    - If UPCR is > 0.5 g/g and ≤ 1 g/g at screening, then a second assessment must be completed with at least 1 week between assessments. If the second assessment is > 1 g/g or has increased by ≥ 0.3 g/g, then the participant is excluded.

4. Evidence of chronic kidney disease defined as eGFR < 45 mL/min per 1.73 m^2 at screening, where
   175 x (Creatinine/88.4)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if of African descent) [5].

5. History of cirrhosis or chronic liver disease unrelated to SLE other than fatty liver disease.

6. History, within 1 year of the Screening Visit, of uncontrolled SLE that would have warranted a BILAG A (except mucocutaneous, constitutional, musculoskeletal) including, but not limited to, hemolytic anemia, neuropsychiatric lupus, or interstitial lung disease.

7. Uncontrolled HTN at the Screening or Randomization Visits defined as a blood pressure > 150/100 with or without treatment, not to exceed 3 complementary antihypertensive treatments.

8. Any of the following laboratory values during screening:
    a. Hemoglobin (Hg) < 8.0 g/dL,
    b. WBC < 2.0 x 10^9 cells/L,
    c. ANC < 1.0 x 10^9 cells/L,
    d. Platelets < 60 x 10^9 cells/L at screening,
        - If platelets < 70 x 10^9 cells/L at screening, platelet count should be retested 2 weeks later. If platelets are < 60 x 10^9 cells/L at retest, participant will be excluded
    e. AST or ALT > 2.5 times the ULN,
    f. Serum IgG levels < 5 g/L

9. Use of ≥ 40 mg/day of prednisone within 4 weeks prior to the Screening Visit or use of > 20 mg/day of prednisone at screening.

10. Unwilling or unable to taper to ≤ 10 mg/day of prednisone or equivalent by the day of randomization.

11. Use of hydroxychloroquine, chloroquine, or quinacrine, if taking, at a prescribed dose that has not been stable for at least 2 months prior to randomization.

12. Use of MMF within 1 year of randomization.

13. Use of CNIs within 3 months of randomization. Topical formulations applied stably for at least one month are allowed.

14. Use of rituximab, obinutuzumab, ocrelizumab, or long-acting B cell depletion agents within 1 year of randomization. Use of agents ≥ 6 months and within 1 year of randomization is permitted if there is evidence of B cell reconstitution as defined as CD19+ counts of ≥ 50 cells/µL.

15. History of intolerance or allergy to MMF, voclosporin, or long-acting corticosteroid preparations.
16. Individuals with known hypersensitivity to Polysorbate 80 (Tween).
17. A woman who is pregnant, breastfeeding, or planning pregnancy from the time of consent until 6 weeks after completion of the study.
18. Any participant with plans for major surgery during the time of the trial.
19. Active infections requiring hospitalization or intravenous antibiotics within 1 month prior to the Screening Visit.
20. Any grade 2 infection or higher from 14 days prior to the Screening Visit and through the screening period that has not resolved by randomization.
21. Acute herpes zoster within 4 months of the Screening Visit.
22. Positive results from a SARS-CoV-2 antigen test administered 2 days prior to and on the day of first randomization.
23. Positive Quantiferon Gold (or equivalent) assay. Indeterminate Quantiferon Gold (or equivalent) assays must be repeated (with same or other interferon gamma release assay per local policy) and shown to be negative. Alternatively, if the Quantiferon Gold (or equivalent) assay remains indeterminate, a participant must have a negative PPD. Finally, if the participant has had the BCG vaccine or has some other condition complicating the interpretation of TB testing, consultation with infection disease specialist must be obtained.
    - Participants diagnosed with latent TB are eligible but must have received appropriate prophylaxis for 30 days prior to initiation of Stage 2 treatment.
24. Serologic evidence at screening of chronic infections including:
    a. HIV infection.
    b. Hepatitis B as indicated by surface antigen or hepatitis B core antibody positivity; if a participant has an isolated positive hepatitis B core antibody, they will be eligible to participate in the study if they are negative for reflex viral load at Screening.
    c. Hepatitis C as indicated by anti-hepatitis C antibody positivity; if a participant is Hepatitis C antibody positive, they will be eligible to participate in the study if they are negative for viral load at Screening.
25. Current, diagnosed, or self-reported drug or alcohol abuse within the last 6 months that, in the opinion of the investigator, would interfere with the ability to comply with study protocol.
26. Recipient of live attenuated vaccine(s) within 8 weeks of the Screening Visit.
27. Use of investigational drugs (excluding SARS-CoV-2 vaccinations or SARS-CoV2 therapeutics) within 8 weeks of the Screening Visit or 5 half-lives, whichever is longer.
28. Past or current mental or physical problems 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 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 MMF as cited in the USPI

Risks cited below are noted in the United States Prescribing Information (USPI) for MMF updated 2/2019 [28].

Contraindications: MMF is contraindicated in patients with a hypersensitivity to MMF, MPA, any component of the drug product, and in patients who are allergic to Polysorbate 80 (Tween).

Embryofetal Toxicity: MMF use has been associated with risk of first trimester pregnancy loss and congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and, according to the package insert, anomalies of the distal limbs, heart, esophagus, kidney and nervous system. Embryofetal Toxicity is listed as a boxed warning in the package insert [28].

Lymphoma and Other Malignancies: Patients receiving MMF, or immunosuppressants in general, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Malignancies are listed as a boxed warning in the package insert [28].

Post-transplant lymphoproliferative disorder (PTLD) developed in 0.4% to 1% of patients receiving MMF (2 g or 3 g) with other immunosuppressive agents in controlled clinical trials of kidney, heart and liver transplant patients. The majority of PTLD cases appear to be related to Epstein Barr Virus (EBV) infection. The risk of PTLD appears greatest in those individuals who are EBV seronegative, a population which includes many young children.

Infections: Patients receiving MMF, or immunosuppressants in general, are at increased risk of developing bacterial, fungal, protozoal and new or reactivated viral infections, including opportunistic infections. The risk increases with the total immunosuppressive load. These infections may lead to serious outcomes, including hospitalizations and death. Serious viral infections reported include: Polyomavirus-associated nephropathy, especially due to BK virus infection; JC virus-associated progressive multifocal leukoencephalopathy Cytomegalovirus (CMV) infections, especially for CMV seronegative transplant patients who receive an organ from a CMV seropositive donor; and viral reactivation in patients infected with Hepatitis B and C. Serious infections are listed as a boxed warning in the package insert [28].

Blood Dyscrasias: Neutropenia and Pure Red Cell Aplasia (PRCA): Severe neutropenia [ANC < 0.5 x 10^3/μL] developed in transplant patients receiving MMF 3 g daily, a dose higher than intended for this study. Neutropenia has been observed most frequently in the period from 31 to 180 days post-transplant in patients treated for prevention of kidney, heart and liver rejection.

Cases of PRCA have been reported in patients treated with MMF in combination with other immunosuppressive agents.

GI Disturbances: Diarrhea and vomiting are common. Gastrointestinal bleeding requiring hospitalization, ulceration and perforations were observed in clinical trials.

5.2 Risks of voclosporin as cited in the Investigator Brochure and Package Insert

Risks cited below are noted in the voclosporin Investigator's Brochure [65] and Package Insert [21].

Contraindications:

- Voclosporin is contraindicated in patients with hypersensitivity or anaphylactic reactions to voclosporin or any constituents [65].
- Voclosporin should not be given with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin). Voclosporin exposure was 18-fold higher in the presence of the strong CYP3A4 inhibitor (ketoconazole) compared to voclosporin administered alone [65].
- Voclosporin should not be given in patients with hypertensive urgency or BP > 165/105 mmHg [21].
- Voclosporin is not recommended for patients with a baseline eGFR < 45 mL/min per 1.73 m^2 unless benefit exceeds risks [21].

Hypertension: Voclosporin can cause or worsen systemic HTN. Mild or moderate HTN is encountered more frequently than severe HTN. Serious adverse drug reactions (SADR) classified by the MedDRA preferred term "hypertension" are considered "expected" for the purpose of regulatory reporting. Life-threatening or fatal SADRs are "unexpected". HTN may require antihypertensive therapy.

Decreases in GFR: Voclosporin can cause chronic and/or acute nephrotoxicity. eGFR should be monitored regularly and dose adjustments considered for decreases in eGFR. In the first 4 weeks of treatment with voclosporin, hemodynamic reductions in eGFR have been observed, which subsequently stabilize. Chronic nephrotoxicity has been observed at levels of CNI suppression needed in organ transplantation. The level of CNI suppression of voclosporin in LN is lower than that generally required in transplantation induction and maintenance. Renal impairment and acute kidney injury occurred more frequently in voclosporin-treated patients than placebo-treated patients.

Serious Infections: Immunosuppressants, including voclosporin, may increase the risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may be serious and have fatal outcomes. Serious infections are listed as a boxed warning in the package insert [21].

Neurotoxicity: Voclosporin, like other CNIs, may cause a spectrum of neurotoxicities, the most severe of which are posterior reversible encephalopathy syndrome (PRES), delirium, seizure, and coma; others include tremors, paresthesias, headache, mental status changes, and changes in motor and sensory functions.

Hyperkalemia: Voclosporin has been reported to cause hyperkalemia which may be exacerbated by use of other agents such as potassium-sparing diuretics, ACE inhibitors and angiotensin receptor blockers.

QTc prolongation: Voclosporin prolongs the QTc interval in a dose-dependent manner after single dose administration at a dose higher than the recommended LN therapeutic dose. The use of voclosporin in combination with other drugs that are known to prolong QTc may result in clinically significant QT prolongation.

Pure Red Cell Aplasia: Although not reported with voclosporin, cases of PRCA have been reported in patients treated with other CNIs.

Lymphomas and Other Malignancies: Voclosporin is an immunosuppressant. Long-term treatment with immunosuppressants increases the risk of developing lymphomas and other malignancies, particularly of the skin. The

risk appears to be related to the intensity and duration of immunosuppression rather than to specific use of a medication. Patients should be advised to avoid or limit unprotected exposure to sunlight and UV light. Malignancy is a boxed warning in the package insert [21].

Other Concerns:

- Voclosporin should be avoided during pregnancy because of the alcohol content of the drug formulation. Nonclinical studies with oral voclosporin showed that low levels of voclosporin crossed the placental barrier. The available data on the use of voclosporin in pregnant women are insufficient to determine whether there is a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. Study product will be discontinued in any participant who becomes pregnant, and the pregnancy will be followed per Section 12.6, *Pregnancy Reporting*.
- Limited transfer to breast milk was also demonstrated in rats. No information is available on the presence of voclosporin in human milk, the effects of voclosporin on the breastfed infant, or the effects of voclosporin on milk production.

5.3 Risks of long-acting corticosteroid injections

Corticosteroids rapidly decrease the numbers and function of peripheral lymphocytes and inflammatory cytokines. Short term, high dose IM injections are generally well tolerated, but it is important to monitor for HTN, fluid retention and common psychiatric side effects including insomnia and agitation. The potential side effects of corticosteroids are well documented and familiar to the lupus clinic. Although the temporary use of steroid injections used in this protocol is not likely to lead to many side effects, it is important for all study staff to be familiar with them and is good clinical practice. Discussions about minimizing steroids will take place with all participants with SLE, who suffer significant morbidity over the many years of illness from these extremely useful but chronically toxic medications.

Potential risk of long term corticosteroid use may result in cardio-renal side effects such as elevation of blood pressure, increased excretion of potassium, and increased calcium excretion; endocrine side effects such as hypothalamic-pituitary adrenal axis suppression, Cushing's syndrome, and hyperglycemia; dermatological side effects such as acne, striae, thin parchment skin, and easy bruising; ophthalmic side effects such as posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and enhanced risk of secondary ocular infections; weight gain; moon facies; increased susceptibility to infections, and osteoporosis. In addition, glucocorticoids can cause dyslipidemia, heart disease, fluid retention, gastrointestinal bleeding and neuropsychiatric effects like mood disorders and psychosis. Many of the risks are for corticosteroid use in general and may not be applicable for the short periods before randomization and re-randomization for which this treatment will be used.

Risks of intramuscular administration of methylprednisolone acetate cited below are noted in the United States Prescribing Information for DEPO-MEDROL® (methylprednisolone acetate injectable suspension, USP) from 2018.

Contraindications:

- Methylprednisolone acetate is contraindicated in patients with known hypersensitivity to the product and its constituents.
- Methylprednisolone acetate is contraindicated in systemic fungal infections, except when administered as an intra-articular injection for localized joint conditions.
- Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.

With the use of triamcinolone acetonide IM, there is a risk of subcutaneous fat atrophy and hypopigmentation which can be minimized by intramuscular injection into the gluteal muscle using at least a 1 1/2 inch needle [72].

5.4 Risks of Withdrawal of Lupus Medications

During Stage 1, consenting participants will withdraw from current lupus medications. Withdrawal of lupus medications per protocol prior to randomization into Stage 2 could lead to disease exacerbation or flare. After signing of consent, the participant will receive a corticosteroid injection, which may be repeated an additional 2 times to achieve amelioration of symptoms. The use of corticosteroid injections which naturally wane in their effects gradually is a mitigation strategy for these risks.

5.5 Special Considerations for COVID-19 or Other Public Health Emergency

Clinical trial conduct may be impacted by the COVID-19 or other infectious disease public health emergency. Infectious disease screening or testing procedures mandated by local health authorities or the health system where the clinical trial is conducted may be performed without the need for a protocol amendment. In certain cases, the participants may not be able to come to the study site, or local institutional policies or other factors may limit access to the research site. The sponsor, study team, and site investigator will determine if alternative methods for conducting assessments and procedures are necessary and feasible, for example telemedicine. The safety of participants is paramount.

Participants will be educated regarding the risk of the infectious disease, and about public health recommendations for precautions.

5.6 Potential Benefits

For Stage 2 (randomization to MMF or corresponding placebo MMF), one or more baseline immunophenotypes may be associated with treatment success (or failure). This knowledge could set the stage for future studies to establish biomarkers that inform treatment option decisions.

Voclosporin, in combination with MMF, has shown benefit in LN. Although it has not been evaluated in SLE without LN, participants treated with voclosporin plus MMF in Stage 3 (randomization to voclosporin plus MMF or MMF alone) may experience a longer period of symptom relief when compared to participants who receive MMF alone.

The knowledge gained from this study may advance our understanding of how molecular and gene expression profiles relate to treatment success (or failure) and suggest strategies for personalized medicine for future study.

6 Investigational Agent

6.1 Investigational Agents

6.1.1 MMF and Placebo for MMF

6.1.1.1 Formulation, Packaging, and Labeling

MMF is an antimetabolite immunosuppressant [28]. It is the 2-morpholinoethyl ester of MPA, an immunosuppressive agent; inosine monophosphate dehydrogenase (IMPDH) inhibitor. The chemical name for MMF is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate. MMF is a white to almost white crystalline powder. It is slightly soluble in water (43 mcg/mL at pH 7.4), freely soluble in acetone, soluble in methanol, sparingly soluble in anhydrous ethanol [28].

Commercially available MMF (250 mg capsules) manufactured by Sandoz will be purchased by NIAID Investigational Product Procurement Center, and overencapsulated, rebottled, blind labeled, packaged, and distributed by DAIT/NIAID Clinical Product Center (CPC) to site investigational pharmacies.

Placebo for MMF will be manufactured by DAIT CPC and will not contain active ingredients. Both MMF and placebo for MMF will be overencapsulated to blind MMF/Placebo capsules.

6.1.1.2 **Dosage, Preparation, and Administration**

MMF and matching placebo for MMF will be provided in 250mg overencapsulated gel capsules and will be administered orally. The blinded overencapsulated MMF/Placebo capsules should not be opened or crushed. Avoid inhalation or direct contact with skin or mucous membranes of the powder contained in blinded overencapsulated MMF/Placebo capsules.

Blinded overencapsulated MMF/Placebo should be stored at 20° to 25°C (68° to 77°F).

Stage 2 Dosing:

- **Week 1**: Participants will receive 500mg MMF/Placebo twice daily
- **Week 2**: Participants will receive 500mg/Placebo in the morning and 1,000mg MMF/Placebo in the evening
- **Weeks 3-48**: Participants will receive 1000mg MMF/Placebo twice daily

Stage 3 Dosing: <u>(Individuals who received placebo MMF in Stage 2)</u>

- **Week 1**: Participants will receive 500mg MMF plus matching placebo for MMF (to appear like a 1000mg dose) twice daily
- **Week 2**: Participants will receive 500mg plus matching placebo for MMF (to appear like a 1000mg dose) and 1000mg in divided doses
- **Weeks 3-24**: 1000mg MMF twice daily

<u>Participants who received MMF in Stage 2</u>

- **Week 1-24**: 1000mg MMF twice daily

6.1.2 **Voclosporin and Placebo for Voclosporin**

6.1.2.1 **Formulation, Packaging, and Labeling**

Voclosporin is a calcineurin-inhibitor immunosuppressant [21]. Chemically, voclosporin is named: Cyclo{{(6E)-(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-6,8-nonadienoyl}-L-2-aminobutyryl-N-methyl-glycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl}. It appears as white to off-white solid matter. At ambient temperature, voclosporin is freely soluble in acetone, acetonitrile, ethanol, and methanol, and practically insoluble in heptanes (USP). Voclosporin is practically insoluble (less than 0.1 g/L at 20ºC) in water and melts above 144ºC with decomposition [21].

The manufacturer Aurinia Pharmaceuticals will supply LUPKYNIS™ (voclosporin) 7.9 mg gel capsules and placebo for voclosporin. Placebo capsules do not contain active ingredients.

DAIT CPC will label and distribute active voclosporin and placebo for voclosporin to the clinical site pharmacies. Clinical site pharmacies will dispense voclosporin/placebo to participants as required per arm of Stage 3.

6.1.2.2 **Dosage, Preparation, and Administration**

Voclosporin will be provided in 7.9 mg gel capsules for oral administration. Placebo for Voclosporin will be provided as gel capsules for oral administration.

The rate and extent of voclosporin absorption is decreased on co-administration with food, therefore, to maximize absorption it is recommended that voclosporin is administered on an empty stomach.

Voclosporin should be stored at 20° to 25°C (68° to 77°F).

Stage 3 Dosing:

- **Weeks 1-24:** 23.7 mg Voclosporin/Placebo (3 x 7.9 capsules) twice daily

Voclosporin/Placebo dose may be modified for renal impairment, see Section 6.4.7, *Decreases in eGFR.*

- Allowed voclosporin/placebo dose reductions include: 15.8 mg or Placebo (2 capsules) orally twice daily and 7.9 mg or Placebo (1 capsule) orally twice daily.

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 agents, including the date and quantity of the product(s) received, to whom the product(s) was dispensed (participant-by-participant accounting), and a detailed accounting of any product(s) accidentally or deliberately destroyed. Details of investigational product(s) distribution to each participating clinical site will be maintained by the DAIT CPC. The investigator must delegate the drug accountability responsibility to a licensed/registered pharmacist at registered investigational pharmacy at the clinical research site. Please refer to the DAIT Pharmacy Guidelines (https://www.niaid.nih.gov/sites/default/files/pharmacy.pdf).

All personnel involved in drug management and preparation must receive proper training based on the DAIT and site requirements prior to study initiation. The Pharmacist of Record should be listed on the Delegation of Responsibility Log (DoR) and is responsible to ensure that any pharmacy personnel involved in any aspect of the drug management, preparation, and dispensing process have completed and documented all DAIT required trainings (Good Clinical Practice (GCP)/Human Subject Protection (HSP), protocol/pharmacy manual, DAIT Pharmacy Guidelines). Only individuals listed on the DoR log and/or the Investigator of Record Agreement (IORA) may manage drug products for this study. All drug disposition and dispensing (receipt, storage, use, return, and disposition) will be maintained by the study site using investigation product(s) and/or placebo-accountability and participant-specific dispensing logs that are approved by DAIT/NIAID and 21 CFR Part 11 compliant. This log will contain the identification of each participant and the date and quantity of investigational product(s) dispensed.

The study clinical research associate (CRA) will conduct accountability of the drugs by monitoring the main Accountability Records and Participant-Specific Accountability logs. The study CRA will also review other pharmacy logs, as applicable. All records regarding the disposition of the investigational product(s) will be available for monitoring and inspection. At the termination of the study, all unused product(s) (expired or un-expired) will be returned to DAIT CPC. For more detailed information on handling of the investigational product(s), please refer to the Pharmacy Manual.

6.3 Assessment of Participant Compliance with Investigational Agents

The number of capsules of study product returned to the site will be counted and recorded at all clinic visits. Participants will also be given a diary to record episodes of intolerance or reasons why a pill may not have been taken.

6.4 Toxicity Prevention and Management

6.4.1 **Hypersensitivity**

Individuals with known hypersensitivity MMF, MPA, any component of MMF, Polysorbate 80 (Tween), long-acting corticosteroid preparations or their constituents, or voclosporin or its constituents will be excluded from participation in the trial.

6.4.2 **Reproductive Risks**

Women on MMF are at increased risk of first trimester pregnancy loss and congenital malformations in children. Data on pregnancy risk is unavailable for voclosporin. Women of childbearing potential will have a pregnancy test at each study visit. Should pregnancy occur, study medications will be discontinued immediately, study visits will continue as scheduled except for study medication, and the pregnancy will be followed per Section 12.6, *Pregnancy Reporting*. Appropriate referrals should be made for counseling on fetal effects of study medication. The pregnancy should be reported to the Mycophenolate Pregnancy Registry, which is a part of the MMF REMS program. Male participants and female partners capable of becoming pregnant are encouraged to use a contraceptive barrier method during the study.

6.4.3 **Malignancy**

Immunosuppression is associated with increased risk of lymphoma and other malignancies, particularly skin cancers. Participants should be advised to avoid or limit unprotected exposure to sunlight and UV light. If evidence of lymphoproliferative disease emerges, work up will be guided by the institution's standard of care requirements. If malignancy (other than non-melanoma skin cancer) is diagnosed, study medications will be discontinued, and the participant will be treated according to standard of care per institutional requirements. If new non-melanoma skin cancer is found and fully treated with local procedures, the participant may continue in the trial as planned based on investigator discretion. Participants over the age of 50 should have age-appropriate cancer screenings at the investigator's discretion prior to enrollment and throughout the course of the study. For additional information, consult the American Cancer Society (ACS) reference below:
http://www.cancer.org/healthy/toolsandcalculators/reminders/screening-recommendationsby-age

6.4.4 **Infections**

Immunosuppression is associated with increased risk of infection. Individuals with active or chronic infections are excluded from the study. Participants will receive guidance recommending vaccinations be up-to-date according to local standards and lymphocyte counts will be monitored through the study. Participants will be followed closely for signs of infection at study visits, and between visits if needed. In the setting of infection, study medications may be withheld based on institutional practices or investigator judgment, for up to 2 weeks and then resumed at scheduled dose. Otherwise, refer to the guidelines in in 6.5, Premature Discontinuation of Investigational Agent in the event of toxicity.

Additionally, low IgG levels are found in less than 10% of patients with SLE and are usually not associated with infection [73]. However significant drops in IgG have been seen with various immune-modulating medications and if

not carefully monitored may increase risk for serious infections and death [26, 43]. We will employ a safety mitigation strategy that was successfully employed in a study of Atacicept, the ADDRESS II trial [74]. At the Screening Visit, participants must have serum IgG levels ≥ 5 g/L. Immunoglobulin levels will be checked throughout the course of the study per Table 8.1 *Schedule of Events*. If at any time during the study these levels fall to < 4 g/L, study medication will be withheld with a retest at one week. If retest demonstrates recovery to ≥ 4.5 g/L, medication may be restarted. If not, another retest may be performed in another week. If IgG does not recover to ≥ 4.5 g/L after the second retest, study medication will be permanently withdrawn as per the guidelines in Section 6.5, *Premature Discontinuation of Investigational Agent.*

6.4.4.1 **SARS-CoV-2 Infections**

Participants are encouraged to receive full COVID-19 vaccination per CDC guidelines. Participants will be tested for SARS-CoV-2 as part of screening as mandated by the entry criteria and throughout the study as clinically indicated. Assessment, prophylaxis, and treatment for infection will be guided by standard of care per institutional requirements; however, individuals participating in ALE10 are at high risk for SARS-CoV-2 infection. Per standard recommendations, a participant with mild to moderate COVID-19 symptoms should be evaluated for treatment with an FDA authorized or approved COVID-19 treatment as soon as possible following confirmation of the infection and within 10 days of symptom onset. Additionally, any participant who has close contact with a SARS-CoV-2 infected individual should be evaluated as soon as possible after exposure. Additional FDA Approvals and EUAs are anticipated for the prevention and treatment of SARS-CoV-2. Site investigators are expected to keep abreast of these approvals and authorizations in order to advise ALE10 trial participants about optimal prevention and treatment. NIH COVID-19 treatment guidelines can be found here: https://www.covid19treatmentguidelines.nih.gov/.

6.4.5 **Gastrointestinal Abnormalities**

Gastrointestinal side effects including nausea and diarrhea are associated with MMF use. If these symptoms exacerbate without other likely explanation, study medications may be withheld for up to 2 weeks and resumed at the scheduled dose. Otherwise, refer to the guidelines in Section 6.5, *Premature Discontinuation of Investigational Agent* in the event of toxicity.

6.4.6 **Hypertension**

Voclosporin may be associated with increased risk of HTN [75]. Individuals with uncontrolled HTN are excluded from participation in the study (See Section 4.3, *Exclusion Criteria* number 7 for additional detail). During the study, blood pressure will be evaluated at each study visit, including once 2 weeks after initiating Stage 3 study therapy. Clinically concerning elevated blood pressure should be managed with antihypertensive therapy. In the event of HTN associated with a SAE or a Grade 3 or above AE that is possibly or definitely related to study medication, study medications may be withheld for up to 2 weeks. If the AE does not resolve down to Grade 2 or below after 2 weeks of withholding medication, study medication should be discontinued. If the AE improves to grade 2 or below but increases again to grade 3 once study medication is reinstituted then study product should be discontinued permanently.

6.4.7 **Decreases in eGFR**

For voclosporin use, regular monitoring of eGFR is recommended per the Investigator Brochure, every 2 weeks for first month then every 4 weeks thereafter. Clinically significant decreases have been observed with voclosporin plus

MMF as well as for MMF alone. For this study, individuals with eGFR < 45 mL/min per 1.73 m^2 at screening are excluded. eGFR will be evaluated at each study visit. It will also be assessed at a Stage 3 Week 2 Safety Check Visit two weeks after initiating Stage 3 therapy. The most recent assessment of eGFR before the Stage 3 Re-randomization Visit should be used as baseline for Stage 3 Week 2 eGFR assessment.

If eGFR < 60 mL/min per 1.73 m^2 and is reduced from Stage 3 baseline by 20-30%, reduce dose by one capsule BID (total of 2 capsules BID). Reassess eGFR in 2 weeks, and if it is still reduced by > 20% from baseline, reduce dose to 1 capsule BID. If eGFR < 60 mL/min per 1.73 m^2 and reduced from Stage 3 baseline by > 30%, withhold voclosporin for 2 weeks, then reassess and consider re-initiating at 1 capsule BID if eGFR is > 80% of baseline.

6.4.8 **Glucose and Diabetes**

The development of new-onset diabetes is in an important, recognized effect of CNI inhibitors. In voclosporin clinical trials, the incidence of AEs related to diabetes and glycemic control was low and similar in both treatment groups, indicating that there is no increase in these types of events with voclosporin treatment. Uncontrolled diabetes may be excluded from the trial per investigator discretion according to the inclusion/exclusion criteria set in Section 4, *Selection of Participants*.

6.4.9 **Hematological Abnormalities**

Individuals meeting thresholds for exclusionary levels of neutrophils, WBC, platelets, and hemoglobin at screening are excluded from the study (See Section 4.3, *Exclusion Criteria* number 8 for additional detail). To monitor potential hematological toxicity, the participants will have a complete blood count at each visit. If any of the following develop without explanation and persist after a repeat check in one week, then study medications will be held for one week and the test repeated:

- neutropenia (neutrophils < 800/mm^3, equivalent to 0.8 x10^9/L),
- leukopenia (WBC < 1500/mm^3, equivalent to 1.5 x10^9/L),
- thrombocytopenia (platelets < 40,000/mm^3, equivalent to 40 x10^9/L), or
- anemia (hemoglobin < 7.0 g/dL).

Study medication may be held up to 2 weeks while the abnormality is monitored weekly for recovery. If recovery to screening value occurs then study medication can be resumed. Otherwise, refer to the guidelines in Section 6.5, *Premature Discontinuation of Investigational Agent* in the event of toxicity. If participants have symptomatic complications from the hematological derangements, this should be treated according to standard of care per institutional requirements.

6.4.10 **Hepatic Abnormalities**

Individuals with AST or ALT > 2.5x ULN at screening are excluded from the study. Liver function tests will be checked every 4 weeks for signs of hepatic toxicity. If transaminases exceed 3x ULN without explanation, then study medications will be held for up to 2 weeks, and the abnormality followed weekly for resolution to screening value. Should resolution occur within 14 days, the study medication may be resumed. Otherwise, refer to the guidelines in 6.5, *Premature Discontinuation of Investigational Agent* in the event of toxicity.

6.5 Premature Discontinuation of Investigational Agent

Study participants who discontinue investigational agent prematurely but are willing and able to remain in the study and undergo evaluation per protocol will be encouraged to do so.

Study therapy may be paused for up to 2 weeks for infections, gastrointestinal abnormalities, HTN, decreased eGFR, hematologic abnormalities and hepatic abnormalities as detailed in Section 6.4, *Toxicity Prevention and Management*.

Study therapy may be prematurely discontinued for any participant for any of the following reasons:

1. Participant decision.
2. Determination of unacceptable toxicity, including but not limited to:
    a. Gastrointestinal abnormalities that do not resolve after study medications are withheld for up to 2 weeks as outlined in Section 6.4.5, *Gastrointestinal abnormalities*;
    b. HTN that does not resolve after study medications are withheld for up to 2 weeks as outlined in Section 6.4.6, *Hypertension;*
    c. Decreased eGFR that does not resolve after study medications are withheld for 2 weeks as outlined in Section 6.4.7, *Decreases in eGFR*;
    d. Hematological Abnormalities that do not resolve after study medications are withheld for up to 2 weeks as outlined in Section 6.4.9, *Hematological Abnormalities*;
    e. Hepatic Abnormalities that do not resolve after study medications are withheld for up to 2 weeks as outline in Section 6.4.10, *Hepatic Abnormalities;*
    f. Grade 4 Leukopenia (WBC < 1000/mm^3, equivalent to 1.0 x10^9/L); and
    g. Grade 4 Neutropenia (Neutrophils < 500/mm^3, equivalent to 0.5 x10^9/L);
3. Treating physician determination of any condition that warrants withdrawal of study medication.
4. Any condition that in the opinion of the DAIT Medical Monitor warrants withdrawal of study medication.
5. The participant becomes pregnant.
6. The participant develops a malignancy (other than non-melanoma skin cancer).
7. Treatment failure, as defined in Section 3.5.1, *Clinical Endpoints* including corticosteroid injection(s) or treatment with a new or increased lupus medication.
8. Toxicity or Infection (see Section 6.4, *Toxicity Prevention and Management*):
    a. If study medication is withheld for more than 14 sequential days due to suspected toxicity or infection.
    b. Grade 4 infection.

7 Other Medications

7.1 Concomitant Medications

Information about the concomitant medications and treatments will be collected at each visit. All concomitant medications given to the participant during the study will be recorded on the electronic case report form (eCRF).

7.1.1 **Protocol-mandated: Corticosteroid Injections**

During Stage 1, at least one IM injection of a long-acting corticosteroid must be given to participants. This may be repeated up to 2 additional times as needed to ameliorate symptoms.

Participants may also receive a long-acting corticosteroid IM injection to ameliorate symptoms during the first 24 weeks of the study due to treatment failure as defined in Section 3.5.1, *Treatment Failure.* An additional corticosteroid injection may be administered during the first 2 weeks of Stage 3 treatment without meeting the definition of treatment failure in Stage 3 and without a requirement to stop Stage 3 study-provided medication, for a

total of 2 corticosteroid injections from the time of Stage 2 Treatment Failure up and including to the Stage 3 Week 2 Visit.

Dose will be dependent on the available formulation. Methylprednisolone acetate (80mg) will be used for all corticosteroid injections administered during the study. If methylprednisolone acetate (80mg) is not available, triamcinolone acetonide (60mg) may be substituted. If triamcinolone acetonide (60mg) is not available, substitution of a therapeutically equivalent long-acting corticosteroid injection may be allowed but must be approved by the study NIAID Medical Monitor.

7.1.2 **Permitted Concomitant Medications for SLE**

7.1.2.1 **Anti-malarial Agents**

Participants can be on concurrent hydroxychloroquine, chloroquine or quinacrine at a prescribed dose that has been stable for at least 2 months prior to randomization. Hydroxychloroquine is approved by the FDA for the treatment of SLE. Hydroxychloroquine has been shown to help prevent flare in SLE, and to improve skin and musculoskeletal activity in particular [76, 77]. Even LN outcomes appear improved on a background of hydroxychloroquine therapy [78].

7.1.2.2 **Prednisone (or equivalent)**

Individuals may screen for the study if taking up to 20 mg/day prednisone (or equivalent) but both the participant and the investigator must be willing and able to taper to 10 mg/day (under cover of long-acting corticosteroids) by the Stage 2 Randomization Visit. Prednisone (or equivalent) may be continued at a stable dose ≤ 10 mg/day once the participant is randomized into the trial. Individuals are not eligible for the study if they have taken ≥ 40 mg/day of prednisone within 4 weeks prior to the Screening Visit.

To accommodate the occasional use of extra corticosteroids for reasons not associated with SLE flares, increases of up to 40 mg/day that are decreased back to the baseline dose within 14 days are permitted, but not on more than one occasion prior to Week 20 in Stage 2 and one occasion prior to Week 20 in Stage 3.

7.1.2.3 **NSAIDS**

Participants may start or continue NSAIDS PRN during the course of the study. NSAIDs should be held on the morning of study visits.

7.1.2.4 **Topical treatments for Lupus**

As needed topical treatments for the treatment of lupus symptoms that are initiated prior to screening may be continued. New topical treatments are restricted after screening.

7.1.3 **Permitted Concomitant Medications for non-SLE Conditions**

Concomitant therapies taken for long-term treatment of pre-existing conditions other than SLE should be continued during the study, provided that they are in accordance with the exclusion criteria (see Section 4.3, *Exclusion criteria*). It is preferred that these medications be stabilized before entry and continued wherever practical without variation of dose or regimen during the study. Participants should also continue to receive SARS-CoV-2 vaccinations per CDC and FDA recommendations and other vaccinations as recommended by their treating physician during the course of the study.

7.2 Prophylactic Medications

There are no protocol-mandated prophylactic medications. However, non-immunosuppressive treatments for symptom control (anti-emetics, antipyretics) in susceptible participants will be allowed as determined appropriate by the local investigator. Participants should continue to take their medications for co- morbid conditions, but these should be reviewed by the investigator prior to the start of the study in order to ensure no prohibited medications are being taken (see Section 7.3, *Prohibited Medications*).

7.3 Prohibited Medications

All participants are to have access to any care deemed medically necessary, but administration of the following medications, for the purposes of this study, are prohibited:

7.3.1 **Live Attenuated Vaccines**

Live attenuated vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines) will be prohibited for the course of the study.

7.3.2 **Immunomodulatory or Immunosuppressive Medications**

No new or increased immunomodulatory or immunosuppressive medications may be added while a participant is on study drug. Participants who require a new or increased immunomodulatory or immunosuppressive medication will be considered as having met primary endpoint (see Section 3.2, *Primary Endpoint*) and will be required to discontinue study drug (see Section 6.5, *Premature Discontinuation of Investigational Agent*) prior to initiating the new or increased lupus therapy.

7.3.3 **Grapefruit Juice**

Grapefruit juice will not be permitted during Stage 3.

7.3.4 **Strong CYP3A4/5 Inhibitors and Inducers**

Strong CYP3A4/5 inhibitors and inducers will be prohibited during Stage 3 of the study. For common examples of Strong CYP3A4/5 inhibitors and inducers, please see Appendix 2. Additionally, please reference the tables in the FDA guidance regarding CYP3A4 inhibitors and inducers: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

7.3.5 **Moderate CYP3A4/5 Inhibitors and Inducers**

Moderate CYP3A4/5 inhibitors and inducers should be avoided during Stage 3 if possible. Voclosporin is a weak inhibitor of P-gp and caution is advised for co-administration of voclosporin with the sensitive P-gp substrate, digoxin, with appropriate monitoring of digoxin performed as clinically indicated and described in the digoxin product labeling. Additionally, please reference the tables in the FDA guidance regarding CYP3A4 inhibitors and inducers: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

7.3.6 **Antacids**

Antacids with magnesium or aluminum hydroxide, proton pump inhibitors, drugs that interfere with enterohepatic recirculation, telmisartan, and calcium-free phosphate binders should be avoided while a participant is on study medication as they may interfere with systemic exposure and reduce MMF efficacy.

8 Study Procedures

8.1 Study Visits

8.1.1 **Screening and Enrollment**

The study will be explained in lay terms to each potential research participant. The potential participant will sign an IRB-approved informed consent form (ICF) before undergoing any study procedures. Once the ICF has been signed, the participant is considered enrolled in the study and will be assigned a unique participant number. At this time, study-specific procedures may be performed. Consented participants will receive an intramuscular injection of a long-acting corticosteroid at screening which may be repeated if needed to achieve amelioration of symptoms. Withdrawal of background lupus medications can start any time after the first corticosteroid injection is given, but must be complete by the Stage 2 Randomization Visit.

The purpose of screening, which begins at the time of signed consent, is to confirm eligibility to enter the study. All screening procedures, assessments, and laboratory measures to determine participant eligibility will be conducted within a 28-day screening window. The assessment of eligibility may take a series of visits that occur on separate days. Blood draws for screening should be performed prior to initiation of any change of therapy, including corticosteroid injection(s) or withdrawal of background medications. The Screening Visit biomarkers should reflect, as much as possible, the biometrics of the participant prior to any study procedures. Participants with abnormal laboratory values that prohibit entry may be re-tested once during the screening, which may last up to 28 days. Participants who screen fail may be rescreened one time and must repeat all screening assessments. Any further rescreening activity requires approval by the medical monitor.

Participants who withdraw from their lupus medications and then screen fail prior to Stage 2 will have a safety follow-up visit 4 weeks ± 10 days after the date of screen fail. Participants will then be treated by their rheumatologist per clinical judgment.

Participants who do not screen fail at screening will undergo review by a committee of at least two adjudicators. The committee will include the protocol chair and the NIAID medical monitor. The committee will have access to a secure website and will receive an email notification when materials for a potential participant have been uploaded. The review packet will contain a paragraph from the investigator, the EULAR/ACR 2019 criteria, SLEDAI, BILAG, and clinical notes. The investigator will be required to answer the following questions:

1. Is active lupus occurring and can it be classified properly?
2. Is current disease activity sufficient to meet inclusion/exclusion criteria? Here the investigator will justify why they scored lupus disease activity the way they did.
3. Is the participant stable enough to participate in the study? Here the investigator will ensure that the participant does not have organ-threatening disease or is too sick to participate in the study.

The committee will confirm entry criteria. Site investigators will need to be available to answer any questions the committee has within 2 business days.

8.1.2 **Evaluation of Eligibility and Randomization for Stage 2**

Participants who meet all eligibility criteria and show improvement will proceed with Stage 2 randomization, treatment, visits, and assessments according to Table 8.1, *Stage* 1 & 2 *Schedule of Events*. See Section 8.2, *Study Procedures and Assessments* for more information on individual clinical and research assessments.

8.1.3 **Study-Provided Medication for Stage 2**

- Stage 2 study-provided medication (MMF or corresponding MMF placebo) is dispensed to eligible participants at the Stage 2 Randomization Visit after confirmation of participant eligibility and completion of all study visit activities, including corticosteroid injection (if applicable). Dosing begins on the day of randomization.
- Study medication compliance is evaluated at all follow-up visits.
- Refer to Section 3.1.2, *Stage 2 Randomization* for additional information.

8.1.4 **Evaluation and Eligibility for Stage 3**

Eligible and consenting participants who have a qualifying Stage 2 treatment failure at or before the Stage 2 Week 24 Visit will immediately proceed with Stage 3 re-randomization according to Table 8.2, *Stage 3 Schedule of Events*. If a qualifying Stage 2 treatment failure is identified after a visit has taken place due to laboratory values, the participant should return for Stage 3 re-randomization within 5 days of discovery of the event. See Section 8.2 *Study Procedures and Assessments* for more information on individual clinical and research assessments.

8.1.5 **Study-Provided Medication for Stage 3**

- Stage 3 study-provided medication (MMF/voclosporin or MMF/corresponding placebo for voclosporin) is dispensed to eligible participants at the Stage 3 Re-Randomization Visit. Dosing begins on the day after re-randomization.
- Study medication compliance is evaluated at all following visits.
- Refer to Section 3.1.3, *Stage 3 Re-Randomization* for additional information.

8.1.6 **Unscheduled Visits**

The investigator may schedule visits in addition to those listed in Table 8.1, Stage 1 & 2 Schedule of Events and Table 8.2, Stage 3 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 will be instructed to contact study personnel and may be asked to return to the study site for an “Unscheduled” visit. See Table 8.1, Stage 1 & 2 Schedule of Events and Table 8.2, Stage 3 Schedule of Events, to see what assessments and procedures should be obtained for an unscheduled visit. In the event that the unscheduled visit is due to a disease flare qualifying as a “treatment failure” (see Section 3.2, Primary Endpoint), see Figure 1, Study Flow Diagram, for more information on how the future path of the participant.

8.1.7 **Early Termination**

An Early Termination Visit should be requested for participants who withdraw from the study prior to study completion. Assessments to be conducted at an early termination visit can be found in Table 8.1, Stage 1 & 2 Schedule of Events and Table 8.2, Stage 3 Schedule of Events.

8.2 Study Procedures and Assessments

8.2.1 General Assessments

- **ICF**
- **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.
- **Comprehensive Physical Examination.** Physical examinations are to include, at least, the following systems: general appearance, skin, head/eyes/ears/nose/neck/throat, respiratory/chest, cardiovascular, abdominal, neurological, & musculoskeletal/extremities. Neurological exam may only be performed based on participant complaint after the screening and Stage 2 Randomization Visit.
- **Vital Signs.** Height will only be collected at screening. Weight, temperature, pulse, and blood pressure will be collected at each visit. Vital signs should be obtained with the participant in a seated position and prior to taking samples for laboratory testing at applicable study visits.
- **ECG**
- **Adverse Event Collection**
- **Concomitant Medications (including Contraceptives).** A current list of prescription and over-the-counter medications, supplements, and treatments for 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 should be captured.
- **Treatment Surveys**

8.2.2 Clinical Laboratory Assessments

Blood and urine for the clinical laboratory assessments listed below will be collected per Table 8.1, Stage 1 & 2 Schedule of Events and Table 8.2, Stage 3 Schedule of Events. All laboratory assessments will be collected after the participant sees the physician so that appropriate clinical and mechanistic labs can be drawn if the participant is a treatment failure. The results will be evaluated for safety by the site investigator. Abnormal tests that meet grading and reporting criteria will be reported as AEs (See Section 12.3.1, Grading Criteria).

- **Hematology** including complete blood count (CBC) with differential.
- **Blood Chemistry** including complete metabolic panel, eGFR, and creatine kinase PRN.
- **Lipids** (triglycerides and cholesterol).
- **Urinalysis** including dipstick, microscopic, and spot protein-creatinine.
- **TBNK Trucount**
    - For participants who have used B cell depleting therapy within 1 year of screening, CD19+ B Cells will also be evaluated at the Screening Visit.
- **Anti-dsDNA, C3, C4**
- **Immunoglobulin G**
- **Autoantibodies** including Antinuclear Antibody (ANA), Extractable Nuclear Antigen Antibodies (ENA) Panel (Smith Antibody, anti-RNP, Anti-SSA, Anti-SSB), and anticardiolipin antibodies.
- **Infectious Disease Testing (Screening Only)** including HIV Testing, Hepatitis B surface antigen and core antibody (with viral load if indicated), Hepatitis C antibody (with viral load if indicated), and TB Testing.

- **Pregnancy Testing (Women of Child-Bearing Potential Only).** Serum human chorionic gonadotropin (HCG) at screening and then urine pregnancy test at all following visits. First date of last menstrual cycle should also be collected at each visit.
- **SARS-CoV-2 Antigen Testing**

8.2.3 **Mechanistic Assessments**

Planned and potential mechanistic assays for this study are noted below. Blood drawn from participants for mechanistic and clinical blood draws may not exceed NIH blood draw limits (550mL over 8 weeks).

All laboratory assessments will be collected after the participant sees the physician so that appropriate clinical and mechanistic labs can be drawn if the participant is a treatment failure.

- **Whole Blood/PBMC/Plasma**
- **Serum**
- **RNA Assays**
- **DxTerity Blood Draw: RNA for Inflammation and Interferon Markers (for Group Stratification)**
- **Urine**

8.2.4 **Disease Activity Assessments**

The original lupus instruments to assess disease flares included an evaluation of proteinuria based on the protein:creatinine ratio derived from a 24-hour urine. For this study, the protein:creatinine ratio will typically be derived from the spot urine assessment although a 24-hour urine may be used if the investigator believes it is indicated.

All PROs (LFA-REAL PRO, SF-36, and Patient Global Impression of disease activity change and severity (PGI-C and PGI-S)) should be completed in a quiet space prior to any other study related assessments.

8.2.4.1 **Hybrid SLEDAI**

The H-SLEDAI is a modification of the SELENA SLEDAI with a simplification of the proteinuria definition [22, 24, 32, 35]. The H-SLEDAI is a one-page assessment that contains 24 items which are scored as either present or absent. The H-SLEDAI captures disease activity within the 28 days prior to the assessment and an item must be attributable to SLE to be marked present. Each item is assigned a weighted score. The total score is the sum of the weighted scores.

8.2.4.2 **BILAG 2004**

The updated version (BILAG 2004) was published in 2010 and is a validated measure of disease activity [79]. BILAG 2004 assesses 97 clinical signs, symptoms and laboratory parameters important in SLE across nine organ systems. Each symptom is scored with respect to severity and progress over the previous 28 days (0 = not present, 1 = improving, 2 = same, 3 = worse, and 4 = new).

As above, each item is recorded as 0, 1, 2, 3, or 4. The BILAG 2004 scoring algorithm categorizes disease activity into 5 different severity levels from A–E. Grade A represents very active disease likely necessitating immunosuppressive drugs and/or a prednisolone (or equivalent) dose of > 20 mg daily or high-dose anti-coagulation. Grade B represents moderate disease activity prompting consideration of a lower dose of corticosteroids, topical steroids, topical immunosuppressive drugs, anti-malarial drugs, or NSAIDS. Grade C

indicates mild stable disease, while grade D implies no disease activity but the system had previously been affected. Grade E indicates no current or previous disease activity.

8.2.4.3 **Physician's Global Assessment**

This instrument has been widely used in SLE trials [80, 81]. This study will implement the PGA as a three inch scale with anchors at one inch intervals. The score is determined by asking the investigator to assess the participant's current disease activity over a continuum between anchors of 0 (no disease) to 1 (cutoff for mild disease) to 2 (moderate disease) and to 3 (maximally severe disease). This assessment is not made relative to the participant's own most improved or severe state but the most remitted and severe state possible in SLE. The scoring procedure requires investigators to compare the current visit to the previous visit in determining the score.

8.2.4.4 **LFA REAL**

The LFA-REAL Clinical Reported Outcome (ClinRO) and PRO provide an integrated system that can directly compare a patient's and clinician's view on individual items that are part of active lupus disease [82, 83] For both the patient and clinician components, the instrument is constructed as a series of individual anchored visual analogue scales with the ability to assess disease by symptom, by organ or by global total disease. All scales default to 0, so it is easy and quick to choose the limited number of symptoms likely to be present at a given time and score their severity.

The patient's component is complementary but not identical to the clinician's component [84, 85]. Unlike the other PROs to be used in this trial, this is a disease activity assessment by the patients, specific to SLE signs and symptoms and it is not a quality of life assessment. Thus, the information it might provide is not redundant to, but might be complementary to other PRO measures.

8.2.4.5 **PGI/CGI Anchor Scales**

To provide evidence that may help interpret a meaningful within-patient score change from the point of view of both clinicians and patients, simple discontinuous scales will be administered for the CGI-C and Clinical Global Impression of Severity (CGI-S) and PGI-C and PGI-S [86-89]. The PGI and CGI-S anchor scales will be administered with a recall period of one month. The CGI-C anchor scale will be administered with both a recall period of one month and as compared to the start of the current Stage of treatment.

8.2.5 **Other Disease-Specific Assessments**

- EULAR/ACR 2019 Classification Criteria (Screening Only) [3]
- SELENA-SLEDAI Flare Index and Thanou Modified Flare Index [4]
- Assessment of Primary Endpoint (Stage 2) and Disease and SLE Treatment Status (Stage 3)
- SF-36 (Patient- Reported) [90]
- Tender and Swollen Joint Count Assessment

Table 8.1. Stage 1 & 2 Schedule of Events

	STAGE 1 (up to 4 weeks)	STAGE 2 (up to 52 weeks)															End of Study
Visit Number	SCRN	STG2-1	STG2-2	STG2-3	STG2-4	STG2-5	STG2-6	STG2-7	STG2-8	STG2-9	STG2-10	STG2-11	STG2-12	STG2-13	Early Termination	Unscheduled	Safety Follow Up[L]
Description	Screening	Random-ization	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24[P]	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48			
Visit Window	-28 Days	Day 0 ± 24 hours	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days			
Blood Draw Volumes[O]																	
Clinical Draw (mL)	29	11	11	11	19	11	11	19	11	11	11	11	11	19	19	19	19
Research Draw (mL)	50	49	49	49	49	49	49	49	49	49	49	49	49	50	49	49	49
Visit Draw Total (mL)	79	60	60	60	60	60	60	60	60	60	60	60	60	69	68	68	68
General Assessments																	
Informed Consent	X																
Stage 1 Inclusion/Exclusion Criteria Assessment	X	X															
Inclusion Criteria Prior to Randomization		X															
Evaluation of Entry Packet by Adjudication Committee	X																
Withdrawal of Lupus Treatment[A, B]	X[L]																
Demographics	X																
Medical History	X																
Comprehensive Physical Exam[K]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X								X[C]								
Adverse Event Collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	STAGE 1 (up to 4 weeks)	STAGE 2 (up to 52 weeks)															End of Study
Visit Number	SCRN	STG2-1	STG2-2	STG2-3	STG2-4	STG2-5	STG2-6	STG2-7	STG2-8	STG2-9	STG2-10	STG2-11	STG2-12	STG2-13	Early Termination	Unscheduled	Safety Follow Up[L]
Description	Screening	Randomization	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24[P]	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48			
Visit Window	-28 Days	Day 0 ± 24 hours	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days			
Disease-Specific Assessments																	
EULAR/ACR 2019 Criteria for SLE	X																
PGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BILAG 2004	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hybrid SLEDAI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SELENA-SLEDAI Flare Index and Thanou Modified Flare Index	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LFA-REAL-CLINRO™	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-I (CGI-C & CGI-S)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of Primary Endpoint[F]			X[D]	X[D]	X[D]	X[D]	X[D]	X[D]								X[D,E,F]	
Disease and SLE Treatment Status									X[E]	X[E]	X[E]	X[E]	X[E]	X[E]	X	X[D,E,F]	
Tender and Swollen Joint Count Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Participant Reported Outcomes[Q]																	
SF-36	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGI-I (PGI-C & PGI-S)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LFA-REAL-PRO™	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local Laboratory Assessments[B]																	
Urine Pregnancy[G]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SARS-CoV-2 Antigen Testing	X[R]	X	X[M]														
TB Testing (Quantiferon Gold)[H]	X																

	STAGE 1 (up to 4 weeks)	STAGE 2 (up to 52 weeks)															End of Study
Visit Number	SCRN	STG2-1	STG2-2	STG2-3	STG2-4	STG2-5	STG2-6	STG2-7	STG2-8	STG2-9	STG2-10	STG2-11	STG2-12	STG2-13	Early Termination	Unscheduled	Safety Follow Up[L]
Description	Screening	Random-ization	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24[P]	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48			
Visit Window	-28 Days	Day 0 ± 24 hours	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days			
Central Laboratory Assessments[B]																	
Hematology (CBC with differential)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipids (triglycerides and cholesterol)	X														X	X[C]	X
Urinalysis (dipstick, microscopic, spot protein-creatinine)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TBNK Trucount	X[S]																
Serum Pregnancy[G]	X																
Anti-dsDNA, C3, C4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunoglobulin G	X				X			X						X	X	X[C]	X
Autoantibodies (ANA, ENA Panel, Anticardiolipin)	X				X			X						X	X	X[C]	X
HIV Testing	X																
Hepatitis B Surface Antigen and Core Antibody Screening (with viral load if indicated)	X																
Hepatitis C Antibody (with viral load if indicated)	X																
Mechanistic Assessments[B]																	
Whole Blood/PBMC/Plasma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	STAGE 1 (up to 4 weeks)	STAGE 2 (up to 52 weeks)														End of Study
Visit Number	SCRN	STG2-1	STG2-2	STG2-3	STG2-4	STG2-5	STG2-6	STG2-7	STG2-8	STG2-9	STG2-10	STG2-11	STG2-12	STG2-13	Early Termination	Safety Follow Up[L]
Description	Screening	Randomization	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24[P]	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Unscheduled	
Visit Window	-28 Days	Day 0 ± 24 hours	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days		
Mechanistic Assessments (continued)[B]																
RNA Assays	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DxTerity Blood Draw: RNA for Inflammation and Interferon Markers (for Group Stratification)	X							X						X		
Urine	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Treatment / Investigational Agent																
Long-acting Corticosteroid IM Injection	X[I]	X[C]														
Randomization to Stage 2 MMF/Placebo MMF		X														
Dispense MMF/ Placebo MMF[J]		X	X[N]	X[N]	X[N]	X[N]	X[N]	X[N]	X	X	X	X	X			
Perform Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	
Treatment Survey															X	X

A. See section 3.1.1 *Stage 1: Treatment* Withdrawal, for details regarding medication withdrawal guidelines.
B. Mechanistic specimens, along with central and local lab specimens, should be collected after the participant sees the study physician and primary endpoint is assessed, but prior to initiating any changes in the participant's lupus medication including lupus treatment withdrawal in Stage 1, the administration of a corticosteroid injection, or stopping study-provided medication/beginning new or increased lupus medications during the course of the study.
C. Treatment/test to be administered if clinically indicated.
D. If at any scheduled or unscheduled visit at any time up to and including the Week 24 Visit during Stage 2 the participant is assessed as a Stage 2 treatment failure, as defined in Protocol Section 3.5.1, *Treatment Failure*, then the participant will proceed in the study as outlined in Section 3.1.2, *Stage 2 Randomization.*
E. If at any scheduled or unscheduled visit at any time after Week 24 Visit during Stage 2 the participant is assessed as a Stage 2 treatment failure, as defined in Protocol Section 3.5.1, *Treatment Failure*, then the participant will proceed in the study as outlined in Section 3.1.2, *Stage 2 Randomization.*
F. If at any scheduled or unscheduled visit a participant is assessed as a Stage 2 treatment failure, as defined in Protocol Section 3.5.1, *Treatment Failure*, coordinators will indicate treatment failure on source and in EDC.
G. Pregnancy tests for women of child-bearing potential only. First date of last period will also need to be collected.
H. To confirm the participant does not meet Exclusion criterion number 24 , they need a negative Quantiferon Gold (or equivalent) assay. See Section 4.3, *Exclusion* Criteria 24 for details regarding TB retest.
I. During Stage 1, participants will receive a corticosteroid injection which may be repeated if needed to achieve amelioration of symptoms. A total of 3 injections may be given up to and including the day of Stage 2 Randomization, prior to Stage 2 dosing. Dose will be dependent on the available formulation.
J. Study-provided medication will not be dispensed if participant is assessed as a Stage 2 treatment failure. The participant will either proceed to Stage 3 or will discontinue study-provided medication.

K. Physical examinations are to include, at least, the following systems: general appearance, skin, head/eyes/ears/nose/neck/throat, respiratory/chest, cardiovascular, abdominal, neurological, & musculoskeletal/extremities. Neurological exam may only be performed based on participant complaint after the screening and Stage 2 Randomization visit.
L. Participants who withdraw from their lupus medications and then screen fail prior to Stage 2 will have a safety follow-up visit 4 weeks ± 10 days after the date of screen fail.
M. Local SARS-CoV-2 antigen testing) should be performed if clinically indicated.
N. MMF/Placebo MMF will not be dispensed if the participant has stopped Stage 2 study-provided medication and has started a new or increased lupus medication due to a treatment failure.
O. Lab volumes to not exceed 550 cc over 8 weeks.
P. Participants who exit the study at Stage 2 Week 24 should complete all End of Study/Safety Follow-Up visit assessments at this time.
Q. Patient-reported outcomes should be completed in a quiet space and prior to any other study assessments.
R. Local SARS-CoV-2 antigen testing must be completed 2 days before the randomization visit. Participants will be required to self-test 2 days prior to the randomization visit and provide proof of negativity.
S. For participants who have used B cell depleting therapy within 1 year of screening, CD19+ B Cells will also be evaluated at the Screening Visit.

Table 8.2. Stage 3 Schedule of Events.

	STAGE 3										End of Study
Visit Number	STG3-1	STG3-2	STG3-3	STG3-4	STG3-5	STG3-6	STG3-7	STG3-8	Early Termination	Unscheduled	Safety Follow Up
Description	Re-randomization	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24			
Visit Window	Day of Stage 2 Treatment Failure +5 Days[N]	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days			
Blood Draw Volumes[L]											
Clinical Blood Draw (mL)	4[K]	4	11	11	19	11	11	19	19	19	19
Research Blood Draw (mL)	1[K]	0	49	49	49	49	49	50	49	49	49
Visit Draw Total (mL)	5[K]	4	60	60	60	60	60	69	68	68	68
General Assessments											
Comprehensive Physical Exam[I]			X	X	X	X	X	X	X	X	X
Vital Signs		X	X	X	X	X	X	X	X	X	X
ECG	X[A]										
Adverse Event Collection		X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X
Disease-Specific Assessments											
PGA			X	X	X	X	X	X	X	X	X
BILAG 2004			X	X	X	X	X	X	X	X	X
Hybrid SLEDAI			X	X	X	X	X	X	X	X	X
SELENA-SLEDAI Flare Index and Thanou Modified Flare Index			X	X	X	X	X	X	X	X	X
LFA-REAL-CLINRO™			X	X	X	X	X	X	X	X	X
CGI-I (CGI-C & CGI-S)			X	X	X	X	X	X	X	X	X
Disease and SLE Treatment Status[B]			X	X	X	X	X	X	X	X	
Tender and Swollen Joint Count Assessment			X	X	X	X	X	X	X	X	X
Participant Reported Outcomes[M]											
SF-36			X	X	X	X	X	X	X	X	X
PGI-I (PGI-C & PGI-S)			X	X	X	X	X	X	X	X	X
LFA-REAL-PRO™			X	X	X	X	X	X	X	X	X
Local Laboratory Assessments[C]											
Urine Pregnancy[D]			X	X	X	X	X	X	X	X	X
SARS-CoV-2 Molecular Testing	X[J]										

	STAGE 3										End of Study
Visit Number	STG3-1	STG3-2	STG3-3	STG3-4	STG3-5	STG3-6	STG3-7	STG3-8	Early Termination	Unscheduled	Safety Follow Up
Description	Re-randomization	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24			
Visit Window	Day of Stage 2 Treatment Failure +5 Days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days			
Central Laboratory Assessments[C]											
Hematology (CBC with differential)			X	X	X	X	X	X	X	X	X
Blood Chemistry		X[H]	X	X	X	X	X	X	X	X	X
Lipids (triglycerides and cholesterol)									X	X[A]	X
Urinalysis (dipstick, microscopic, spot protein-creatinine)			X	X	X	X	X	X	X	X	X
Anti-dsDNA, C3, C4			X	X	X	X	X	X	X	X	X
Immunoglobulin G	X[K]				X			X	X	X[A]	X
Autoantibodies (ANA, ENA Panel, Anticardiolipin)					X			X	X	X[A]	X
Mechanistic Assessments[C]											
Whole Blood/PBMC/Plasma			X	X	X	X	X	X	X	X	X
Serum			X	X	X	X	X	X	X	X	X
DxTerity Blood Draw: RNA for Inflammation and Interferon Markers (for Group Stratification)[L]	X[K]							X			
RNA Assays			X	X	X	X	X	X	X	X	X
Urine			X	X	X	X	X	X	X	X	X
Study Treatment / Investigational Agent											
Long-acting Corticosteroid IM Injection		X[E]	X[A]								
Randomization to Stage 3 MMF+Voclosporin/MMF+Placebo voclosporin	X										
Dispense MMF+Voclosporin/MMF+Placebo voclosporin [F,G]	X		X	X	X	X	X				
Perform Drug Accountability			X	X	X	X	X	X	X	X	
Treatment Survey									X		X

A. Treatment/test should be administered if clinically indicated.
B. If at any scheduled or unscheduled Stage 3 visit the participant is assessed as a Stage 3 treatment failure, then the participant will proceed in the study as outlined in Protocol Section 3.1.3: *Stage 3 Re-Randomization*.
C. Mechanistic specimens, along with central and local lab specimens, should be collected after the participant sees the study physician and primary endpoint is assessed, but prior to initiating any changes in the participants lupus medication including lupus treatment withdrawal at screening, the administration of a corticosteroid injection, or stopping study-provided medication/beginning new or increased lupus medications during the course of the study.

D. Pregnancy tests for women of child-bearing potential only. First date of last period will also need to be collected.
E. An additional corticosteroid injection may be given up to 2 weeks after re-randomization whether or not it was given at time of Stage 2 treatment failure as well for a total of 2 corticosteroid injections from the time of Stage 2 Treatment Failure up to and including the Stage 3 Week 2 Visit.
F. MMF 1000mg BID+Voclosporin (23.7 BID) or MMF 1000mg BID+Placebo voclosporin. Participants who previously received placebo MMF in stage 2 will receive a two-week taper-up of MMF.
G. Study-provided medication will not be dispensed if participant receives a corticosteroid injection or has started new or increased lupus medications. The participant will stop Stage 3 study drug.
H. Creatinine for eGFR only
I. Physical examinations are to include, at least, the following systems: general appearance, skin, head/eyes/ears/nose/neck/throat, respiratory/chest, cardiovascular, abdominal, neurological, & musculoskeletal/extremities Neurological exam may only be performed based on patient complaint.
J. Local SARS-CoV-2 molecular testing (or alternative viral test per institutional standard) should be performed if clinically indicated.
K. If not already collected as a part of the Stage 2 Visit.
L. Lab volumes to not exceed 550 cc over 8 weeks.
M. Patient-reported outcomes should be completed in a quiet space and prior to any other study assessments.
N. The re-randomization visit should be completed on the date that treatment failure is identified + 5 days.

9 Mechanistic Assays

9.1 Hypothesis-driven assays based on preliminary data

We have recently developed innovative assays that will be applied to the samples in this protocol [1, 14, 15, 91]. Our preliminary data indicates that MMF treatment is associated with upregulation of expression of genes for CR3, TWEAK, FYN, IL16, IL17RA, and/or IL2RB. We will seek to confirm or refute these findings in the current study and also test for the protein expression. All except CR3 are soluble mediators and will be quantified either by a multiplex bead-based assay [14, 15] that we have optimized or by ELISA. Expression of CR3 will be measured by flow cytometry in 2 aliquots, one for total CR3 and one for activated CR3. In addition, we will use our established multiplex bead based assay for 50 soluble mediators and further characterize this population.

We will examine the early flare phenotype to determine whether this phenotype is altered in those who respond to treatment and/or whether this is a population resistant to treatment. We previously characterized this subset of lupus patients most likely to flare if treatment is not added, characterized by differential gene expression in monocyte, T cell, interferon, and inflammation modules, as well as significantly higher frequencies of activated (aCD11b+) neutrophils and monocytes, and activated (CD86hi) naïve B cells [92].

At the Screening Visit, all participants will be assigned to one of 3 consolidated clusters of phenotypes in SLE, that cover the 7 overlapping clusters we derived from gene co-expression network analysis (WGCNA) [1, 91]. Later, using more comprehensive, immunophenotyping on batched samples, we will determine whether response to MMF or MMF plus voclosporin segregates to 1 or 2 SLE immunophenotypic clusters, or whether we must look deeper at the individual immune expression modules that comprise the clusters or even at the individual gene level to characterize response to these treatments.

9.2 Exploratory Investigation of Diverse Pathologies with in SLE

We will use a structured, multi-level evaluation of the phenotypic clusters described above to establish whether the following questions can be answered:

1. Can baseline samples predict the immune factors/patterns of participants more likely to respond to MMF as a single agent versus the need to add voclosporin?
2. If some participants have a phenotype associated with high rates of response, but these individuals do not respond as expected, can interrogation of gene and protein expression patterns reveal the reason(s)? For example, can we differentiate those for whom the treatment did not meet its intended target from those for whom it did, but who may have additional pathways operating to prevent clinical improvement?
3. Will some of those latter participants have evidence of active pathways that will predict response when voclosporin is added to the regimen that would not have been present before MMF was added?

10 Biospecimen Storage

With informed consent, laboratory samples will be stored in a biorepository for future studies at OMRF. Stored samples will include serum, plasma, urine, RNA, and DNA.

11 Criteria for Participant and Study Completion and Premature Study Termination

11.1 Participant Completion

Study completion can occur in either Stage 2 or Stage 3 and the time of completion will depend on study trajectory of each participant as described in Figure 1, *Study Flow Diagram*. Completion of the study in Stage 2 can occur with either a Stage 2 Week 24 Visit where all End of Study/Safety Follow-Up assessments are conducted, a Stage 2 End of Study/Safety Follow-Up visit or an Early Termination Visit. The final study visit can follow any visit up to the Stage 2 Week 48 visit.

Completion of the study in Stage 3 can occur with either a Stage 3 End of Study/Safety Follow-Up Visit or an Early Termination Visit. The final study visit can follow any visit up to the Stage 3 Week 24 visit.

Participants who request early termination will be encouraged to return for the Safety Follow-Up Visit.

Those who cannot tolerate the study medication or develop an adverse reaction necessitating early discontinuation of the study-provided medication will continue in the study (if they agree) without receiving further study-provided medication.

11.2 Participant Stopping Rules and Early Termination Criteria

Participants may be prematurely terminated 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 dies.
3. The DAIT Medical Monitor no longer believes participation is in the best interest of the participant.
4. The investigator no longer believes participation is in the best interest of the participant.
5. The study is stopped.
6. The participant is “lost to follow-up.”

11.3 Participant Replacement

Randomized participants who never initiate Stage 2 study treatment will not count towards the target accrual of 120.

11.4 Early Study Withdrawal

If a participant withdraws or is withdrawn from the study for any reason, they will be encouraged to return for the safety follow up visit for their final visit.

11.5 Study Stopping Rules

See Section 12.8.2.2 Ad Hoc DSMB Meetings and Section 12.8.2.2.1 Temporary Suspension of Randomization and Dosing for ad hoc DSMB Safety Review for more information on study stopping rules.

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. AEs 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 DAIT/NIAID. Appropriate notifications will also be made to site principal investigators (PI) and the single IRB of record.

Information in this section complies with the International Conference on Harmonisation (ICH) Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice, 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: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_60.

12.2 Definitions

12.2.1 **Adverse Event (AE)**

Any untoward or unfavorable medical occurrence associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research (modified from the definition of adverse events in the 1996 ICHE-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 (SAR)**

Any AE for which there is a reasonable possibility that the investigational drug [or investigational study therapy regimen] caused the AE. 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)).

12.2.3 **Unexpected Adverse Event**

An AE or SAR is considered "unexpected" if it is not listed in the Investigator Brochure or 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.

12.2.4 **Serious Adverse Event (SAE)**

An AE 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)):

a. Death.

b. 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.

c. Inpatient hospitalization or prolongation of existing hospitalization.

d. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

e. Congenital anomaly or birth defect.

f. 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 AEs 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 other than exceptions listed below. 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 AEs. The NCI-CTCAE has been reviewed by the Protocol Chair and has been deemed appropriate for the participant population to be studied in this protocol.

AEs 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 = medically significant adverse event
Grade 4 = life-threatening or urgent intervention indicated adverse event
Grade 5 = death

Events grade 2 or higher and all Grade 1 or higher COVID-19 events will be recorded on the appropriate AE eCRF for this study.

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.), an AE is defined as an increase in grade from screening or from the last post-screening value that doesn't meet grading criteria. 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 AE if changes in therapy or monitoring are implemented as a result of the event/result.

Liver function abnormalities will be graded using alternative criteria which are based on CTCAE version 4.0, and are 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 AE to the study therapy regimen or study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE eCRF. Final determination of attribution for safety reporting will be determined by DAIT/NIAID. The relationship of an AE 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	Unrelated	The adverse event is clearly not related; there is insufficient evidence to suggest a causal relationship.
RELATED CATEGORIES		
2	Possible	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Definite	The adverse event is clearly related.

12.4 Collection and Recording of Adverse Events

12.4.1 **Collection Period**

AEs will be collected from the time of consent until a participant completes study participation or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study.

12.4.2 **Collecting Adverse Events**

AEs (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 AE 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 AEs and SAEs as described previously (see Section 12.2, *Definitions*) on the appropriate AE 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 (without withdrawing consent)/or is withdrawn from the study, whichever occurs first. For AEs where an abnormal value or result of a clinical or laboratory evaluation is observed (see Section 12.3.1, *Grading Criteria*), resolution is defined as the first value post-abnormality that is in the normal range (Grade 0).

12.5 Reporting of Serious Adverse Events and Adverse Events

12.5.1 **Reporting of Adverse Events to DAIT/NIAID**

This section describes the responsibilities of the site investigator to report AEs to DAIT/NIAID reporting of AEs is required by 21 CFR and ICH E6 guidelines. Unless otherwise noted below in Section 12.5.2, Reporting of SAEs and Section 12.5.3, *Reporting of BILAG A Flares to DAIT/NIAID*, AEs must be recorded on the AE eCRF within five (5) days of discovery of the event.

12.5.2 **Reporting of Serious Adverse Events to DAIT/NIAID**

Site investigators will report all SAEs (see Section 12.2.4, *Serious Adverse Event*), regardless of relationship or expectedness within 24 hours of discovering the event. For SAEs, all requested information on the AE/SAE eCRF will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE eCRF will be updated and submitted.

12.5.3 **Reporting of BILAG A Flares to DAIT/NIAID**

This section describes the responsibilities of the site investigator to report BILAG As to DAIT/NIAID via the AE/SAE eCRF. Timely reporting of AEs is required by 21 CFR and ICH E6 guidelines.

Site investigators will report all new BILAG As other than those noted at the screening visit, regardless of relationship or expectedness within 24 hours of discovering the event. For BILAG As, all requested information on the AE/SAE eCRF will be provided even if the BILAG A is not classified as an SAE. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE eCRF will be updated and submitted.

12.5.4 **Reporting to FDA**

This clinical study has been granted exemption from 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).

12.5.5 **Reporting of Adverse Events to the IRB**

All investigators shall report AEs, including expedited reports, in a timely fashion to the single IRB of record in accordance with applicable regulations and guidelines.

SAEs that are determined by DAIT/NIAID to have potential impact on the safety of all trial participants will be distributed by the DAIT/NIAID (or designee) to all participating site investigators and the single IRB of record.

12.6 Pregnancy Reporting

The investigator shall be informed immediately of any pregnancy in a study participant. A pregnant participant shall be instructed to stop taking investigational study medication. The investigator shall counsel the participant and discuss the risks of continuing with the pregnancy and the possible and unknown effects on the fetus. Monitoring of the pregnant participant shall continue until the conclusion of the pregnancy.

The investigator shall report all pregnancies to DAIT/NIAID via the SCCC within 1 business day of becoming aware of the event using the Pregnancy eCRF. All pregnancies identified during the study shall be followed to conclusion and the outcome of each must be reported. The Pregnancy eCRF shall be updated and submitted to the SCCC when details about the outcome are available.

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 SCCC using the SAE reporting procedures described above (Section 12.5.1, *Reporting of Serious Adverse Events to DAIT/NIAID*).

If a pregnancy occurs in a partner of a participant, the male participant whose partner gets pregnant will inform the investigator of the pregnancy. The participant will be encouraged to use barrier methods for the remainder of the pregnancy. The pregnant partner should see their Obstetrician. Data on partner pregnancies will not need to be collected for this study.

12.6.1 **Mycophenolate REMS Program**

ALE10 investigators are required to enroll in the FDA's Mycophenolate REMS program. An investigator will be required to report any pregnancy occurring in an ALE10 female participant while she is taking MMF or within the first 6 weeks following discontinuation of MMF treatment to the Mycophenolate Pregnancy Registry, which is part of the MMF REMS program. Participants will be required to participate in MMF REMS program as well.

12.7 Reporting of Other Safety Information

An investigator shall promptly notify DAIT/NIAID via the SCCC within 24 hours when an "unanticipated problem involving risks to participants or others" is identified, which is not otherwise reportable as an AE.

12.8 Review of Safety Information

12.8.1 **Medical Monitor Review**

The DAIT/NIAID Medical Monitor shall receive monthly reports from the SCCC compiling new and accumulating information on AEs, SAEs, and pregnancies recorded by the study sites 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 SCCC (See Sections 12.5.1, *Reporting of SAEs to DAIT/NIAID*, and 12.6, *Pregnancy Reporting*).

12.8.2 **DSMB Review**

12.8.2.1 **Planned DSMB Reviews**

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.

SAEs that are determined by DAIT/NIAID to have potential impact on the safety of all trial participants will be distributed by DAIT/NIAID to the DSMB and all participating site investigators.

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 that occurs during the study.
- BILAG A flares in Cardiorespiratory, Neuropsychiatric, Gastrointestinal, Ophthalmic, Renal, or Hematological Systems occurring in
    - 3 or more of the first 10 randomized participants or
    - 30% or more of randomized participants at any time point after the 11th participant is randomized.
- Infections requiring hospitalization or > 1 dose of intravenous antibiotics in
    - 3 or more of the first 10 randomized participants or
    - 30% or more of randomized participants at any time point after the 11th participant is randomized.

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

12.8.2.2.1 **Temporary Suspension of Randomization and Dosing for ad hoc DSMB Safety Review**

If any of the events listed in Section 12.8.2.2, *Ad hoc DSMB Reviews*, occur, the chair of the DSMB will be notified and a review of the safety data will be performed. The DSMB will have the discretion to recommend actions regarding study conduct, and will determine if enrollment in the study should be stopped and/or administration of study medications should be halted.

If a death occurs during the study, a temporary halt in consenting and screening of new participants as well as randomizing participants to Stage 2 will be implemented until after DSMB completes review of the safety data. Participants who have been consented and screened but not yet randomized into Stage 2 will be permitted to withdraw from their lupus medications per protocol during the randomization halt. If participants who have withdrawn from their lupus medications exceed their 28 day screening window during the ad hoc DSMB review period, an extension will be granted and the participant will be allowed to randomize once the ad hoc DSMB allows for resumption of randomization. Participants on study can continue with their assigned treatment, and participants deemed as a Stage 2 treatment failure at or before the Stage 2 week 24 can move into Stage 3 and be re-randomized.

If an ad hoc DSMB is called for excessive BILAG A flares or infections, the study will proceed as planned pending DSMB review of the data. However, if 2 weeks have elapsed and the DSMB has not met, then no new participants will be consented, screened, or randomized into Stage 2 until after the DSMB completes review of the safety data. Participants who have been consented and screened but not yet randomized into Stage 2 will be permitted to withdraw from their lupus medications per protocol during the randomization halt. If participants who have withdrawn from their lupus medications exceed their 28 day screening window during the ad hoc DSMB review period, an extension will be granted and the participant will be allowed to randomize once the ad hoc DSMB allows for resumption of randomization. Participants on study can continue with their assigned treatment, and participants deemed as a Stage 2 treatment failure at or before the Stage 2 week 24 can move into Stage 3 and be re-randomized.

13 Statistical Considerations and Analytical Plan

13.1 Overview

This is a multicenter, double blind, placebo-controlled clinical trial of participants with non-organ-threatening SLE. The study will be conducted in 3 stages. Stage 1 will be a treatment withdrawal phase where participants must demonstrate adequate improvement with long-acting corticosteroids in order to proceed to Stage 2. Stage 2 will be a randomization phase comparing MMF versus corresponding MMF placebo. The purpose of Stage 2 is to assess the primary endpoint, which investigates the effectiveness of 24 weeks of MMF within previously identified immunologically-homogenous subsets of SLE patients. Stage 3 is a re-randomization phase comparing MMF plus voclosporin or MMF plus placebo for voclosporin. Stage 3 is intended to be an exploratory investigation of baseline gene expression patterns and their associations with response.

13.2 Endpoints

Endpoints are listed in Sections 3.2, *Primary Endpoint*, 3.3, *Secondary Endpoints,* and 3.4, *Exploratory Endpoints*.

13.3 Measures to Minimize Bias

The following measures will be employed to minimize bias:

- Randomization to treatment assignment to avoid selection bias.
- Double blind design to avoid ascertainment bias.
- Use of central laboratories for consistency in assay procedures and measurements for clinical and mechanistic endpoints.

13.4 Analysis Plan

13.4.1 Analysis Populations

13.4.1.1 Stage 2 Analysis Populations

Modified Intent to Treat Population:

The modified Intent-to-Treat population (mITT) will consist of all Stage 2 randomized participants who received at least one dose of MMF or MMF placebo. The mITT population will be used for all Stage 2 efficacy analyses and will include participants under the treatment to which they were randomized, regardless of compliance with assigned treatment.

Per Protocol Populations:
Two per protocol (PP) populations will be defined for Stage 2 analyses.

The PP1 population will consist of mITT participants who:

- Have either completed the Stage 2 Week 24 visit without experiencing a Stage 2 failure or have experienced a treatment failure on or prior to Stage 2 Week 24;
- Have ≥ 80% compliance with MMF or MMF placebo administration from randomization through the Stage 2 Week 24 visit or until treatment failure (whichever comes first), where compliance is assessed by numbers of capsules of study product returned to the site;
- Have no protocol violations or ineligible entry criteria deemed likely to affect the efficacy outcomes of interest either through Week 24 of Stage 2 or treatment failure (whichever comes first).

The PP2 population will consist of mITT participants who:

- Have either completed the Stage 2 Week 48 visit without experiencing a Stage 2 failure or have experienced a treatment failure on or prior to Stage 2 Week 48;
- Have ≥ 80% compliance with MMF or MMF placebo administration from randomization through the Stage 2 Week 48 visit or until treatment failure (whichever comes first), where compliance is assessed by numbers of capsules of study product returned to the site;
- Have no protocol violations or ineligible entry criteria deemed likely to affect the efficacy outcomes of interest either through Week 48 of Stage 2 or treatment failure.

A blinded data review panel will evaluate deviations from the protocol including, for example, violations of entry criteria, departures from assigned treatment regimen, modifications of concurrent therapy, failure to complete study visits, or administration of study procedures outside the specified visit windows to determine if occurrence of these deviations should exclude participants from the PP1 or PP2 population.

The PP1 population will be used for the Stage 2 analysis of the primary endpoint and secondary/exploratory endpoints assessed at Stage 2 Week 24, the PP2 population will be used in the analyses of the secondary/exploratory Stage 2 efficacy endpoints which are assessed over the entire 48 week treatment period.

13.4.1.2 **Stage 3 Analysis Populations**

Modified Intent to Treat Population:
The Stage 3 modified Intent-to-Treat population (mITT3) will consist of all Stage 3 randomized participants who received at least one dose of MMF plus voclosporin or MMF plus placebo for voclosporin. The mITT3 population will be used for all Stage 3 efficacy analyses and will include participants under the treatment to which they were randomized, regardless of compliance with assigned treatment.

Per Protocol Population:
The Stage 3 PP population (PP3) will consist of mITT3 participants who:

- Have either completed the Stage 3 Week 24 visit without experiencing a Stage 3 failure or have experienced a treatment failure on or prior to Stage 3 Week 24;

- Have ≥ 80% compliance with MMF + voclosporin or MMF + placebo for voclosporin administration from randomization through the Stage 3 Week 24 visit or until treatment failure (whichever comes first), where compliance is assessed by numbers of capsules of study product returned to the site;
- Have no protocol violations or ineligible entry criteria deemed likely to affect the efficacy outcomes of interest throughout the entire study.

A blinded data review panel will evaluate deviations from the protocol including, for example, violations of entry criteria, departures from assigned treatment regimen, modifications of concurrent therapy, failure to complete study visits, or administration of study procedures outside the specified visit windows to determine if occurrence of these deviations should exclude participants from the PP3 population.

The PP3 population will be used in the analyses of the Stage 3 secondary efficacy endpoints.

13.4.1.3 **Safety Population**

The safety population will include all participants who receive at least one IM injection of a long-acting corticosteroid or who initiate withdrawal of lupus medications in Stage 1. The safety population will be used for all safety analyses. Analysis performed on the safety population will be according to the treatment actually received in both Stage 2 and Stage 3.

13.4.2 **Primary Analysis of Primary Endpoint**

The primary endpoint is the cumulative incidence of treatment failure at or before the Stage 2 Week 24 visit. Time to treatment failure is defined as the interval from the day of Stage 2 randomization until the day of treatment failure (as defined in Section 3.2, Primary Endpoint). Participants who withdraw from the study early without evidence of treatment failure will be censored at day of the last assessment they were determined to be failure-free. The risk of treatment failure over the period of Stage 2 randomization through 24 weeks of follow-up will be presented graphically using Kaplan-Meier product limit estimates of the survival function in subgroups defined by treatment arm and by immunologically-homogenous subsets. The Kaplan-Meier estimates of event-free survival and confidence intervals using Greenwood's formula for standard error will be reported by subgroup at Stage 2 Week 24. The primary analysis will be a stratified two-sample test of the cumulative incidence of treatment failure at Stage 2 Week 24 using a 2-sided □=0.05.

The ultimate goal of Stage 2 is to evaluate the potential effectiveness of MMF within the 7 previously-identified immunologically-homogeneous clusters for lupus. Regardless of the outcome of the stratified test for the pooled analysis, within-cluster landmark two-sample tests will be performed for comparisons of the cumulative incidence of treatment failure at Stage 2 Week 24 for each cluster. Due to the limited samples sizes anticipated in each immunologically-defined subgroup, no correction for multiple comparisons will be made, and p-values of < 0.10 will be considered notable findings but will be interpreted with caution given the high probability of a family-wise error with multiple comparisons under a strong null hypothesis of no treatment benefit.

13.4.3 **Supportive Analyses of the Primary Endpoint**

As a supportive analyses, the risk of treatment failure over the entire 48 week period of Stage 2 will be summarized using Kaplan-Meier product limit estimates, and a stratified log-rank test will be conducted with complete follow-up of participants. Additional covariates including participant and disease characteristics at study entry and in Stage 1 treatment withdrawal, and time-dependent covariates during Stage 2 will be explored in a multivariable Cox models

using main effects and interaction terms. Multivariable models will be fully defined in the statistical analysis plan (SAP). Finally, in addition to considering heterogeneity from immunologically defined subsets and other observed factors, a supportive analysis will explore the use of frailty models to consider variability from additional unobserved factors using random effects terms.

13.4.4 Analyses of Secondary Safety Endpoints

Safety analyses will be performed on the safety sample and will be assessed by summarizing AEs separately for each stage of the study. The length of time participants are followed within each stage is variable and could depend on if a participant meets treatment failure. To account for potential differential duration of study participation, AE summaries by treatment group will include the number of events per person-year in addition to the number and percentage of events and participants experiencing events. AEs and SAEs will be summarized by system organ class, preferred term, and severity grade.

Safety endpoints identified in Section 3.3.2 Safety Endpoints, will be summarized and listed separately for each stage of the study. For each such endpoint, the number of events per person-year as well as numbers and percentages of events and participants who experience these events will be summarized overall in Stage 1 and by treatment group in Stage 2 and 3. No formal statistical testing will be performed to compare safety between treatment groups.

13.4.5 Analyses of Secondary Efficacy Endpoints

The key secondary efficacy endpoint is clinical response at Stage 2 Week 24, defined by the BICLA (see Section 3.3.1, Efficacy Endpoints). A Fisher's exact test (2-sided □=0.05) will be performed to test the hypothesis that there is no difference in the proportion of responders between treatment groups. This analysis will also be repeated at Stage 3 Week 24. An additional supportive Stage 3 analysis will use the most recent assessment before the Stage 3 Day 0 visit as the reference (see Section 3.5.3, BILAG-based Combined Lupus Assessment (BICLA)).

For Stage 3, the cumulative incidence of participants who experience a treatment failure in Stage 3 will be evaluated. The primary analysis will be repeated considering treatment failures occurring during the time period from Stage 3 re-randomization through Stage 3 Week 24.

Time to treatment failure will also be evaluated in Stage 3, where the Kaplan-Meier estimation and log-rank tests from the supportive analysis of the primary analysis will be repeated for the time period from Stage 3 re-randomization through Stage 3 Week 24.

Given the unknown samples sizes and subgroups defined by Stage 2 treatment assignment, all inferential analyses for Stage 3 are considered supportive; p-values for test of differences among groups will be presented without adjustment for multiple comparisons, and p-values of < 0.10 will be considered notable findings.

13.4.6 Analyses of Exploratory Endpoints

Details of the exploratory analysis of clinical endpoints will be outlined in the SAP. For mechanistic endpoints, exploratory analyses will be conducted separately for subgroups allocated to each Stage 2 treatment arm because participants entering Stage 3 from the different treatment arms are not comparable at the point of re-randomization. Mechanistic plans are to explore baseline (pre-re-randomization) gene expression and protein level patterns among those who respond (or do not respond) to MMF and MMF plus voclosporin, and to describe differences between the 2 arms. Response will be defined using BICLA at 24 weeks post re-randomization.

13.4.7 **Descriptive Analyses**

Descriptive analyses will include baseline and demographic characteristics, use of medications, and AEs, with separate tables for SAEs, and infections.

Summary statistics for baseline and demographic characteristics, disposition, and medication use will be provided for the mITT and PP populations. These data will be presented in the following manner:

- Continuous data (e.g. age, weight, and height) will be summarized by mean, standard deviation, median, and range.
- Categorical data (e.g. sex and race) will be presented as counts and percentages.

13.5 Interim Analyses

Interim analyses of data will be reported to the DSMB at planned DSMB meetings and as requested by the DSMB. Planned interim analyses for the DSMB will focus on study conduct and participant safety and may include information on enrollment, randomization, site activation status, major protocol deviations, participant status and demographics, and safety analyses. In addition, the DSMB may review selected disease flare data.

No other interim analyses for futility or efficacy are planned.

13.6 Statistical Hypotheses

The null and alternative hypotheses for the primary analysis of the primary endpoint are defined as follows for the cumulative incidence of treatment failure at Stage 2 Week 24 in the i-th arm and j-th immunologically-defined subgroup, $1 - S_{i,j}(24)$,

$$H_0\colon\ S_{MMF,j}(24) = S_{Placebo,j}(24) \text{ for all } j = 1 \text{ to } 7$$
$$H_A\colon\ S_{MMF,j}(24) \neq S_{Placebo,j}(24) \text{ for } j \in \{1, \ldots, 7\}$$

This hypothesis will be evaluated first for the mITT population pooled over all immunologic cluster. Step-down evaluations will then evaluate the cumulative incidence of treatment failure at Stage 2 Week 24 separately for each cluster.

13.7 Sample Size Considerations

The goal of Stage 2 of the study is to evaluate the potential effectiveness of MMF within previously-identified immunologically-homogeneous clusters of lupus patients. To place these cluster comparisons in the context of a successful trial, target enrollment is based on power to show superiority of MMF over placebo in a pooled lupus population.

In previous studies using BOLD designs in lupus populations [22, 93, 94] where long-acting corticosteroids were administered during the treatment withdrawal stage, survival free-from-failure at 6 months in untreated or placebo-treated participants ranged from 5-20% [25]. These studies included participants with a range of disease activity, had differing rules on implementation of background steroids and different definitions for treatment failure. By limiting steroids and carefully adhering to entry criteria to recruit an appropriate population with active lupus disease activity, and by defining treatment failure to include individuals who receive rescue medications post-randomization or who withdraw from treatment prematurely, a placebo survival at 24 weeks of 15% or less should be achievable. In the MMF arm, a minimum clinically meaningful improvement would be 35% survival at 24 weeks.

A study design with 120 participants randomized 1:1 to placebo or MMF will have between 74% to ≥ 95% power if placebo survival at Stage 2 Week 24 ranges from 15% to 10% and MMF survival at Stage 2 Week 24 ranges from 35% to 50%(2-sided, α=0.05); power is ≥ 80% when MMF survival at Stage 2 Week 24 is at least 37%. Power for a two-sample landmark analysis was computed for a Z-Test with unpooled variance using binomial enumeration.

In addition, a simulation study was conducted to determine the power for the supportive analysis using log-rank tests for time until treatment failure under assumptions of non-constant and non-proportional hazards based on the results of previous studies using BOLD designs in lupus populations [22, 93, 94]. Specifically, under an assumption the baseline hazard doubles at Week 12 with an attenuation of long-acting corticosteroids, a proportional hazard corresponding to an increase in survival at Stage 2 Week 24 from 15% to 35% with MMF (HR = 0.55) results in 80.0% power. When all treatment benefit from MMF is restricted to after Week 12, power of the log-rank test decreases to 61.3%, but there remains power to detect larger treatment effects (power = 87.9% when $S_{MMF,24}$ = 45% and $S_{Placebo,24}$ = 15%).

The baseline immunologic cluster would be a useful marker for identifying individuals with a propensity to respond to MMF if some clusters have a very poor response and others have a large response. Hence, the by-cluster comparisons are powered to identify clusters with an MMF response of 60-80% survival at Stage 2 Week 24, which is well above that expected for the overall population.

Table 13.1 gives the number required per arm in a given cluster to achieve 80% power to detect large differences in survival over 24 weeks between arms (based on log-rank test, □=0.1, 2-sided). For example, if the underlying placebo survival is 10% at 24 weeks, then 6-9 per arm within a given cluster gives 80% power to detect survival in the MMF arm ranging from 60-80%. Power for within-cluster comparisons will be maximized if numbers per arm are equal. Although stratifying randomization by baseline cluster assignment (7 clusters) is not feasible, stratification by gene expression signature (3 levels) serves as a first-cut approximation to the cluster assignment and should facilitate balance between arms.

Table 13.1. Cluster comparisons: # per arm to achieve 80% power on comparison of survival over 24 weeks

*Survival at Stage 2 Week 24: MMF

*Survival at Stage 2 Week 24: Placebo	60%	65%	70%	75%	80%
5%	7	6	6	5	5
10%	9	8	7	6	6
15%	13	11	9	8	7

* Assumed underlying %survival in the population of MMF (or placebo) -treated patients.

Although the number per cluster will be random, if the 7 clusters are evenly distributed in the lupus population, then the number achieved for any given cluster will likely include 11 to 24 individuals (i.e. > 90% chance) or approximately 5 to 12 per arm. Hence, we are likely to have adequately powered comparisons for at least some clusters.

For Stage 3, we anticipate that at least 48 (80%) among those randomized to placebo in Stage 2 and approximately 36 (60%) among those randomized to MMF in Stage 2 will be eligible for re-randomization to MMF or MMF plus voclosporin. For Stage 3 analyses, we will have 4 groups defined by the cross-classification of Stage 2 and Stage 3 treatment assignments, as follows:

	Stage 2 Randomization	
Stage 3 Re-randomization	**MMF**	**Placebo MMF**
MMF + voclosporin	$n_{\_MMF\_Combo}$ (~18)	$n_{\_placebo\_Combo}$ (~24)
MMF + placebo voclosporin	$n_{\_MMF\_MMF}$ (~18)	$n_{\_placebo\_MMF}$ (~24)

Stage 3 is intended to explore baseline (pre-re-randomization) gene expression patterns and their associations with response (or non-response) to MMF and MMF plus voclosporin, and to describe differences in those associations between the 2 arms. Gene expression patterns may include immunologically-homogeneous clusters defined at screening, gene expression at the Stage 2 Day 0 Randomization Visit, or differential expression observed during the Stage 2 treatment period. Among those randomized to placebo in Stage 2, if we re-randomize 24 to MMF, we anticipate 8-12 responders (i.e. 35-50% who have not failed by Stage 2 Week 24) and 12-16 non-responders on which to evaluate baseline gene expression patterns. In the MMF plus voclosporin arm, the number of responders is expected to be at least as high as MMF alone. Stage 3 is exploratory and not powered to test a pre-specified hypothesis.

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 identify individuals.

15 Quality Assurance and Quality Control

The PI is required to keep accurate records to ensure that the conduct of the study is fully documented. The PI 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 (NIH).

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 participants screening or enrollment number, the DAIT data center will not collect personally identifying information such as the participants name or social security number. Participants s 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 to 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 as appropriate.

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 PI has the responsibility to identify, document and report protocol deviations as directed by 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. Risk assessment must occur by the investigator and study sponsor. The investigator should ensure a procedure 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 investigator/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 investigator to the IRB per IRB reporting requirements. The study sponsor will determine reportability of the deviation 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 investigator or designee listed on the IORA 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. The consent/assent process will be documented in the research or medical records.

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. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor 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 the sponsor.

The study monitor or other authorized representatives of the sponsor 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 sites will permit access to such records.

18 Publication Policy

The Autoimmune Centers of Excellence policy on the publication of study results will apply to this trial. Authorized study personnel may find details regarding the policy on the ACE study portal.

19 Appendices

19.1 Appendix 1: Mycophenolate REMS Program Acceptable Methods for Females of Reproductive Potential

<table>
<tr><th colspan="4">Acceptable Contraception Methods for Females of Reproductive Potential*</th></tr>
<tr><td>Option 1

Methods to Use Alone</td><td colspan="3">• Intrauterine devices (IUDs)
• Tubal sterilization
• Participant’s partner had a vasectomy</td></tr>
<tr><td colspan="4">OR</td></tr>
<tr><td rowspan="2">Option 2

Choose One Hormone Method AND One Barrier Method</td><td>Hormone Methods

choose 1</td><td></td><td>Barrier Methods

choose 1</td></tr>
<tr><td>Estrogen and Progesterone

• Oral contraceptive pill
• Transdermal patch
• Vaginal ring

Progesterone-only
• Injection
• Implant</td><td>AND</td><td>• Diaphragm with spermicide
• Cervical cap with spermicide
• Contraceptive sponge
• Male condom
• Female condom</td></tr>
<tr><td colspan="4">OR</td></tr>
<tr><td rowspan="2">Option 3

Choose One Barrier Method from each column (must chose two methods)</td><td>Barrier Methods

choose 1</td><td></td><td>Barrier Methods

choose 1</td></tr>
<tr><td>• Diaphragm with spermicide
• Cervical cap with spermicide
• Contraceptive sponge</td><td>AND</td><td>• Male condom
• Female condom</td></tr>
</table>

* Females of reproductive potential include girls who have entered puberty and all women who have a uterus and have not passed through menopause.

19.2 Appendix 2: Examples of CYP3A4/5 Inhibitors and Inducers

The table below lists examples of CYP3A4/5 Inhibitors and Inducers. It is not an all-inclusive list.

CYP3A4 Inducers	CYP3A4 Inhibitors	P-gp Inducers	P-gp Inhibitors	P-gp SUBSTRATES
carbamazepine	allopurinol	aspirin	amiloride	dipyridamole
corticosteroids	amiodarone	paclitaxel	amiodarone	digoxin
efavirenz	amprenavir	Other CNI	atorvastin	diltiazem
modafinil	cimetidine		carvedilol	losartan
nevirapine	diltiazem		digoxin	quinidine
omeprazole	erythromycin		diltiazem	Other CNIs
phenytoin	fluconazole		dipyridamole	
rifampin	grapefruit juice		felodipine	
St. John's Wort	isoniazid		lidocaine	
	ketoconazole		lovastatin	
	nifedipine		nifedipine	
	quinolones		quinidine	
	tamoxifen		simvastatin	
	verapamil		verapamil	

19.3 Disease-Specific Assessments

19.3.1 EULAR/ACR Classification Criteria for SLE [3]

Table 1. Definitions of SLE classification criteria*

Criteria	Definition
Antinuclear antibodies (ANA)	ANA at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test at least once. Testing by immunofluorescence on HEp-2 cells or a solid-phase ANA screening immunoassay with at least equivalent performance is highly recommended
Fever	Temperature >38.3°C
Leukopenia	White blood cell count <4,000/mm³
Thrombocytopenia	Platelet count <100,000/mm³
Autoimmune hemolysis	Evidence of hemolysis, such as reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated LDH, AND positive Coombs' (direct antiglobulin) test
Delirium	Characterized by 1) change in consciousness or level of arousal with reduced ability to focus, 2) symptom development over hours to <2 days, 3) symptom fluctuation throughout the day, 4) either 4a) acute/subacute change in cognition (e.g., memory deficit or disorientation), or 4b) change in behavior, mood, or affect (e.g., restlessness, reversal of sleep/wake cycle)
Psychosis	Characterized by 1) delusions and/or hallucinations without insight and 2) absence of delirium
Seizure	Primary generalized seizure or partial/focal seizure
Non-scarring alopecia	Non-scarring alopecia observed by a clinician†
Oral ulcers	Oral ulcers observed by a clinician†
Subacute cutaneous OR discoid lupus	Subacute cutaneous lupus erythematosus observed by a clinician:† Annular or papulosquamous (psoriasiform) cutaneous eruption, usually photodistributed If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted). OR Discoid lupus erythematosus observed by a clinician:† Erythematous-violaceous cutaneous lesions with secondary changes of atrophic scarring, dyspigmentation, often follicular hyperkeratosis/plugging (scalp), leading to scarring alopecia on the scalp If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular and/or periappendageal lymphohistiocytic infiltrate. In the scalp, follicular keratin plugs may be seen. In longstanding lesions, mucin deposition may be noted)
Acute cutaneous lupus	Malar rash or generalized maculopapular rash observed by a clinician† If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted. Perivascular neutrophilic infiltrate may be present early in the course)
Pleural or pericardial effusion	Imaging evidence (such as ultrasound, x-ray, CT scan, MRI) of pleural or pericardial effusion, or both
Acute pericarditis	≥2 of 1) pericardial chest pain (typically sharp, worse with inspiration, improved by leaning forward), 2) pericardial rub, 3) EKG with new widespread ST elevation or PR depression, 4) new or worsened pericardial effusion on imaging (such as ultrasound, x-ray, CT scan, MRI)
Joint involvement	EITHER 1) synovitis involving 2 or more joints characterized by swelling or effusion OR 2) tenderness in 2 or more joints and at least 30 minutes of morning stiffness
Proteinuria >0.5 g/24 hours	Proteinuria >0.5 g/24 hours by 24-hour urine or equivalent spot urine protein-to-creatinine ratio
Class II or V lupus nephritis on renal biopsy according to ISN/RPS 2003 classification	Class II: Mesangial proliferative lupus nephritis: purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposit. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy Class V: Membranous lupus nephritis: global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations

Table 1. *(Cont'd)*

Criteria	Definition
Class III or IV lupus nephritis on renal biopsy according to ISN/RPS 2003 classification	Class III: Focal lupus nephritis: active or inactive focal, segmental, or global endocapillary or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations Class IV: Diffuse lupus nephritis: active or inactive diffuse, segmental, or global endocapillary or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Positive antiphospholipid antibodies	Anticardiolipin antibodies (IgA, IgG, or IgM) at medium or high titer (>40 APL, GPL, or MPL, or >the 99th percentile) or positive anti-β_2GPI antibodies (IgA, IgG, or IgM) or positive lupus anticoagulant
Low C3 OR low C4	C3 OR C4 below the lower limit of normal
Low C3 AND low C4	Both C3 AND C4 below their lower limits of normal
Anti-dsDNA antibodies OR anti-Sm antibodies	Anti-dsDNA antibodies in an immunoassay with demonstrated ≥90% specificity for SLE against relevant disease controls OR anti-Sm antibodies

* SLE = systemic lupus erythematosus; LDH = lactate dehydrogenase; CT = computed tomography; MRI = magnetic resonance imaging; EKG = electrocardiography; ISN = International Society of Nephrology; RPS = Renal Pathology Society; anti-β_2GPI = anti–β_2-glycoprotein I; anti-dsDNA = anti–double-stranded DNA.
† This may include physical examination or review of a photograph.

19.3.2 **BILAG 2004**

BILAG-2004 INDEX Centre: Date: Initials/Hosp No:

- **Only record manifestations/items due to SLE Disease Activity**
- **Assessment refers to manifestations occurring in the last 4 weeks (compared with the previous 4 weeks)**
- **TO BE USED WITH THE GLOSSARY**

Record: ND Not Done
0 Not present
1 Improving
2 Same
3 Worse
4 New
Yes/No OR Value (where indicated)
*Y/N Confirm this is due to SLE activity (Yes/No)

CONSTITUTIONAL
1. Pyrexia - documented > 37.5°C ( )
2. Weight loss - unintentional > 5% ( )
3. Lymphadenopathy/splenomegaly ( )
4. Anorexia ( )

MUCOCUTANEOUS
5. Skin eruption - severe ( )
6. Skin eruption - mild ( )
7. Angio-oedema - severe ( )
8. Angio-oedema - mild ( )
9. Mucosal ulceration - severe ( )
10. Mucosal ulceration - mild ( )
11. Panniculitis/Bullous lupus - severe ( )
12. Panniculitis/Bullous lupus - mild ( )
13. Major cutaneous vasculitis/thrombosis ( )
14. Digital infarcts or nodular vasculitis ( )
15. Alopecia - severe ( )
16. Alopecia - mild ( )
17. Peri-ungual erythema/chilblains ( )
18. Splinter haemorrhages ( )

NEUROPSYCHIATRIC
19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional state ( )
24. Psychosis ( )
25. Acute inflammatory demyelinating polyradiculoneuropathy ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )
29. Polyneuropathy ( )
30. Seizure disorder ( )
31. Status epilepticus ( )
32. Cerebrovascular disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia (isolated) ( )
37. Lupus headache - severe unremitting ( )
38. Headache from IC hypertension ( )

MUSCULOSKELETAL
39. Myositis - severe ( )
40. Myositis - mild ( )
41. Arthritis (severe) ( )
42. Arthritis (moderate)/Tendonitis/Tenosynovitis ( )
43. Arthritis (mild)/Arthralgia/Myalgia ( )

Weight (kg):	**Serum urea (mmol/l):**
African ancestry: Yes/No	**Serum albumin (g/l):**

CARDIORESPIRATORY
44. Myocarditis - mild ( )
45. Myocarditis/Endocarditis + Cardiac failure ( )
46. Arrhythmia ( )
47. New valvular dysfunction ( )
48. Pleurisy/Pericarditis ( )
49. Cardiac tamponade ( )
50. Pleural effusion with dyspnoea ( )
51. Pulmonary haemorrhage/vasculitis ( )
52. Interstitial alveolitis/pneumonitis ( )
53. Shrinking lung syndrome ( )
54. Aortitis ( )
55. Coronary vasculitis ( )

GASTROINTESTINAL
56. Lupus peritonitis ( )
57. Abdominal serositis or ascites ( )
58. Lupus enteritis/colitis ( )
59. Malabsorption ( )
60. Protein losing enteropathy ( )
61. Intestinal pseudo-obstruction ( )
62. Lupus hepatitis ( )
63. Acute lupus cholecystitis ( )
64. Acute lupus pancreatitis ( )

OPHTHALMIC
65. Orbital inflammation/myositis/proptosis ( )
66. Keratitis - severe ( )
67. Keratitis - mild ( )
68. Anterior uveitis ( )
69. Posterior uveitis/retinal vasculitis - severe ( )
70. Posterior uveitis/retinal vasculitis - mild ( )
71. Episcleritis ( )
72. Scleritis - severe ( )
73. Scleritis - mild ( )
74. Retinal/choroidal vaso-occlusive disease ( )
75. Isolated cotton-wool spots (cytoid bodies) ( )
76. Optic neuritis ( )
77. Anterior ischaemic optic neuropathy ( )

RENAL
78. Systolic blood pressure (mm Hg) value ( ) Y/N*
79. Diastolic blood pressure (mm Hg) value ( ) Y/N*
80. Accelerated hypertension Yes/No ( )
81. Urine dipstick protein (+=1, ++=2, +++=3) ( ) Y/N*
82. Urine albumin-creatinine ratio mg/mmol ( ) Y/N*
83. Urine protein-creatinine ratio mg/mmol ( ) Y/N*
84. 24 hour urine protein (g) value ( ) Y/N*
85. Nephrotic syndrome Yes/No ( )
86. Creatinine (plasma/serum) µmol/l ( ) Y/N*
87. GFR (calculated) ml/min/1.73 m² ( ) Y/N*
88. Active urinary sediment Yes/No ( )
89. Active nephritis Yes/No ( )

HAEMATOLOGICAL
90. Haemoglobin (g/dl) value ( ) Y/N*
91. Total white cell count (x 10^9/l) value ( ) Y/N*
92. Neutrophils (x 10^9/l) value ( ) Y/N*
93. Lymphocytes (x 10^9/l) value ( ) Y/N*
94. Platelets (x 10^9/l) value ( ) Y/N*
95. TTP ( )
96. Evidence of active haemolysis Yes/No ( )
97. Coombs' test positive (isolated) Yes/No ( )

Revision: 1/Sep/2009

19.3.3 **Hybrid SLEDAI**

SLEDAI SCORE				
#	**Descriptor**	**Definition**	**Present**	**Weight**
1	**Seizure**	Recent onset (last 28 days). Exclude metabolic, infectious, or drug cause, or seizure due to past irreversible CNS damage.	☐	**8**
2	**Psychosis**	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.	☐	**8**
3	**Organic brain syndrome**	Altered mental function with impaired orientation, memory, or other intelligent function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.	☐	**8**
4	**Visual disturbance**	Retinal and eye changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate, or hemorrhages in the choroid, optic neuritis, scleritis, or episcleritis. Exclude hypertension, infection, or drug causes.	☐	**8**
5	**Cranial nerve disorder**	New onset of sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.	☐	**8**
6	**Lupus headache**	Severe, persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.	☐	**8**
7	**CVA**	New onset of cerebrovascular accident(s). Exclude arteriosclerosis or hypertensive causes.	☐	**8**
8	**Vasculitis**	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.	☐	**8**
9	**Arthritis**	More than two joints with pain and signs of inflammation (i.e., tenderness, swelling, or effusion).	☐	**4**
10	**Myositis**	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.	☐	**4**
11	**Urinary casts**	Heme-granular or red blood cell casts.	☐	**4**
12	**Hematuria**	> 5 red blood cells/high power field. Exclude stone, infection, or other causes.	☐	**4**

SLEDAI SCORE				
#	Descriptor	Definition	Present	Weight
13	Proteinuria	> 0.5 protein:creatinine ratio (mg:mg)	☐	4
14	Pyuria	> 5 white blood cells/high power field. Exclude infection.	☐	4
15	Rash	Ongoing inflammatory lupus rash.	☐	2
16	Alopecia	Ongoing abnormal, patchy, or diffuse loss of hair due to active lupus.	☐	2
17	Mucosal ulcers	Ongoing, oral or nasal ulcerations due to active lupus.	☐	2
18	Pleurisy	Classic and severe pleuritic chest pain, or pleural rub, or effusion, or new pleural thickening due to lupus.	☐	2
19	Pericarditis	Classic and severe pericardial pain, or rub, or effusion, or electrocardiogram, or echo confirmation.	☐	2
20	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.	☐	2
21	Anti-dsDNA	> 25% binding by Farr assay or above normal range for testing laboratory.	☐	2
22	Fever	> 38°C. Exclude infectious cause.	☐	1
23	Thrombo-cytopenia	< 100,000 platelets/mL	☐	1
24	Leukopenia	< 3,000 white blood cells/mL Exclude drug causes.	☐	1

Total Score (sum of weights next to descriptors marked present): _____

19.3.4 SELENA-SLEDAI Flare Composite

MILD OR MODERATE FLARE		SEVERE FLARE	
☐	Change in SLEDAI instrument score of 3 points or more (but not more than 12)	☐	Change in SLEDAI instrument score greater than 12
☐	New/Worse: • Discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus • Nasopharyngeal ulcers • Pleuritis • Pericarditis • Arthritis • Fever (SLE)	☐	New/Worse: • CNS-SLE • Vasculitis • Nephritis • Myositis • Platelet Count < 60,000 • Hemolytic anemia: Hb < 70g/L or decrease in Hb > 30g/L *Requiring: double prednisone or prednisone increase to > 0.5 mg/kg/day, or hospitalization
☐	Increase in prednisone, but not to > 0.5 mg/kg/day	☐	Increase in prednisone to > 0.5 mg/kg/day
☐	Added NSAID or hydroxychloroquine for SLE activity	☐	New cyclophosphamide, azathioprine, or methotrexate, for SLE activity
☐	≥ 1.0 increase in PGA score, but not to more than 2.5	☐	Hospitalization for SLE activity
		☐	Increase in PGA to > 2.5

19.3.5 **Thanou Modified SFI**

Thanou Modification: CLASSIC SELENA SLEDAI FLARE INDEX

(Can be used with any version of the SLEDAI)

Green is added Red is subtracted. Thus, original form can be used with the one addition in green and analyzed as either the classic or modified version

Mild or Moderate Flare Please rate severity of this flare: mild □ moderate □

□ Change in SELENA-SLEDAI instrument score of 3 points or more (but not to more than 12)
□ New/worse: Discoid, photosensitive, profundus, bullous lupus,
Nasopharyngeal ulcers
cutaneous vasculitis,
Pleuritis
Pericarditis
Arthritis
Fever (SLE)
□ Increase in prednisone, but not to >0.5 mg/kg/day
□ Added NSAID or hydroxychloroquine for SLE activity
□ ≥1.0 increase in PGA score, but not to more than 2.5

Severe Flare □

□ Change in SELENA-SLEDAI instrument score to greater than 12
□ New/worse: CNS-SLE
Vasculitis
Nephritis
Myositis
Plt <60,000
Hemolytic anemia: Hb <70 g/L or decrease in Hb >30 g/L
Requiring: double prednisone, or prednisone increase to >0.5 mg/kg/day, or hospitalization
□ Increase in prednisone to >0.5 mg/kg/day
□ New cyclophosphamide, azathioprine, methotrexate for SLE activity
□ Hospitalization for SLE activity
□ Increase in Physician's Global Assessment score to >2.5

19.3.6 **LFA-REAL CLINRO**

LFA-REAL™ (RAPID EVALUATION OF ACTIVITY IN LUPUS)

[CLINICIAN REPORT]

DIRECTIONS: Thinking of the past month, put one line ( ) anywhere through each scale below to assess the severity of lupus activity in each symptom/organ for the patient. Score only lupus disease activity (not chronic damage). If there is no activity in a particular symptom/organ, mark 0 (none) for that organ/system. Rate each active symptom/organ separately. Use "other" scales for symptoms/organs not listed here. The sum of organ scores provides the global disease activity. When performing monthly assessments, look back at your last form and place your mark considering the patient's progress during the past month.

Examples:

A moderate arthritis, not quite severe might be rated like this:

None 0 1 2 3 Worst Imaginable

mild moderate severe

A mild arthritis, getting better this month might look like this:

None 0 1 2 3 Worst Imaginable

mild moderate severe

How severe was each organ/system disease activity over the past month?

	Symptom score	Organ score
MUCOCUTANEOUS - GLOBAL		____mm
Mucocutaneous components:		
a. RASH	____mm	
b. ALOPECIA	____mm	
c. MUCOSAL ULCERS	____mm	
MUSCULOSKELETAL – GLOBAL		____mm
Musculoskeletal components:	____mm	
a. ARTHRALGIA / ARTHRITIS	____mm	
b. MYALGIA/MYOSITIS		

None 0 1 2 3 Worst Imaginable

mild moderate severe

How severe was each organ/system disease activity over the past month?

	Symptom score	Organ score
CARDIORESPIRATORY (please specify symptom) _____		
None — 0 — mild — 1 — moderate — 2 — severe — 3 — Worst Imaginable		____mm
NEUROPSYCHIATRIC (please specify symptom) _____		
None — 0 — mild — 1 — moderate — 2 — severe — 3 — Worst Imaginable		____mm
RENAL (give one score for nephritis, may specify CLASS if known) _____		
None — 0 — mild — 1 — moderate — 2 — severe — 3 — Worst Imaginable		____mm
HEMATOLOGIC (please specify symptom) _____		
None — 0 — mild — 1 — moderate — 2 — severe — 3 — Worst Imaginable		____mm
CONSTITUTIONAL (please specify symptom) _____		
None — 0 — mild — 1 — moderate — 2 — severe — 3 — Worst Imaginable		____mm
VASCULITIS (please specify symptom) _____		
None — 0 — mild — 1 — moderate — 2 — severe — 3 — Worst Imaginable		____mm

Optional, additional scales may be used to rate multiple features within one of the specified organs or to rate features in more rarely involved organs (e.g. GI, ophthalmic, etc.)

OTHER (Use for additional features, please specify organ and symptom): _____		
None — 0 — mild — 1 — moderate — 2 — severe — 3 — Worst Imaginable		____mm
OTHER (Use for additional features, please specify organ and symptom): _____		
None — 0 — mild — 1 — moderate — 2 — severe — 3 — Worst Imaginable		____mm
OTHER (Use for additional features, please specify organ and symptom): _____		
None — 0 — mild — 1 — moderate — 2 — severe — 3 — Worst Imaginable		____mm
	Total Score	**_____mm**
	(Right column only)	

19.3.7 **LFA-REAL PRO**

LFA-REAL™ (RAPID EVALUATION OF ACTIVITY IN LUPUS)
[PATIENT REPORT]

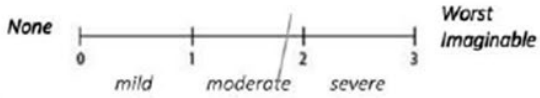
DIRECTIONS: Thinking of the past month, put one line ( ) anywhere through each scale below to best describe how severe each lupus symptom has been for you.

Focus only on current symptoms from your active Lupus. If you are sure that your symptoms are not from your active lupus (for example, asthma, injury or infection), then do not report. If you did not experience a particular symptom, mark 0 (none) for that symptom.

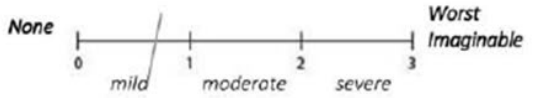
If you have filled out this form before, look back at your last form and place your mark considering your progress during the past month.

EXAMPLES:

A moderate symptom, not quite severe might be rated like this:



A mild symptom, getting better this month might look like this:



How severe was each symptom over the past month?

Administrative use only:

RASH

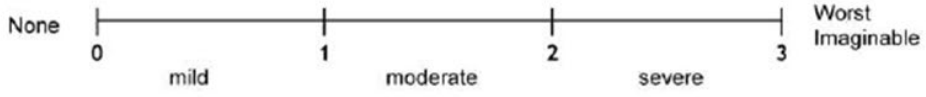
____mm

SYMPTOMS OF ARTHRITIS

a. JOINT PAIN

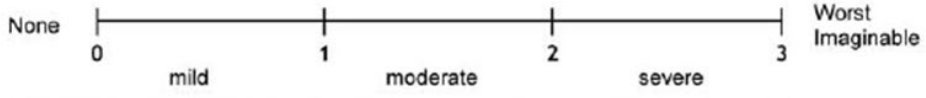
____mm

b. JOINT SWELLING



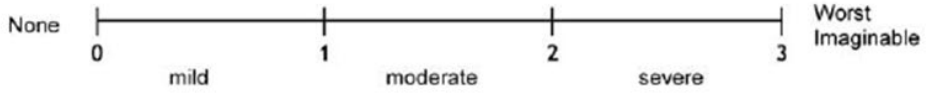
____mm

c. JOINT STIFFNESS



____mm

d. OVERALL ARTHRITIS *(Consider Joint pain, swelling and stiffness together)*



____mm

How severe was each symptom over the past month?

	Administrative use only:
MUSCLE PAIN OR ACHES	
None — 0 — 1 — 2 — 3 — Worst Imaginable (0 mild, 1 moderate, 2 severe)	_____mm
FATIGUE	
None — 0 — 1 — 2 — 3 — Worst Imaginable (0 mild, 1 moderate, 2 severe)	_____mm
FEVER	
None — 0 — 1 — 2 — 3 — Worst Imaginable (0 mild, 1 moderate, 2 severe)	_____mm
HAIR LOSS	
None — 0 — 1 — 2 — 3 — Worst Imaginable (0 mild, 1 moderate, 2 severe)	_____mm
BODY SYMPTOMS *(Check all that apply)*	
☐ chest pain ☐ shortness of breath ☐ swelling in legs ☐ other	
None — 0 — 1 — 2 — 3 — Worst Imaginable (0 mild, 1 moderate, 2 severe)	_____mm
	Total Score _____mm *(Right column only)*

Is there anything else to report? Use this space to explain your answers or report other symptoms.

19.3.8 CGI–I (CGI-S, CGI-C)

CLINICAL GLOBAL IMPRESSION OF SEVERITY OF LUPUS (CGI-S)

Please choose the response below that best describes the severity of this patient's lupus disease activity during the past month:

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe

CLINICAL GLOBAL IMPRESSION OF CHANGE IN LUPUS (CGI-C)

Please choose the response below that best describes the overall change in this patient's lupus disease activity during the past month:

- ☐ Much better
- ☐ Moderately better
- ☐ No change
- ☐ Moderately worse
- ☐ Much worse

(After Screening Only) Please choose the response below that best describes the overall change in this patient's lupus disease activity during the past month as compared to the start of the current Stage and initiation of study-provided medication:

- ☐ Much better
- ☐ Moderately better
- ☐ No change
- ☐ Moderately worse
- ☐ Much worse

19.3.9 PGI-I (PGI-S and PGI-C)

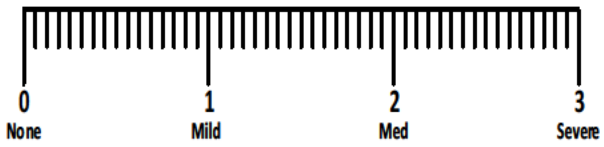
PATIENT'S GLOBAL IMPRESSION OF SEVERITY OF LUPUS (PGI-S)
Please choose the response below that best describes the severity of your lupus symptoms during the past month: ☐ None ☐ Mild ☐ Moderate ☐ Severe
PATIENT'S GLOBAL IMPRESSION OF CHANGE IN LUPUS (PGI-C)
Please choose the response below that best describes the overall change in your lupus symptoms during the past month: ☐ Much better ☐ Moderately better ☐ No change ☐ Moderately worse ☐ Much worse

19.3.10 **PGA**

PHYSICIAN GLOBAL ASSESSMENT:

(3in)

Please rate the participant's current lupus disease activity on the scale, with 0 being no disease activity and 3 being severe disease activity.



Length of line *(from 0 to vertical line)* _____in.

19.3.11 **SF-36**

RAND > RAND Health > Surveys > RAND Medical Outcomes Study > 36-Item Short Form Survey (SF-36) >

36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

2. **Compared to one year ago**, how would you rate your health in general **now?**

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health?**

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
14. **Accomplished less** than you would like	○ 1	○ 2
15. Were limited in the **kind** of work or other activities	○ 1	○ 2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	○ 1	○ 2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
18. **Accomplished less** than you would like	○ 1	○ 2
19. Didn't do work or other activities as **carefully** as usual	○ 1	○ 2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ○ 1 - Not at all
- ○ 2 - Slightly
- ○ 3 - Moderately
- ○ 4 - Quite a bit
- ○ 5 - Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

- 1 - None
- 2 - Very mild
- 3 - Mild
- 4 - Moderate
- 5 - Severe
- 6 - Very severe

---

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- 1 - Not at all
- 2 - A little bit
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks.** For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
24. Have you been a very nervous person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
25. Have you felt so down in the dumps that nothing could cheer you up?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
26. Have you felt calm and peaceful?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
27. Did you have a lot of energy?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
28. Have you felt downhearted and blue?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
29. Did you feel worn out?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
30. Have you been a happy person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
31. Did you feel tired?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- ○ 1 - All of the time
- ○ 2 - Most of the time
- ○ 3 - Some of the time
- ○ 4 - A little of the time
- ○ 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	○ 1	○ 2	○ 3	○ 4	○ 5
34. I am as healthy as anybody I know	○ 1	○ 2	○ 3	○ 4	○ 5
35. I expect my health to get worse	○ 1	○ 2	○ 3	○ 4	○ 5
36. My health is excellent	○ 1	○ 2	○ 3	○ 4	○ 5

ABOUT

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