C O N F I D E N T I A L

Autoimmunity Centers of Excellence

Protocol # ALE06

An Investigator-Initiated, Phase II, Randomized, Withdrawal Study of Mycophenolate Mofetil (MMF) in Patients with Stable, Quiescent Systemic Lupus Erythematosus (SLE)

Short Title: Randomized MMF Withdrawal in SLE

non-IND

Version 2.0, 07 April 2015

Sponsor: Division of Allergy, Immunology, and Transplantation (DAIT)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health (NIH)

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INVESTIGATOR SIGNATURE PAGE

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Please print, sign, and date at the indicated location below. A copy should be kept for your records and the original signature page sent to the SACCC.

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) – 21 CFR Parts 45, 50, 56, and 312, and the International Conference on Harmonization (ICH) document "Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance" dated April 1996. Further, I will conduct the study in keeping with local, legal, and regulatory requirements.

As a Principal Investigator on this protocol, I agree to conduct "An Investigator-Initiated, Phase II, Randomized, Withdrawal Study of Mycophenolate Mofetil (MMF) in Patients with Stable, Quiescent Systemic Lupus Erythematosus (SLE)." 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 written permission of the NIAID.

Principal Investigator (Print)

Principal Investigator Signature

Date

PROTOCOL SYNOPSIS

Title of the Protocol: An Investigator-Initiated, Phase II, Randomized, Withdrawal Study of Mycophenolate Mofetil (MMF) in Patients with Stable, Quiescent Systemic Lupus Erythematosus (SLE)

ACE Protocol Number: ALE06

Protocol Chair(s): Tammy Utset, MD, MPH and Eliza Chakravarty, MD

Sponsor: DAIT/NIAID, NIH

Primary Objective: To describe the effect of withdrawal from MMF on risk of clinically significant disease reactivation in quiescent SLE patients who have been on long-term MMF therapy

Study Arms:

- MMF maintenance arm: These subjects will continue MMF treatment (1000-3000 mg/day) for the rest of their study participation (up to Week 60).
- MMF withdrawal arm: These subjects will taper off MMF per the protocol-specified schedule over 12 weeks and remain off MMF for the rest of their study participation (up to Week 60 or until the primary endpoint of disease reactivation is met, whichever comes first).

Study Design: One hundred twenty eligible subjects will be randomized in a 1:1 ratio to one of the two study treatment arms – continuing MMF treatment for 60 weeks or tapering off MMF within 12 weeks. All subjects will continue on their anti-malarials and may continue the use of their corticosteroids.
Subject visits to assess endpoints will occur every 4 weeks from Day 0 through Week 24 and then at Weeks 32, 40, 48, and 60. As disease flares occur, subjects will be brought in for urgent, flare or endpoint visits to document symptoms, collect biological samples, and determine whether primary endpoint has been met.

Endpoints:

Primary Endpoint

The primary endpoint is the probability in each arm of experiencing clinically significant disease reactivation by 60 weeks after randomization. Clinically significant SLE reactivation requires both:

1) A SELENA-SLEDAI*-defined mild/moderate or severe flare and
2) Increased immunosuppressive therapy on a sustained basis as defined by one of the following criteria:
    a. Sustained activity: Subject has significant prolonged SLE flare requiring steroid increase/burst to ≥ 15 mg/day prednisone (or its equivalent) for more than four weeks.
    b. Frequent relapsing/remitting:
        i. Subject flares requiring an increase/burst of steroids and is successfully tapered to < 15 mg/day within four weeks, but this occurs on two or more occasions, or
        ii. Intra-articular, intra-muscular or IV steroids, on more than one occasion.
    c. Clinical activity of sufficient severity to warrant resumption of or an increased dose of MMF or addition of other major immunosuppressive including azathioprine or methotrexate. Regardless of steroid use, if the investigator observes disease activity of sufficient severity to warrant resumption, addition or increase in dosage of major immunosuppressant in the setting of a SELENA-SLEDAI*-defined flare, subject has met the primary endpoint.

Secondary Disease Activity Endpoints

- Time from Day 0 to clinically significant disease reactivation (as defined in Section 3.2, *Description of Primary Endpoint*). The time of clinically significant disease reactivation is defined as the date of the first SELENA-SLEDAI* assessment that meets (or goes on to meet) the criteria in Section 3.2, *Description of Primary Endpoint*.
- The probability of experiencing any SELENA-SLEDAI* flare and the probability of experiencing any severe SELENA-SLEDAI* flare by Week 60, in aggregate and within subgroups defined by disease manifestation (renal disease / extra-renal disease) and by baseline MMF dosing group (<2000 mg per day / ≥ 2000 mg per day).
- Time from initiation of withdrawal to first SELENA-SLEDAI* flare and time to first severe SELENA-SLEDAI* flare.
- The probability of experiencing any BILAG* A flare by Week 60.
- Proportion of subjects in the renal subgroup with BILAG* Renal A flare by Week 60

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- Change in SLICC/DI from baseline to Weeks 24, 48, and 60.
- The probability of adding aggressive adjunctive therapy to MMF (including IV immunoglobulin or rituximab) or change in MMF therapy to cytotoxic drug (e.g., cyclophosphamide) due to flare.
- Cumulative systemic steroid dose (PO, IV, IM) at Week 60.
- Change in FACIT fatigue score from baseline to Weeks 24, 48, and 60.
- Change in SF-36® PF and PCS domains from baseline to Weeks 24, 48, and 60.
- Change in Lupus QoL-US© from baseline to Weeks 24, 48, and 60.
- The following endpoints will be assessed to describe the ability of subjects to recover from clinically significant disease reactivation:
    - Time from clinically significant disease reactivation to improvement in BILAG* from maximum level during flare;
    - Time from clinically significant disease reactivation to recovery to baseline BILAG* scores or BILAG* C, whichever is worse;
    - Cumulative excess systemic steroid dose from time of clinically significant disease reactivation to return to pre-flare dose or end of trial participation;
    - Time from clinically significant disease reactivation to return to pre-flare steroid dose.

Secondary Safety Endpoints

- All Grade 3-5 adverse events, as defined by the National Cancer Institute (NCI) – Common Terminology Criteria for Adverse Events (CTCAE) system, which are defined as possibly, probably, or definitely related to SLE.
- All Grade 3-5 adverse events, as defined by the NCI-CTCAE system, which are defined as possibly, probably, or definitely related to MMF.
- All NCI-CTCAE Grade 3-5 adverse events.
- All serious adverse events.
- All infection related events.
- All malignancies.
- All NCI-CTCAE Grade 3-5 hematological events.
- Mortality possibly, probably, or definitely related to SLE.
- All-cause mortality, defined as any death occurring at any time after randomization

Secondary Mechanistic Assessments

- Levels of C3, C4, and anti-dsDNA at Baseline, Week 20, at the time of first flare, and immediately prior to first flare.
- Changes in levels of C3, C4, and anti-dsDNA from Baseline to Week 20, from Baseline to the time of first flare, and from Baseline to the time point immediately prior to first flare.
- Levels of antibodies to Sm, ribonucleoprotein (RNP), SSA/Ro, and SSB/La at Baseline
- Changes in levels of antibodies to Sm, RNP, SSA/Ro, and SSB/La from Baseline to Week 60
- Levels of interferon-regulated chemokines at Baseline, Week 20, at the time of first flare, and time points immediately prior to and after first flare.
- Changes in levels of interferon-regulated chemokines from Baseline to Week 20, from Baseline to the time of first flare, and from Baseline to the time points immediately prior to and after first flare.
- Levels of inflammatory and other cytokines at Baseline, Week 20, at the time of first flare and at time points immediately prior to and after first flare.
- Changes in levels of inflammatory and other cytokines at Baseline, Week 20, at the time of first flare and at time points immediately prior to and after first flare.
- Presence/Absence of gene expression patterns (e.g. fingerprint or signature) at Baseline, Week 20, at time of first flare, and timepoints immediately prior to and after first flare.
- Change in gene expression patterns from Baseline to Week 20, from Baseline to the time of first flare, and from Baseline to the time points immediately prior to and after first flare.

Sample Size: 120 eligible subjects will be randomized within 24 months and each will be followed for up to Week 60, for a total study duration of 3 ¼ years.

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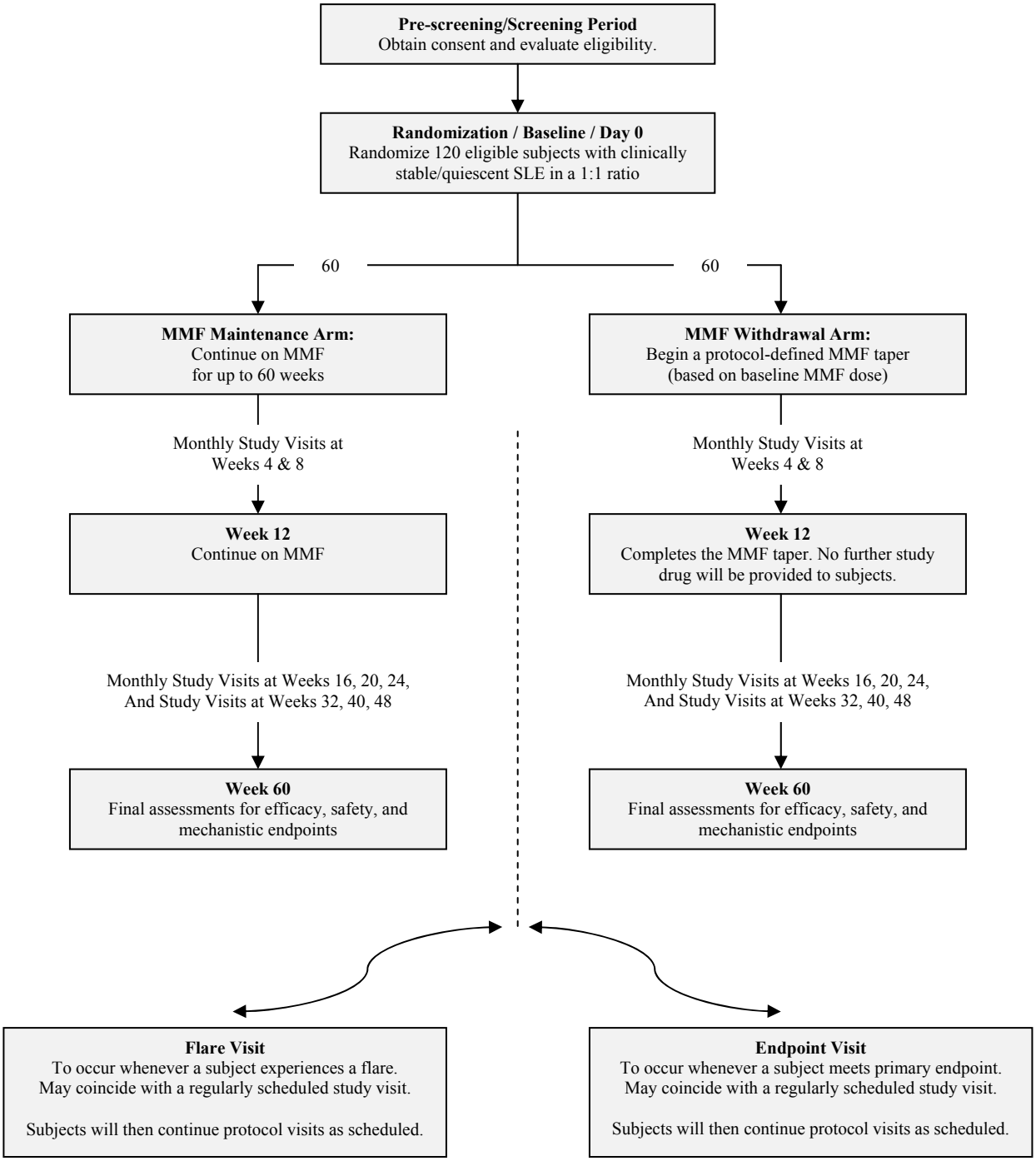
Data Analyses: For the **primary analysis**, the risk difference in disease reactivation by Week 60 will be estimated and 95% score confidence intervals calculated, where the risk difference is defined as the difference in the probability of disease reactivation by Week 60 between the treatment groups. The observed risk estimates will be used to compute the "% Confidence that the true increase is ≤ α" as a function of values for the "Acceptable increase in risk with withdrawal of MMF (α)". The primary endpoint analysis will be based on the ITT population. All **secondary analyses** will be conducted in an exploratory fashion with p-values and confidence intervals presented as descriptive statistics with no adjustments for multiple comparisons. As part of secondary analyses, appropriate contrasts will be constructed using model-based approaches. Analyses will be conducted on the ITT population and the per protocol population.

Lay Summary:

One hundred twenty eligible subjects who have been on long term MMF for SLE and who have had inactive disease for at least 24 weeks will be enrolled. Half the subjects will continue on MMF and half the subjects will be tapered off their MMF within 12 weeks. All subjects will continue hydroxychloroquine and small doses of prednisone as needed. Subject visits to assess endpoints will occur every 4 weeks from Day 0 through Week 24 and then at Weeks 32, 40, 48, and 60.

FLOW DIAGRAM OF PROTOCOL



ABBREVIATIONS

Ab	Antibody (antibodies)
ACE	Autoimmunity Centers of Excellence
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
APGAR	Appearance, pulse, grimace, activity, and respiration
AST	Aspartate Transaminase
AZA	Azathioprine
BID	Twice a day
BILAG*	British Isles Lupus Assessment Group *Note: ALE06 will typically use a spot urine protein:creatinine ratio rather than a 24-hour urine assessment.*
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic Acid
dsDNA	Double-stranded Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
FACIT	Functional Assessment of Chronic Illness Therapy
FACS	Fluorescence-Activated Cell Sorting
FDA	Food and Drug Administration
FD&C	Federal Food, Drug, and Cosmetic Act
GCP	Good Clinical Practice
HCQ	Hydroxychloroquine
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IgG	Immunoglobulin G
IgM(s)	Immunoglobulin M
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intention-to-Treat or Intent-to-Treat
IV	Intravenous
MCV	Mean corpuscular volume

mITT	Modified Intention-to-Treat or Intent-to-Treat
MMF	Mycophenolate Mofetil
m-SLEDAI	Modified SLEDAI
MTX	Methotrexate
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NS	Not significant
NSAID(s)	Nonsteroidal Anti-Inflammatory Drug(s)
OHRP	Office of Human Research Protection
PBMC(s)	Peripheral Blood Mononuclear Cell(s)
PCR	Polymerase Chain Reaction
PCS	Physical Component Summary
PO	Per os (by mouth)
PI	Principal Investigator
PF	Physical Functioning
PP	Per Protocol
PPD	Purified Protein Derivative
QD	Once a day
QFT-G-IT	QuantiFERON®-TB Gold In-Tube Test
QoL	Quality of Life
qPCR	Quantitative Polymerase Chain Reaction
RDW	Red Cell Distribution Width
REMS	Risk Evaluation and Mitigation Strategy
RhoFED	Rho Federal Systems Division, Inc.
RNA	Ribonucleic Acid
RNP	Ribonucleoprotein
SACCC	Statistical and Clinical Coordinating Center
SAE	Serious Adverse Event
SAM	Significance Analysis of Microarrays
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SDI	SLICC/ACR Damage Index
SELENA-SLEDAI*	Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus-Disease Activity Index *Note: ALE06 will typically use a spot urine protein creatinine ratio rather than a 24-hour urine assessment.*
SF-36®	Short Form Health Survey
SLE	Systemic Lupus Erythematosus
SLICC/DI*	Systemic Lupus International Collaborating Clinics/American College of Rheumatology Disease Damage Index for Systemic Lupus Erythematosus *Note: ALE06 will typically use a spot urine protein:creatinine ratio rather than a 24-hour urine assessment.*

SSA/Ro	Sjogren's Syndrome A / Rogers
SSB/La	Sjogren's Syndrome B / Lane
SP	Safety Population
Tfh	Follicular T helper cells
Tregs	T regulatory cells
ULN	Upper limit of normal
WBC	White blood cell count

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1 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Disease Background

SLE is a chronic systemic autoimmune disease characterized by great heterogeneity in symptoms, patterns of activity, and in prognosis. Common symptoms include severe fatigue, fever, joint pain, rashes, hair loss, serositis, and cytopenias. In addition, the majority of patients make antibodies against nuclear antigens and specific antigens such as native deoxyribonucleic acid (DNA). A large component of the pathogenesis is felt to be driven by these antibodies, which form immune complexes and lead to activation of the complement system. Current therapies for SLE are nonspecific, often inadequately effective, and have substantial potential toxicities. When patients do achieve prolonged clinical control of disease, it is often unclear if the control is due to the maintenance use of potentially toxic immunosuppressant therapy or due to natural variation in their disease activity. Stopping points for immunosuppressants in patients who have previously had severe manifestations of SLE are unknown, due to the difficulty in differentiating true disease quiescence from disease suppression.

1.1.1 Description and Epidemiology of Disease

SLE is a systemic autoimmune disease characterized by an autoimmune response to nucleosomal antigens. Onset is most common in the 30s or 40s, with approximately a 90% female predominance. It can also begin in childhood and at advanced ages, with lower frequencies. Prevalence is estimated at 1/2000 women and it is more common in ethnic minorities including African-Americans and Latinos. Symptoms and organ involvement vary greatly, with arthritis, rashes, and systemic symptoms such as fever and weight loss being common symptoms. The syndrome can be mild, or it can be severe. The most common serious manifestation is lupus nephritis, occurring in up to 40% of SLE patients. Overall mortality rates in SLE are approximately 15% at 10 years, with lupus nephritis and brain involvement being markers of a poor prognosis. Early deaths (< 8 years) most often are related to disease activity or infection, while later deaths most often represent thrombosis and accelerated atherosclerosis. Cross-sectional epidemiological studies suggest that approximately 40-53% of SLE patients have chronic active disease, while 14-35% are relapsing-remitting, and 25-37% have periods of long-term quiescence [1-3]. Additionally, the overall natural history of SLE is that of high activity early in disease course, and gradual dissipation of disease activity over time [4, 5].

1.1.2 Current Treatment for Disease

SLE is a chronic disease with a limited repertoire of therapeutic options. Only hydroxychloroquine (HCQ), corticosteroids, salicylates, and (recently) belimumab are currently approved by the Food and Drug Administration (FDA) for the treatment of SLE [6]. Substantial literature documents the utility of HCQ in SLE. HCQ substantially decreases the flare rate in SLE, as well as decreasing damage accrual, improving survival, and improving pregnancy outcomes [7-9]. It is well tolerated with an excellent toxicity profile.

Barring contraindications, this drug clearly should be used in SLE patients as a standard of care. Nonetheless, HCQ alone is often inadequate to control disease during highly active phases, resulting in the addition of corticosteroid therapy. When corticosteroid dose requirements are excessive or inadequate, potentially toxic immunosuppressive agents such as methotrexate, azathioprine, and MMF are added to control active disease and reduce or eliminate steroid dependency. Such immunosuppressive therapies are non-FDA approved but widely used despite scarce clinical trial data to support their use [10], likely due to the severe and predictable toxicities of chronic corticosteroid therapy.

1.2 Summary of Pre-Clinical and Clinical Studies

1.2.1 Pre-Clinical Studies

MMF inhibits inducible inosine-5'-monophosphate dehydrogenase, resulting in depletion of guanosine nucleotides in T and B lymphocytes. Thus, both cellular and antibody-mediated immune responses are affected by MMF. While less well substantiated, MMF may also affect adhesion molecule expression and decrease the production of inducible nitric oxide by activated macrophages [11].

1.2.2 Clinical Studies

In regards to SLE, MMF was initially studied in the specific setting of proliferative lupus nephritis, and randomized clinical trials in that setting have demonstrated non-inferiority to cyclophosphamide as induction therapy [12, 13], as well as maintenance therapy for up to three years [14]. The role of MMF for lupus nephritis beyond the three-year time point is not known. Subsequently, numerous case reports and case series have reported efficacy of MMF in the treatment of hematological and dermatological manifestations of SLE [15], and a small, randomized, placebo-controlled cross-over trial has demonstrated efficacy with lupus arthritis [16]. Despite the lack of controlled clinical trials in extra-renal SLE, MMF is used widely in this setting, likely due to good tolerability and the clinical impression of effectiveness [17]. This impression of excellent tolerability compared to other immunosuppressants may be inaccurate. In the EXPLORER trial of rituximab in moderate to severe SLE, subjects on MMF had numerically higher rates of serious adverse events (16.7%) versus subjects on methotrexate (MTX) (9.3%) or azathioprine (AZA) (12.5%, p = NS [not significant]). Infectious serious adverse events (SAEs) were also numerically higher in the MMF-treated subjects (7.0%) compared to MTX (4.3%) or AZA (2.3%, p = NS) (Genentech, personal communication, July 2011). There is also evidence that MMF at 3000 mg/day, a standard dose for lupus nephritis that is also used in refractory extra-renal SLE, may have greater risk of infection than lower doses of MMF [18]. Without controlled studies, it is not possible to correctly interpret risks and benefits of immunosuppressant therapy, and differentiate increased risks of the study drug from background rates of disease complications. There is little incentive for pharmaceutical-sponsored research on this topic, as the drug is now available in generic form.

While acute disease activity such as active nephritis and arthritis appear to respond to MMF initiation, the clinical course of SLE is unpredictable and the long-term utility of major immunosuppressants to maintain control after acute periods of activity is unclear. Randomized clinical trial data do support the use of HCQ in preventing flare [7]; because of the highly variable clinical course of SLE, medications with greater potential toxicity such as MMF need rigorous study to determine what, if any, role they have in the maintenance of clinical quiescence in moderate or severe SLE. Apparent disease "control" on drugs such as MMF may represent spontaneous disease amelioration rather than drug-dependent disease suppression in many cases. Since HCQ, a well-tolerated, inexpensive drug with few side effects, is known to reduce substantially the risk of flares, an important question is whether long-term use of major immunosuppressant drugs such as MMF is necessary or effective in preventing flare-ups in the subset of SLE patients whose disease had been sufficiently severe to initiate MMF in the past. One retrospective study [19] found flare rates by British Isles Lupus Assessment Group index (BILAG) to be reduced in the first year of MMF treatment relative to the year prior to MMF, but they could not document sustained reduction in flare rate in subsequent years of MMF therapy. Obviously, prospective data is needed to determine the role of MMF as maintenance therapy in extra-renal SLE, and in lupus nephritis beyond two or three years of therapy.

1.3 Study Product Background

1.3.1 Current Licensing of Product

MMF is currently licensed to prevent rejection of solid organ transplants.

1.3.2 Other Diseases in Which Product Use Has Been Described

MMF has been used off label in myasthenia gravis, atopic dermatitis, idiopathic thrombocytopenic purpura, graft-versus-host disease, psoriasis, and a variety of rheumatic diseases including SLE, scleroderma, vasculitis, rheumatoid arthritis, inflammatory myopathy, and connective-tissue disease associated interstitial lung disease [20].

1.4 Known and Potential Risks and Benefits of Study Participation

Currently there are no standards on when to withdraw major immunosuppressive medications in SLE patients with long term controlled or quiescent disease. These decisions are made case-by-case, without evidence on the benefits and risks of stopping medication. This trial proposes to enroll subjects who would be clinically eligible to be withdrawn from medication based on reasonable standard of care and randomize this decision. There are risks both from continuation of the medication and from activation of the underlying disease. This study provides the opportunity for 50% of participants to withdraw from MMF and be intensely monitored for the following 48 weeks. Although most often well tolerated, MMF has well documented toxicities in the setting of solid organ transplantation. Long term use is associated with an increased risk of lymphoproliferative disease including malignant lymphoma (0.4-1.0%). Non-melanoma skin cancer is also increased (1.6-4.2%). It is a known

teratogen (pregnancy category D) and is currently under a risk evaluation and mitigation strategy (REMS) program (see Section 7.6.1, *Mycophenolate REMS Program*), and may interfere with the effectiveness of oral contraceptive pills. Bone marrow suppression is uncommon, but classically manifests as neutropenia and less frequently anemia (including pure red cell aplasia) or thrombocytopenia. Patients have increased risks of common and opportunistic infections, including progressive multifocal leukoencephalopathy (PML). Commonly reported side effects are difficult to differentiate from the side effects of concurrent therapy in the setting of solid organ transplantation, and include hypertension, peripheral edema, hypercholesterolemia, electrolyte abnormalities, abdominal upset including nausea and diarrhea, anxiety, and headache. Serious side effects have been reported as an increased risk of gastrointestinal hemorrhage (rare), anemia, leukopenia, severe neutropenic disorder (2-3.6%), and opportunistic infections [21].

These known drug toxicities of MMF need to be held in perspective against the significant potential for organ damage, mortality, and impaired daily function in SLE, and the predictably severe side effects of chronic moderate to high doses of corticosteroids and/or cyclophosphamide in cases of very severe disease.

MMF is known to be efficacious in the treatment of lupus nephritis [12-14], and a small randomized trial of MMF for lupus arthritis suggests it is useful in treating arthritis as well [16]. Otherwise, much literature in the form of case reports and case series suggest that MMF is efficacious for SLE skin disease, hematological disease, and a variety of other SLE manifestations [15]. In addition, MMF is thought possibly to have anti-fibrotic effects, which may further benefit SLE patients by inhibiting the vascular lesion of non-inflammatory endothelial hyperplasia seen in SLE (particularly in neuropsychiatric SLE) and the related condition antiphospholipid syndrome, and fibrotic damage to the kidney in the setting of lupus nephritis. Additionally, the purported effects of MMF on nitric oxide may improve endothelial dysfunction, which is widespread in SLE and is felt to be a precursor lesion to atherosclerosis [11]. Thus, there is reasonable and growing data to suggest MMF is beneficial in the acute control of SLE. What is not known, and a driving question of this study, is whether MMF should be continued chronically or stopped when SLE becomes clinically quiescent. This decision is based on the balance of the risks of chronic MMF versus the risks of SLE flare.

Active SLE is clearly associated with increased damage and mortality [22]. Thus, if MMF withdrawal results in significant deterioration of SLE control, these patients may be at risk for a more severe clinical course than patients who chronically maintain MMF therapy. A comparison of flare rates in SLE patients on and off MMF will be a key endpoint of this study, as will accrual of damage and excess corticosteroid exposure due to flare.

Based on the observational unpublished data from a subset of 49 patients in the Johns Hopkins Lupus Cohort who were on long term MMF for a minimum of one year (M. Petri, personal communication, October 2010), the probability of experiencing disease reactivation (described as at least one Systemic Lupus Erythematosus-Disease Activity Index [SLEDAI]-defined flare requiring additional treatment) by month 16 was estimated at 0.10 (95% confidence interval [CI] [0.02, 0.19]) for subjects remaining on MMF. This is compared to

total SLE population risks of flare approximating 0.8/year. However, we are selecting a population with prolonged clinical quiescence and the rates of flare in these specific circumstances are unknown.

1.5 Rationale for Study

There is a great need for information on which SLE patients can safely discontinue major immunosuppressants after a significant period of disease quiescence. Currently the "stopping point" for such drugs is unknown in a potentially serious disease such as SLE. However, the clinical course of SLE is unpredictable, and it is possible that significant numbers of subjects will tolerate discontinuation of MMF without flare, especially on a background of continued HCQ therapy. Continuation of MMF results in increased risks of lymphoproliferative disease, hematological derangements, and infections, including severe opportunistic infections. Discontinuation of MMF may lower the risk for significant infection, but most likely will increase to some degree the risk for SLE flare. These flares themselves may generally be mild and easily treated, favoring the risk/benefit ratio of staying off MMF despite a modest increased risk of flare. In some cases, a flare could be severe and require intensive corticosteroid and/or immunosuppressant therapy, along with impaired quality of life and physical function in the subjects for the duration of their flare and even with possible accrual of damage related to flare or its therapy. To minimize the risk of severe, damage-accruing flare, we will exclude patients with severe renal dysfunction and history of severe neuropsychiatric SLE. This study will examine the potential for the identification of low risk patients for discontinuation of this therapeutic agent, both on clinical and demographic grounds, and by biological markers of disease activity.

This study provides an opportunity to address a relevant clinical question, has the potential to impact SLE clinical care, and provides longitudinal blood specimens from well-characterized patients to potentially help identify biomarkers or explain mechanisms of disease flare. The goal of the trial is to obtain data comparing risks and benefits of continuing versus withdrawing MMF. The hope is that the study will provide physicians with some rationale for medical decision making. It is important to note that in practice the decision to withdraw from MMF is multifactorial; one has to weigh the increased risk of flare against decreased risk of lymphoproliferative disease, hematological derangements, and infections as well as the impact of chronic medication use on quality of life and plans for pregnancy. How the risks and benefits should be weighed is highly individual. The primary analysis, however, is designed to maximize the information available for decision making (Section 8.3.2.1, *Primary Endpoint Analysis*). Depending on the actual effect estimates, estimated confidence level, and level of acceptable risk, the results from this trial may or may not facilitate a decision regarding withdrawal for an individual patient, but should provide sufficient information for some clinical cases. Furthermore, the data will be of value for assessing feasibility and designing a larger more definitive trial, if such a trial were to be launched. In addition, this trial offers an opportunity to ask very practical questions about how results of mechanistic analyses might also guide clinical care, as well as core questions about the basis of the autoimmune process and the mechanism of action of MMF in SLE.

The primary outcome index to measure flare in this study is the Safety of Estrogens in Lupus Erythematosus National Assessment SLE disease activity (SELENA-SLEDAI) flare index. Multiple disease activity indices have been developed and successfully indicate disease activity in SLE; the most commonly used have been various versions of the SLEDAI and the BILAG. Superiority of one index over another in the setting of randomized clinical trials has not been clarified [23]. The SELENA-SLEDAI flare index was successfully used in the Combined Oral Contraceptives in Women with Systemic Lupus trial [24] and The Effect of Combined Estrogen and Progesterone Hormone Replacement Therapy on Disease Activity in Systemic Lupus: A Randomized Trial [25]. The two studies are known as the SELENA studies. Both of these studies enrolled quiet or minimally active SLE patients and tracked their clinical course for flare. Thus, the SLE population targeted for this study resembles the SELENA studies in which this instrument was successful. In contrast, the BILAG has been used in clinical trials in which flaring SLE patients are enrolled to receive a therapeutic agent and has successfully measured improvement. More recently, a combined index using the SLEDAI, the BILAG, and a physician's global assessment (SLE Responder Index) was successfully used in the phase III studies of belimumab in SLE [6]. This study showed clinical benefit with belimumab whether the combined index, the SLEDAI alone, or the BILAG alone were used. Thus, showing improvement in SLE randomized clinical trials appears feasible with a variety of indices.

However, both instruments have limitations when measuring flare. False positive B flares are common with the BILAG instrument and complicate its use and interpretation [26, 27]. It is also very lengthy and time-consuming relative to the SELENA-SLEDAI. However, mild or moderate flares by SELENA-SLEDAI do not always correlate with a need to change therapy and thus may not represent clinically significant change. Previous literature suggests that approximately 40% of all SELENA-SLEDAI flares (mild, moderate, or severe) require treatment [28]. Thus, to increase specificity of clinically significant flare in this study, we have required dually that a SELENA-SLEDAI-defined flare and substantial increase or re-institution of SLE medication is required.

The BILAG will be used as a secondary outcome instrument to assist in comparison of results to other studies using the BILAG, and to assist in descriptions of types and severities of disease activity, which occur in the study.

1.5.1 Rationale for the Inclusion Criteria

Inclusion criteria require patients to have been clinically stable/quiescent for a sustained time period, such that by standard care principles they could consider discontinuation of MMF. The longer sustained period of MMF treatment in the setting of renal involvement reflects the randomized clinical data indicating benefit from MMF maintenance therapy for two or more years. Serological activity will not prohibit entry into the trial, as the predictive capacity of serologies for SLE flare are questionable in the setting of prolonged clinical quiescence [29]. Because we do not wish to have serological activity prohibit trial enrollment, a modification of the SLEDAI, the m-SLEDAI, will be used at screening to determine eligibility. The m-SLEDAI is identical to the SLEDAI except for the exclusion of double-stranded DNA antibodies (anti-dsDNA) and hypocomplementemia [1]. An m-SLEDAI score of < 4 at

screening will allow enrollment in the trial. Minor/transient or nonspecific clinical symptoms are allowed at entry (see Appendix A, *Definition of Mild Disease)*, as major immunosuppressant therapy would not be warranted for such symptoms. If the subject is on prednisone therapy for SLE, the dose must have been ≤ 10 mg/day (or equivalent dose of alternative corticosteroid) for 12 weeks and stable for 4 weeks prior to randomization as a reflection that the subject has been clinically quiescent (see Section 5.5.2, *Prednisone (or Equivalent)* for the definition of "stable dose").

1.5.2 Rationale for the Exclusion Criteria

Subjects will be excluded if their SLE has substantial activity within six to twelve months, as the clinical question posed in this study is whether MMF is helpful as maintenance therapy in clinically quiescent SLE. Also, patients with high risk for organ damage will be excluded as the cost of relapse in very severe SLE may be too high to offset the risk of continuing MMF. Specifically, patients with substantial proteinuria (> 1.0 on spot protein/creatinine ratio) and thus may still have active nephritis will be excluded, as well as patients with relatively recent histories of severe neuropsychiatric SLE (within 12 months). Subjects requiring more than 10 mg/day of prednisone (or equivalent steroid) in the 12 weeks prior or more than 25 mg/day in the 24 weeks prior to screening due to SLE activity are excluded as they have not had prolonged clinical quiescence. Subjects with chronic renal insufficiency (serum creatinine above 2.0 mg/dL at screening) will be excluded, because a renal flare in subjects with tenuous renal function may result in end stage renal disease, and thus affects risk/benefit ratio of stopping MMF. In addition, toxicity from MMF is more likely with advanced renal insufficiency. Concurrent therapy with major immunosuppressive agents (MTX, leflunomide, azathioprine, 6-mercaptopurine, calcineurin inhibitors or anti-tumor necrosis factor agents), intravenous (IV) immunoglobulin or plasmapheresis within 12 weeks of randomization is exclusionary as the concurrent therapy may affect flare rates in the study population. Subjects treated with cyclophosphamide within 24 weeks of randomization are excluded, as use of cyclophosphamide would indicate severe disease activity in the recent past. B cell depleting agents such as anti-CD20 are excluded for two calendar years prior to randomization, because they have been reported to have prolonged benefit in some patients and also may affect the nature of B cell populations in mechanistic studies [30]. Belimumab must be discontinued for at least 24 weeks prior to randomization, because modification of B cell populations by belimumab may affect risk of flare when MMF is withdrawn. Patients who have had solid organ transplantations are excluded, as their immunosuppressive regimen must be maintained for graft survival. Patients who have had stem cell transplantation are by definition very severe SLE patients who are best managed outside of this clinical trial. Active co-morbid conditions likely to require systemic steroid therapy will be exclusionary, because these patients may have multifactorial and thus misleading total corticosteroid requirements, which is a secondary outcome measure in this study. Subjects with major infectious issues are excluded, because discontinuation of MMF would be the standard of care in quiescent SLE patients with infectious complications.

1.5.3 Rationale for the MMF Withdrawal Arm

The MMF withdrawal arm will provide effect estimates of discontinuing MMF in SLE subjects who had previously had prolonged clinical stability while taking MMF. This will include disease reactivation as described by the primary endpoint, need for additional medications to control SLE, and impact on quality of life. Subjects will be randomized 1:1 to continue or withdraw MMF in an unblinded manner. Subjects who enter the trial will have been maintained on MMF 1000-3000 mg/day because these are common dose ranges used to treat SLE. Those subjects who are randomized to MMF withdrawal will have a standardized taper over three months (see Section 3.1, *Description of Study Design*) so that all MMF withdrawal subjects are off MMF at Week 12. There is no evidence-based literature to support a three-month taper versus abrupt discontinuation of MMF in this setting. However, the rationale of taper would be that partial withdrawal of the drug each month may unmask smoldering SLE at a mild phase, if the subject is dependent on the MMF for SLE control. Thus, the intent of taper is to decrease risk of more severe flare to the subjects. The particular taper schedule will be determined by the baseline MMF dose, and MMF will be decreased in increments of 500-1000 mg at four week intervals. Although different starting doses will result in more rapid tapers for some subjects, the 12-week taper will allow easy comparison of subjects at set time points after study entry. Additionally, all subjects will be required to be on an anti-malarial agent as these drugs are standard of care for SLE. Anti-malarials have been shown to help prevent flare with a very favorable safety profile, and may be protective against flare as the major immunosuppressant agent is discontinued. After week 36 of the study (six months after MMF discontinuation) subjects may also taper glucocorticoids if felt appropriate by clinical status per the investigator. This is because standard of care practice would be to taper steroids if disease is quiescent, as steroids can have long term health hazards in SLE including osteoporosis, avascular necrosis, and potentially accelerated atherosclerosis. SLE activity will be assessed monthly until Week 24, every other month until Week 48, and at the primary endpoint at Week 60.

1.5.4 Rationale for the Continued MMF Treatment Arm

Subjects randomized to continue MMF represent the control arm in this study. Levels of disease activity among controls will be compared to those observed for subjects withdrawn from MMF. Additionally, MMF has potential toxicities including infectious complications and hematological derangements. Our control group will allow comparison of disease complications and drug toxicities on and off MMF in the setting of quiescent SLE. Subjects in the MMF treatment arm will continue their baseline level of MMF unless MMF-related toxicity occurs and will similarly be concurrently treated with anti-malarial agents. Parallel ability to taper corticosteroids after 36 weeks in stable patients will keep non-MMF variables constant between groups and be consonant with good clinical practice. Ability to titrate low dose prednisone downward will also be informative when examining cumulative steroid exposures between MMF and withdrawal arms, since corticosteroids will go up with flare but also go down with lack of flare.

1.5.5 Rationale for Mechanistic Studies

Mechanistic studies will focus on several issues. First, are there clinical or immunological baseline predictors to inform the practitioner in which patients it may be safest to discontinue MMF in quiescent SLE? Multiple potential markers will be examined for this purpose, including demographic data, disease duration, serological activity, baseline autoantibody profile, cytokine characteristics, and gene expression patterns by microarray. We will also utilize the cytokine and gene expression information to examine, in part, the immunologic and anti-inflammatory effects of MMF in SLE patients to explore potential mechanisms of action of MMF in SLE.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Primary Objective

The primary objective of this trial is to describe the effect of withdrawal from MMF on risk of clinically significant disease reactivation in quiescent SLE patients who have been on long-term MMF therapy.

2.2 Secondary Objectives

2.2.1 Secondary Disease Activity Objectives

- To describe the effect of MMF withdrawal on measures of disease activity (including time to flare and severity of flare) in aggregate and in subgroups defined by demographics, disease manifestation (renal disease/extra-renal disease) and by baseline MMF dosing group (< 2000 mg per day / ≥ 2000 mg per day).
- To describe the effect of MMF withdrawal on damage accrual, needed medications, and subject quality of life.
- To describe the effect of MMF withdrawal on time to recovery from clinically significant disease reactivation and needed medications in the subgroup defined by disease reactivation during follow-up.

2.2.2 Secondary Safety Objectives

- To describe the effect of MMF withdrawal on measures of safety and drug related toxicities.

2.2.3 Secondary Mechanistic Objectives

- To identify baseline autoantibody, cytokine/chemokine, and gene expression characteristics that are associated with an increased risk of SLE flare.

- To identify autoantibody, cytokine/chemokine, and gene expression characteristics present at Week 20 or changes in those characteristics from baseline to Week 20 that are associated with an increased risk of flare.
- To identify autoantibody, cytokine/chemokine and gene expression changes associated with withdrawal of MMF apart from flare.

Markers of particular interest include:

- Serologic markers: dsDNA antibodies, C3 levels, C4 levels, and antibodies toward Sm, ribonucleoprotein (RNP), SSA/Ro, & SSB/La;
- Presence/absence of a "B cell fingerprint" assessed by gene expression profiling;
- Presence/absence of an "Interferon-α biosignature" assessed by gene expression profiling;
- Levels of cytokines or chemokines associated with the interferon-α and γ pathway (measured by bead based assays or ELISA).

3 STUDY DESIGN

3.1 Description of Study Design

This is a Phase II, unblinded, randomized controlled trial of MMF withdrawal in patients with clinically quiescent SLE on longstanding MMF therapy (1000-3000 mg/day for at least one year in the case of extra-renal indication for MMF or for at least two years in the case of renal indications for MMF), who have been on stable doses of MMF, hydroxychloroquine or chloroquine, and corticosteroids (if applicable) for at least 12 weeks prior to randomization, and have an m-SLEDAI of < 4 at screening.

One hundred twenty eligible subjects will be randomized in a 1:1 ratio to one of the two study treatment arms below.

- MMF maintenance arm: These subjects will continue MMF treatment (1000-3000 mg/day) for the rest of their study participation (up to Week 60).
  - Baseline MMF dose = 3000 mg/day
    - Up to 60 weeks on 3000mg/day MMF
  - Baseline MMF dose = 2500 mg/day to 2750 mg/day
    - Up to 60 weeks on 2500mg/day MMF
  - Baseline MMF dose = 2000 mg/day to 2250 mg/day
    - Up to 60 weeks on 2000mg/day MMF
  - Baseline MMF dose = 1500 mg/day to 1750 mg/day
    - Up to 60 weeks on 1500mg/day MMF
  - Baseline MMF dose = 1000 mg/day to 1250 mg/day
    - Up to 60 weeks on 1000mg/day MMF

- MMF withdrawal arm: These subjects will taper off MMF over 12 weeks and remain off MMF for the rest of their study participation (up to Week 60 or until the primary endpoint of disease reactivation is met, whichever comes first).
    - Baseline MMF dose = 3000 mg/day
        - Four weeks on 1000 mg MMF twice a day (BID)
        - Four weeks on 1000mg (morning) & 500mg MMF (evening) QD
        - Four weeks on 500 mg MMF BID
        - Up to 48 weeks on no MMF
    - Baseline MMF dose = 2500 mg/day to 2750 mg/day
        - Four weeks on 1000mg MMF BID
        - Four weeks on 1000mg (morning) & 500mg (evening) MMF QD
        - Four weeks on 500 mg MMF BID
        - Up to 48 weeks on no MMF
    - Baseline MMF dose = 2000 mg/day to 2250 mg/day
        - Four weeks on 1000mg (morning) & 500mg (evening) MMF QD
        - Four weeks on 500mg MMF BID
        - Four weeks on 500 mg MMF QD
        - Up to 48 weeks on no MMF
    - Baseline MMF dose = 1500 mg/day to 1750 mg/day
        - Four weeks on 500mg MMF BID
        - Four weeks on 500 mg MMF BID
        - Four weeks on 500 mg MMF QD
        - Up to 48 weeks on no MMF
    - Baseline MMF dose = 1000 mg/day to 1250 mg/day
        - Four weeks on 500 mg MMF BID
        - Four weeks on 500 mg MMF QD
        - Four weeks on 500 mg MMF QD
        - Up to 48 weeks on no MMF

Concurrent therapy with anti-malarial agents (hydroxychloroquine or chloroquine) is required and low doses of glucocorticoids are permitted per Section 5.5, *Concurrent Medications*.

Subject visits to assess endpoints will occur every 4 weeks from Day 0 through Week 24 and then at Weeks 32, 40, 48, and 60. As disease flares occur, subjects will be brought in for an urgent flare or endpoint visit to document symptoms, collect biological samples, and determine whether primary endpoint has been met.

Accrual of subjects is expected to take 36 months.

3.1.1 Stratification, Randomization, and Blinding

Subjects will be randomized in a 1:1 ratio to either continue or withdraw from MMF. Given the relatively small number of subjects expected per site and the importance of ensuring balance on key disease-defining characteristics an adaptive procedure based on Frane [31] minimization concepts will be used to increase the likelihood of balance in treatment arms. The baseline characteristics that will be considered are study site, disease manifestation (renal disease, which will include subjects who presently have renal disease as well as those who have had renal manifestations in the past, versus non-renal disease, which will include subjects who have never had renal disease), and baseline MMF dose (< 2000 mg per day versus ≥ 2000 mg per day).

Subjects and investigational staff responsible for clinical care will not be blinded to the randomized treatment assignment. The cumbersome scheme that would have been needed to maintain the blind required that subjects take different numbers of pills from multiple bottles. Implementation of the scheme would have placed undue burden on the subjects and had a high potential for dosing errors. Knowledge of the assigned treatment also has the advantage of facilitating rapid response in the event of a serious flare.

Unblinding the trial has the potential to impact the estimated rates of disease reactivation, because the definition of this endpoint includes subjective elements. In order to assess the magnitude and direction of the impact on these estimates, a second blinded clinician will also conduct the physical exams scheduled for Weeks 8, 12, 16, and 20. If at Week 20, the subject has a mild/moderate or severe SELENA-SLEDAI flare, the blinded physician should also participate in the Week 24 visit. These time points were selected, because we anticipate that most flares will occur early in the study. The blinded physician will also receive any additional blinded subject records needed to complete the SELENA-SLEDAI and a questionnaire about the need to change medications. This information will be used to compare the rate of disease reactivation among blinded and unblinded assessors.

Statistical and project staff at the SACCC and the DAIT Medical Monitor and Project Manager will be unblinded to individual treatment assignments as well.

3.1.1.1 Subject Completion and Replacement

Accrual will continue until 120 eligible subjects either initiate the taper of MMF or begin their ALE06-provided MMF. A subject is considered to have completed the study if he/she has completed the Week 60 visit.

3.2 Description of Primary Endpoint

The primary endpoint is the probability in each arm of experiencing clinically significant disease reactivation by 60 weeks after randomization. The 60-week time point is to allow 48 weeks of observation off MMF and minimize dropout, which is likely to occur as the trial lengthens. Clinically significant SLE reactivation requires both:

1) A SELENA-SLEDAI*-defined mild/moderate or severe flare
   and
2) Increased immunosuppressive therapy on a sustained basis as defined by one of the following criteria:
   a. Sustained activity: Subject has significant prolonged SLE flare requiring steroid increase/burst to ≥ 15 mg/day prednisone (or its equivalent) for more than four weeks.
   b. Frequent relapsing/remitting:
      i. Subject flares requiring an increase/burst of steroids and is successfully tapered to < 15 mg/day within four weeks, but this occurs on two or more occasions, or
      ii. Intra-articular, intra-muscular or IV steroids, on more than one occasion.
   c. Clinical activity of sufficient severity to warrant resumption of or an increased dose of MMF or addition of other major immunosuppressive including azathioprine or methotrexate. Regardless of steroid use, if the investigator observes disease activity of sufficient severity to warrant resumption, addition or increase in dosage of major immunosuppressant in the setting of a SELENA-SLEDAI*-defined flare, subject has met the primary endpoint.

**ALE06 will typically use a spot urine protein:creatinine ratio rather than a 24-hour urine assessment for the SELENA-SLEDAI. However, if indicated, results from a 24-hour urine collection may be used.*

3.3 Description of Secondary Endpoints

3.3.1 Secondary Disease Activity Endpoints

- Time from Day 0 to clinically significant disease reactivation (as defined in Section 3.2, *Description of Primary Endpoint*). The time of clinically significant disease reactivation is defined as the date of the first SELENA-SLEDAI* assessment that meets (or goes on to meet) the criteria in Section 3.2, *Description of Primary Endpoint*.
- The probability of experiencing any SELENA-SLEDAI* flare and the probability of experiencing any severe SELENA-SLEDAI* flare by Week 60, in aggregate and within subgroups defined by disease manifestation (renal disease/extra-renal disease) and by baseline MMF dosing group (<2000 mg per day / ≥ 2000 mg per day).
- Time from initiation of withdrawal to first SELENA-SLEDAI* flare and time to first severe SELENA-SLEDAI* flare.
- The probability of experiencing any BILAG* A flare by Week 60.
- Proportion of subjects in the renal subgroup with BILAG* Renal A flare by Week 60

- Change in Systemic Lupus International Collaborating Clinics/American College of Rheumatology Disease Damage Index for Systemic Lupus Erythematosus (SLICC/DI)* from baseline to Weeks 24, 48, and 60.
- The probability of adding aggressive adjunctive therapy to MMF (including IV immunoglobulin or rituximab) or change in MMF therapy to cytotoxic drug (e.g., cyclophosphamide) due to flare.
- Cumulative systemic steroid dose (PO, IV, IM) at Week 60.
- Change in Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score from baseline to Weeks 24, 48, and 60.
- Change in SF-36® Physical Functioning (PF) and Physical Component Summary (PCS) domains from baseline to Weeks 24, 48, and 60.
- Change in Lupus Quality of Life (QoL)-US© from baseline to Weeks 24, 48, and 60.
- The following endpoints will be assessed to describe the ability of subjects to recover from clinically significant disease reactivation:
    - Time from clinically significant disease reactivation to improvement in BILAG* from maximum level during flare;
    - Time from clinically significant disease reactivation to recovery to baseline BILAG* scores or BILAG* C, whichever is worse;
    - Cumulative excess systemic steroid dose from time of clinically significant disease reactivation to return to pre-flare dose or end of trial participation;
    - Time from clinically significant disease reactivation to return to pre-flare steroid dose.

**ALE06 will typically use a spot urine protein:creatinine ratio rather than a 24-hour urine assessment for the BILAG, SELENA-SLEDAI, and SLICC/DI. However, if indicated, results from a 24-hour urine collection may be used.*

3.3.2 Secondary Safety Endpoints

- All Grade 3-5 adverse events, as defined by the National Cancer Institute (NCI) – Common Terminology Criteria for Adverse Events (CTCAE) system, which are defined as possibly, probably, or definitely related to SLE.
- All Grade 3-5 adverse events, as defined by the NCI-CTCAE system, which are defined as possibly, probably, or definitely related to MMF.
- All NCI-CTCAE Grade 3-5 adverse events.
- All serious adverse events.
- All infection related events.
- All malignancies.
- All NCI-CTCAE Grade 3-5 hematological events.
- Mortality possibly, probably, or definitely related to SLE.
- All-cause mortality, defined as any death occurring at any time after randomization.

3.3.3 Secondary Mechanistic Assessments

- Levels of C3, C4, and anti-dsDNA at Baseline, Week 20, at the time of first flare, and immediately prior to first flare.

- Changes in levels of C3, C4, and anti-dsDNA from Baseline to Week 20, from Baseline to the time of first flare, and from Baseline to the time point immediately prior to first flare.
- Levels of antibodies to Sm, RNP, SSA/Ro, and SSB/La at Baseline.
- Changes in levels of antibodies to Sm, RNP, SSA/Ro, and SSB/La from Baseline to Week 60.
- Levels of interferon-regulated chemokines at Baseline, Week 20, at the time of first flare, and at time points immediately prior to and after first flare.
- Changes in levels of interferon-regulated chemokines from Baseline to Week 20, from Baseline to the time of first flare, and from Baseline to the time points immediately prior to and after first flare.
- Levels of inflammatory and other cytokines at Baseline, Week 20, at the time of first flare and at time points immediately prior to and after first flare.
- Changes in levels of inflammatory and other cytokines at Baseline, Week 20, at the time of first flare and at time points immediately prior to and after first flare.
- Presence/Absence of gene expression patterns (e.g. fingerprint or signature) at Baseline, Week 20, at time of first flare, and at time points immediately prior to and after first flare.
- Change in gene expression patterns from Baseline to Week 20, from Baseline to the time of first flare, and from Baseline to the time points immediately prior to and after first flare.

4 SELECTION OF SUBJECTS

Written informed consent must be obtained prior to the subject undergoing any study-related procedure, including screening tests and washout periods for prohibited medications, when applicable.

4.1 Inclusion Criteria

Subjects who meet all of the following criteria are eligible for enrollment into the study:

1. Able and willing to give written informed consent and comply with requirements of the study.
2. Age 18 - 70 years, inclusive, at randomization.
3. Diagnosis of SLE, per ACR criteria [32].
4. m-SLEDAI score < 4 at screening visit (SLEDAI score without serologies).
5. Physician Global Assessment (0-3) score of 1 or less at screening visit.
6. On a stable dose of MMF (1000-3000 mg/day) for at least 12 weeks prior to randomization.
7. Total duration of stable or decreasing MMF therapy must be at least
    a. two years for subjects initiating MMF for renal indications (with or without concurrent extra-renal manifestations), or
    b. one year for subjects initiating MMF for extra-renal indications.
8. If the subject is on prednisone or other corticosteroid, the following criteria must be met:

   a. the dose may not exceed 10 mg/day (or its equivalent) for the 12 weeks prior to randomization. However, temporary (up to 4 total days) increases, not to exceed 20mg/day, are permitted.
   b. the dose must be held stable for the four weeks prior to randomization (no temporary increases within 4 weeks of randomization are permitted).
9. If the subject has a history of B cell depleting therapy within the past 3 years, presence of CD19 positive cells must be documented within 12 weeks prior to screening.
10. On maintenance HCQ or chloroquine at a stable dose for at least 12 weeks prior to randomization.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria are disqualified from enrollment in the study:

1. A history of life-threatening neuropsychiatric SLE within 1 calendar year prior to randomization.
2. Any of the following laboratory abnormalities at the screening visit:
   a. Proteinuria as defined by a spot protein/creatinine ratio > 1.0 mg/mg;
   b. Serum creatinine > 2.0 mg/dL (equivalent to 177.2 μmol/L);
   c. Transaminases > 2.5x the upper limit of normal (ULN);
   d. Hemoglobin < 9 g/dL, unless the subject has documented hemoglobinopathy;
   e. White blood count (WBC) < 2000/mm^3 (equivalent to < 2 x10^9/L);
   f. Neutrophils < 1000/mm^3 (equivalent to < 1 x10^9/L);
   g. Platelet count < 75,000/mm^3 (equivalent to < 75 x 10^9/L).
3. Prednisone > 25 mg/day (or its equivalent) within 24 weeks prior to randomization for lupus activity.
4. Concomitant immunosuppressants including but not limited to azathioprine, methotrexate, 6-mercaptopurine, leflunomide, calcineurin inhibitors, anti-tumor necrosis factor agents within 12 weeks prior to randomization.
5. Plasmapheresis or IV immunoglobulin within 12 weeks prior to randomization.
6. Cyclophosphamide therapy within 24 weeks prior to randomization.
7. Concomitant therapy with belimumab within 24 weeks prior to randomization.
8. B cell depleting therapy within two calendar years of randomization.
9. Experimental therapy within the 24 weeks, or five half-lives of the agent, whichever is longer, prior to randomization.
10. Solid organ or stem cell transplantation.
11. Identified definitive diagnosis of another autoimmune disease that may require immunosuppression for treatment, including but not limited to: rheumatoid arthritis, scleroderma, primary Sjogren's syndrome, primary vasculitis, psoriasis, multiple sclerosis, ankylosing spondylitis, and inflammatory bowel disease.
12. Chronic infections including, but not limited to, human immunodeficiency virus (HIV), active tuberculosis (TB, currently receiving therapy), hepatitis B or hepatitis C, or latent systemic fungal infection.
13. At or within 12 weeks of screening,
    - history of or current positive purified protein derivative (PPD) (> 5 mm induration regardless of prior Bacillus Calmette-Guérin (BCG) vaccine

administration) or positive QuantiFERON unless documentation exists of completion of at least one month of prophylaxis for latent TB or completed treatment for active TB
- an indeterminate QuantiFERON® unless followed by a subsequent negative PPD or negative QuantiFERON®.

14. History of malignancy within the last five years, except for resected basal or squamous cell carcinoma, treated cervical dysplasia, or treated in situ cervical cancer Grade I.
15. Pregnant or lactating, or intention to pursue pregnancy within three months after the completion of the study.
16. Unable or unwilling to use reliable methods of contraception, as outlined in the Mycophenolate REMS brochure for health care providers, from four weeks prior to 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 L.
17. Drug or alcohol abuse within one calendar year of randomization.
18. Other medical or psychiatric conditions that the investigator feels would place the subject at special risk by participation in this protocol.

4.2.1 Co-enrollment Guidelines

While participating in ALE06, subjects may not be in another clinical trial, but may be in observational registries or cohorts as long as the total combined volume of blood to be drawn does not exceed the NIH limit and objectives do not confound the current study.

4.3 Strategies for Recruitment and Retention

In most cases, subjects with mild or quiescent disease (see Appendix A, *Definition of Mild Disease)* will be recruited from the academic clinical practices of participating rheumatologists who have large SLE populations and are experienced in the use of disease activity instruments in SLE. Advertising via local and national community resources could also be considered.

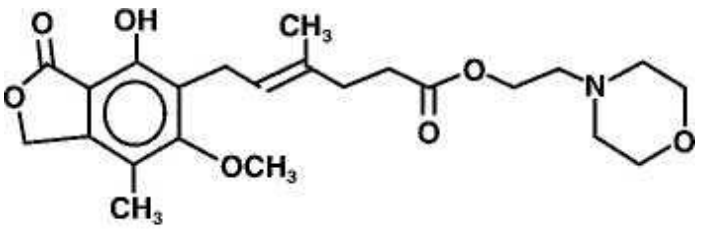
5 TREATMENT OF SUBJECTS

5.1 Description of Study Product

5.1.1 Product Description

MMF is the 2-morpholinoethyl ester of mycophenolic acid, an immunosuppressive agent, and inosine monophosphate dehydrogenase 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. It has molecular formula of $C_{23}H_{31}NO_7$, a molecular weight of 433.50, and the following structural formula.



5.1.2 Packaging and Labeling of Study Product

MMF will be purchased from Teva Pharmaceutical Industries, Ltd., labeled and rebottled by Eminent Services Corporation, and distributed by sites to all subjects as required per arm.

5.1.3 Storage and Handling of Study Product

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

ALE06 will utilize the USP Controlled Room Temperature Guidelines (section 10.30.60) and any excursions from the 15° to 30°C (59° to 86°F) range specified therein will be reported to the study sponsor [33].

As part of the trial, we will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all trial drugs in accordance with Title 21 CFR Parts 312.57 and 312.62.

5.2 Dosage Regimen

Subjects will enter the trial on 1000-3000 mg/day of MMF and will be randomized to remain on MMF treatment or to be tapered off MMF within 12 weeks as described in Section 3.1, *Description of Study Design*.

5.3 Administration of Study Product

Subjects on the MMF maintenance arm will receive a new supply of MMF at each study visit from Baseline through Week 48.

Subjects on the MMF withdrawal arm will receive a new supply of MMF at each study visit from Baseline through Week 8.

For additional information on criteria for withholding or discontinuing study product, see Section 5.4, *Prevention and Management of Toxicity for MMF*.

5.3.1 Administration of Study Product in Response to SLE Reactivation

For subjects who experience clinically significant SLE reactivation (see Section 3.2 *Description of the Primary Endpoint*) before Week 60, the treatment should be guided by the following and the treating investigator's medical judgment:

- If the flare seems likely to respond to a burst of prednisone alone, the subject may continue on ALE06-provided MMF and the appropriate prednisone dose should be prescribed. If the subject has been withdrawn from MMF and the flare is likely to respond to a steroid burst alone, the appropriate steroid dose may be prescribed without additional immunosuppression.

- If the flare is not likely to respond to a burst of prednisone alone, then:

    - if the subject is taking MMF < 3000 mg/day, the subject will discontinue ALE06-provided study drug, and the subject should be prescribed MMF at a higher dose than what (s)he is currently taking. Other alternative or additional immunosuppressive therapy per investigator's discretion may be used. An appropriate steroid taper may be prescribed.
    - if the subject is currently taking MMF 3000 mg/day and the flare is so severe that either cyclophosphamide or adjunctive therapy plus MMF would be used, the subject will discontinue ALE06-provided study drug and the site principal investigator (PI) will prescribe immunosuppression as indicated. As guidance, BILAG* A flares in Renal, Neuropsychiatric, or Hematological domains may represent such severe flares.

See Section 5.10, *Treatment Discontinuation and Subject Withdrawal* for additional information.

5.4 Prevention and Management of Toxicity for MMF

Subjects will be monitored for potential toxicities of MMF at all study visits scheduled through Week 60.

5.4.1 Malignancy

Increased risk of lymphoproliferative disease and non-melanoma skin cancers will be addressed by the physical examinations conducted at each visit. If evidence of lymphoproliferative disease emerges, work up will be guided by the institution's standard of care requirements. If malignancy (other than skin cancers described below) is diagnosed, the study drug will be discontinued and the subject will be treated according to standard of care per institutional requirements. If new non-melanoma skin cancer is found and fully treatable with local procedures, the subject may continue in the trial as planned based on investigator discretion.

5.4.2 Hematological Abnormalities

To monitor potential hematological toxicity, the subjects will have a complete blood count at each visit. If 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) develop without another more likely explanation and persist after a repeat check in one week, then study drug will be held for one week and the test repeated. Study drug may be held up to two weeks while the abnormality is monitored weekly for recovery. If recovery occurs then study drug can be resumed. Otherwise, refer to the guidelines in Section 5.10.1, *Study Treatment Discontinuation* in the event of toxicity. If subjects have symptomatic complications from the hematological derangements, this should be treated according to standard of care per institutional requirements.

5.4.3 Hepatic Abnormalities

Liver function tests will be checked every 8 to 12 weeks for signs of hepatic toxicity. If transaminases exceed 3x ULN and other more likely causes are not identified, then study drug will be held for up to two weeks, and the abnormality followed weekly for resolution. Should resolution occur within 14 days, the study drug may be resumed. Otherwise, refer to the guidelines in Section 5.10.1, *Study Treatment Discontinuation* in the event of toxicity.

5.4.4 Infections

Both common and opportunistic infections have been described in subjects on MMF. Subjects will be followed closely for signs of infection at study visits, and between visits if needed. Assessment and treatment for infection will be guided by standard of care per institutional requirements. In the setting of infection, study drug may be withheld based on institutional practices or investigator judgment, for up to two weeks and then resumed at scheduled dose. Otherwise, refer to the guidelines in Section 5.10.1, *Study Treatment Discontinuation* in the event of toxicity. Pneumocystis carinii pneumonia prophylaxis medications may be used based on institutional practice to lower the risk of this specific opportunistic infection, but is not mandated by the protocol.

5.4.5 Gastrointestinal Abnormalities

Gastrointestinal side effects including nausea and diarrhea may occur with MMF use. If these symptoms exacerbate without other likely explanation, study drug may be withheld for up to two weeks and resumed at the scheduled dose. Otherwise, refer to the guidelines in Section 5.10.1, *Study Treatment Discontinuation* in the event of toxicity.

5.4.6 Reproductive Risks

Women on MMF and of childbearing potential will have a routine pregnancy test at screening, Week 12, 24, 40, and 60, and additionally as clinically indicated. Should pregnancy occur, study treatment would be discontinued immediately, study visits will continue as scheduled except for study drug, and the pregnancy will be followed per Section

7.6, *Pregnancy Reporting.* Appropriate referrals should be made for counseling on fetal effects of study drug. The pregnancy should be reported to the Mycophenolate Pregnancy Registry which is a part of the MMF REMS program.

Male subjects and female partners capable of becoming pregnant are encouraged to use a contraceptive barrier method during the study.

5.5 Concurrent Medications

5.5.1 Anti-malarial Agents

Subjects will be on concurrent anti-malarial agents (hydroxychloroquine or chloroquine). 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 [7, 8]. Even lupus nephritis outcomes appear improved on a background of hydroxychloroquine therapy [34].

5.5.2 Prednisone (or Equivalent)

Once the subject is randomized into the trial, the prednisone (or other corticosteroid) dose must be stable through Week 36 (24 weeks following protocol taper of MMF), in the absence of flares as described in Section 3.2, *Description of Primary Endpoin*t. Further taper of prednisone after that point is by the investigator's discretion based on the subject's clinical status.

A stable dose is defined as maintenance of the baseline dose, which must be ≤ 10 mg prednisone/day (or equivalent dose of an alternate corticosteroid). However, to accommodate the occasional use of extra corticosteroids by patients for reasons not associated with SLE flares, increases of up to 20 mg/day that are decreased back to the baseline dose within 4 days are permitted, but not on more than 2 occasions during the study. These short increases in dose may not be accompanied by a documented flare.

For subjects taking prednisone (or equivalent) every other day (QOD), to calculate their daily dose (per the requirements above), halve their QOD dose.

5.6 Prohibited Medications

All subjects are to have access to any care deemed medically necessary, but administration of the following medications, for the purposes of this study, are prohibited, and will be considered major protocol deviations unless subject has met primary endpoint as described in Section 3.2, *Description of Primary Endpoint*:

- Immunosuppressant agents are prohibited except for glucocorticoids (as described in Section 3.2, *Description of Primary Endpoint*), hydroxychloroquine/chloroquine and MMF for subjects in the MMF maintenance arm and for subjects in the MMF withdrawal arm during the tapering period.

- Prohibited immunosuppressant agents include, but are not limited to, those referenced in Section 4.2, *Exclusion Criteria*: azathioprine, methotrexate, 6-mercaptopurine, leflunomide, calcineurin inhibitors, anti-tumor necrosis factor agents, plasmapheresis, IV immunoglobulin, cyclophosphamide, belimumab, abatacept, B cell depleting therapy, experimental therapy.

5.7 Toxicity Management Plan for Concurrent Therapy: Hydroxychloroquine or Chloroquine

Hydroxychloroquine may affect the eye, specifically the retina on rare occasions. Serious rare reported associations include torsade de pointes, agranulocytosis, aplastic anemia, leucopenia and thrombocytopenia, hepatic failure, drug-induced myopathy, neuromyopathy, seizure, hearing loss, and angiodema [35].

Chloroquine is a closely related compound which may be substituted for hydroxychloroquine when a more potent anti-malarial is needed, particularly for refractory cutaneous SLE. No common adverse events are reported, but rare serious events include atrioventricular block, heart failure, Stevens-Johnsons syndrome, neutropenia, anaphylaxis, seizure, and retinopathy [36].

Guidelines recommend periodic retinal monitoring for HCQ and chloroquine [37, 38]. Retinal monitoring should follow institutional practice. Should concern for retinal toxicity from anti-malarial therapy arise based on retinal examination, this medication should be discontinued. Subjects may continue in the trial uninterrupted if anti-malarials are stopped for medical reasons.

Hematological or hepatic toxicities with anti-malarials are extremely rare in clinical use for SLE and no mandated monitoring is required for these toxicities. Complete blood counts and hepatic function will be performed at study visits as part of routine monitoring for disease activity and potential MMF toxicity. Should hematological or hepatic toxicities (NCI-CTCAE Grade 3-5) occur in the absence of more likely causes, anti-malarial therapy may be held per investigator's discretion while the toxicity is monitored. Anti-malarials may be resumed per investigator's discretion if there does not appear to be a clear relationship of toxicity to anti-malarial use after observation over time.

5.8 Other Standard of Care Recommendations

Ideally, relevant concurrent therapy such as angiotensin inhibitor/angiotensin receptor blockers should be held constant throughout the trial. Osteoporosis treatment and prevention medications, as well as treatment for other comorbid conditions, should be considered based on investigator discretion due to subject characteristics and preferences.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used on an as-needed basis if the investigator feels the medical status of the subject permits the use of these drugs. NSAIDs can be associated with impairment in renal function and should be used with caution in subjects with a history of lupus nephritis even if serum creatinine is normal at enrollment.

Should subjects experience deterioration in renal function NSAIDs should be discontinued and renal function retested. NSAIDs also increase the risk of peptic ulcer disease and GI bleeding, and should be used with caution and with concurrent proton pump inhibitors in high-risk subjects.

5.9 Procedures for Monitoring Subject Compliance

For the MMF maintenance arm, pill counts of the MMF will be performed at each visit, Week 4 through Week 60, to assess compliance.

For the MMF withdrawal arm, pill counts of the MMF will be performed at each visit, Week 4 through Week 12, to assess compliance.

5.10 Treatment Discontinuation and Subject Withdrawal

5.10.1 Study Treatment Discontinuation

Study drug provided by the sponsor will be discontinued for any individual subject under the following conditions:

1. At any time during the study at the request of the subject or subject's guardian.
2. If investigators or NIAID determine that the subject's health, safety, and/or well-being are threatened.
3. For either disease activity or toxicity guidelines as outlined below:
    - Disease Activity: If the subject meets the primary endpoint of clinically significant disease reactivation, the study drug will be discontinued and subject treated at the discretion of the investigator per Section 5.3.1, *Administration of Study Product in Response to SLE Reactivation*, but the subject will continue study visits. Clinically significant disease reactivation is defined in Section 3.2 *Description of Primary Endpoint*.
    - Toxicity or Infection:
        - If the subject must discontinue study drug for more than 14 sequential days due to ongoing, suspected MMF toxicity, then study drug will be discontinued, but the subject will continue study visits.
        - If the subject has study drug withheld for a cumulative total of 28 days or greater in the setting of multiple or recurrent MMF toxicity, study drug will be discontinued, but the subject will continue study visits.
4. If the subject is female and becomes pregnant.
5. Subject non-compliance with treatment regimens or failure to keep appointments.

Subjects who discontinue protocol-specified treatment requirements will be treated as medically indicated according to discretion of the treating physician.

5.10.1.1 Procedures for Discontinuation of Protocol-Specified Treatment Requirements

Whenever possible, subjects who have been discontinued from study treatment for disease activity or toxicity should complete all remaining scheduled study visits including all exams, procedures, assessments, and tests. Furthermore, if study treatment discontinuation is due to safety concerns, subjects will be given appropriate care under medical supervision beyond the last scheduled study visit, if necessary, per Sections 7.3.4, *Recording Adverse Events,* and 7.3.5, *Recording Serious Adverse Events*. If the site PI determines that completion of these visits is not clinically appropriate for the subject or if the subject or subject's guardian elects not to complete these visits, the subject will be withdrawn from the study per the guidelines in Section 5.10.2, *Subject Withdrawal from the Study*.

5.10.2 Subject Withdrawal from the Study

When a subject is withdrawn from the study, protocol-specified treatment requirements are discontinued, and all study-related visits, exams, procedures, assessments, tests and data collection are terminated. Individual subjects will be withdrawn from the study under the following conditions:

1. The subject or subject's guardian withdraws consent.
2. The investigator or NIAID believes it is in the best interest of the subject.
3. The subject is lost to follow-up.
4. The study is terminated.

5.10.2.1 Procedures for Subject Withdrawal from the Study

Whenever possible, subjects to be withdrawn from the study will be asked to consent to an end-of-study evaluation, which includes all scheduled exams, procedures, and laboratory tests planned for the Week 60 visit. Furthermore, if discontinuation is due to safety concerns, subjects will be given appropriate care under medical supervision beyond the last scheduled study visit, if necessary, until the symptoms of any AE resolve or the subject's condition becomes stable. After this end-of-study visit, the PI (or designated treating physician) may continue to follow the subject to manage clinical care, but no additional study-related data will be collected.

5.10.3 Safety Stopping Guidance

The DSMB will review any event that potentially impacts safety at the request of the protocol chair or DAIT/NIAID. The DSMB will have discretion to recommend actions regarding study conduct and continuation as a consequence of any planned or unplanned monitoring activity.

The DSMB will be informed in real time of the following event:

- Any immediately life-threatening event or death that occurs in the study, which is possibly, probably, or definitely related to study participation.

In addition, the following events will trigger both a comprehensive DSMB Emergency Safety Review and a temporary halt in enrollment:

- Events that result in permanent discontinuation of study intervention occurring in
  - 3 of the first 10 subjects randomized to the MMF withdrawal or
  - 30% of subjects randomized to MMF withdrawal at any time point after the 11th subject is randomized.
- BILAG* A flares occurring in
  - 3 of the first 10 subjects randomized to MMF withdrawal or
  - 30% of subjects randomized to MMF withdrawal at any time point after the 11th subject is randomized.
- Severe SELENA-SLEDAI* flares occurring in
  - 3 of the first 10 subjects randomized to MMF withdrawal or
  - 30% of subjects randomized to MMF withdrawal at any time point after the 11th subject is randomized.

In the event of a temporary halt in enrollment, no new subjects will be consented, randomized or start on study product; subjects already on study product will continue unless they are the focus of the DSMB review. Subjects in the screening phase of the study may continue to undergo minimal risk procedures (e.g., blood tests), but more than minimal risk procedures should be deferred. Randomization will not occur until the DSMB review is complete. After careful review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

In addition, at each planned Data Review Meeting, the DSMB will review the estimated risk difference for disease reactivation (i.e. $risk_{\_MMFwithdrawal} - risk_{\_MMF\ maintenance}$) and consider whether or not the trial should be stopped for safety concerns. (See Section 8.4 *Interim Analysis* for details.)

6 ASSESSMENT OF SAFETY AND DISEASE ACTIVITY

6.1 Assessments of Safety

To assess safety in this population, peripheral blood cell counts, liver function, and serum creatinine will be monitored before enrollment and at frequent intervals thereafter. A physical examination will be conducted at each study visit. The information from these assessments will be used to characterize the frequency of all AEs, all SAEs, as well as the other safety endpoints noted in Section 3.3.2, *Secondary Safety Endpoints*.

6.2 Assessments of Disease Activity

Clinically significant disease reactivation (defined in Section 3.2 *Description of Primary Endpoint*) is the primary endpoint of this trial. Disease activity will be monitored by evaluating clinical outcomes at screening and serially throughout the trial.

The m-SLEDAI* will be assessed at screening and the SELENA-SLEDAI* along with medications will be assessed at each study visit to evaluate clinically significant disease reactivation. SLE disease activity will also be assessed by administration of the BILAG* and the SLICC/DI*. The original lupus instruments include 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 spot urine assessment is not available.

Quality of life will be assessed by administration of the FACIT, SF-36®, and Lupus QoL©.

6.3 Mechanistic Studies

Secondary mechanistic objectives overall are to define biomarkers, which are associated with increased risk of disease flare in SLE patients.

6.3.1 Serologic Markers

Serum for serologic markers including C3, C4, and antibodies to dsDNA, Sm, RNP, SSA/Ro and SSB/La will be collected at every scheduled visit and every Flare Visit.

C3, C4, and dsDNA antibodies (anti-dsDNA) are needed at each visit as part of the SELENA-SLEDAI* scoring system, but will also be analyzed as independent markers to define the utility of the markers in predicting which subjects will meet the primary endpoint of clinical disease activation.

Antibodies to Sm, RNP, SSA/Ro, and SSB/La will be measured from a serum specimen at Baseline and Week 60 for all subjects. To evaluate these markers as predictors of flare, samples collected at pre-flare, flare, and post-flare time points may be analyzed for those subjects who flare. For subjects who do not flare, samples may be analyzed at three additional time points for comparison to the results for flaring subjects..

6.3.2 Cytokine and Chemokine Analysis

Serum for cytokines and chemokines will be collected at every scheduled visit and every Flare Visit and stored until the study is completed.

Hypotheses:

i. Subjects with elevated levels of interferon associated cytokine or chemokines at baseline will be significantly more likely to flare and will have earlier time to flare following MMF withdrawal than those with elevated levels of interferon associated cytokine or chemokines who remain on MMF;
ii. Subjects who flare will have elevated levels of interferon associated cytokines or chemokines at the visit prior to flare compared to the baseline visit, and an increase in levels of interferon associated cytokine or chemokines will be predictive of clinically significant flare.

Once sample collection is completed for all subjects, assays for interferon related cytokines and chemokines will be performed on selected serum samples using commercially-available bead-based assays or sandwich ELISAs. For subjects who flare, samples collected at Baseline (Day 0), Week 20, and at pre-flare, flare, and post-flare time points will be analyzed. For subjects who do not flare, samples to be analyzed will include: Baseline, Week 20, and three additional time points.

6.3.3 Transcript Profiling Studies

RNA for transcript analysis will be collected at every scheduled visit and every Flare Visit and stored until the study is completed.

Hypotheses:

i. Subjects with an "Immunologically Active B Cell Fingerprint" will be more likely to flare than subjects with an "Inactive B Cell Fingerprint";
ii. Subjects with an "Interferon-α Signature" will be more likely to flare than subjects who lack an Interferon-α Signature.

Transcript profiling for gene expression will be performed on the subset of subjects who flare (estimated at ~15) and matched subjects who do not flare (estimated at 30). For flaring subjects, RNA transcripts will be analyzed at each of 5 time points (Baseline, Week 20, first flare, and the time points immediately prior to and after first flare). For the subjects who do not flare, RNA transcripts will be analyzed at Baseline, Week 20, and time points comparable to the pre-flare, flare, and post-flare time points for matched flaring subjects. All samples will be analyzed at the end of the study, after all flares have been identified. Differences in gene expression at Baseline will be explored among subjects who do and do not flare. In addition, differences in gene expression among treatment arms will also be investigated.

6.3.4 Future Use Assays

Leftover serum, plasma, and/or RNA from the planned mechanistic studies (Section 6.3.2 and 6.3.3) will be stored until the end of the study and used only to confirm mechanistic studies already performed and described above.

If appropriate consents are given, samples for unspecified, IRB approved, future use to study SLE, the immune system, and the effect of treatment on SLE will be collected as specified below:

- **Future Use: PBMCs/Plasma** will be collected as follows:
  - For subjects who do not experience any flares requiring an increase in prednisone or immunomodulatory medication, collect PBMCs/Plasma at Baseline, Week 20, and Week 60.
  - For subjects who experience a mild/moderate flare where increased prednisone is prescribed, collect PBMCs/Plasma at Baseline, Week 20, and the first Flare Visit where increased medication is prescribed.

        - If an increase in prednisone is followed at a subsequent visit with an increase in immunomodulatory medication, then a fourth sample should be collected. Specimens should be collected prior to the beginning treatment at the increased dose.
    - For subjects who experience a severe flare where increased immunomodulatory medication is prescribed, collect PBMCs/Plasma at Baseline, Week 20, and the first Flare Visit where increased medication is prescribed. Specimens should be collected prior to beginning treatment at the increased dose.
- **Future Use: Plasma** only will be collected at Weeks 4,8,12,16, 24, 32, 40, and 48. In addition, if a specimen (s) has been previously collected for a qualifying flare, plasma only will be collected at Week 60 or Endpoint.
- **Future Use: Urine** will be collected at Baseline, Week 20, any (and all) Flare Visits where increased prednisone or immunomodulatory medication is prescribed, or at Week 60 if no flare occurs
- **Future Use:** DNA will be extracted from the PBMC specimen and stored for unspecified, IRB approved, future use.

Depending on the clinical results of the study, B & T Cell FACS may be done using the stored PBMC specimen described above.

Subjects will be able to opt-out of the storage of these samples during the consent process with the exception of samples drawn for the B and T cell FACS analysis. These studies will be run on all participants in the study if the clinical data warrants them.

Any future research on these samples will be reviewed and approved by an IRB prior to its conduct. Only coded samples would be provided to approved researchers.

6.3.5 Blood Draw Prioritization

Should the subject have been experiencing severe anemia (hemoglobin < 8g/dL) or have poor venous access, the blood draw limit is 30 mL and the priority of samples to collect is as follows:

- Safety draws: chemistries, hematologies, anti-dsDNA, C3, C4 (10-13 mL, depending on visit)
- Serum for Cytokines/Chemokines/Antibodies to Sm, RNP, SSA/Ro, SSB/La (except limit blood draw to approximately 2.5 mL)
- RNA Assays (except limit blood draw to 2.5 mL)
- Future use: PBMCs & Plasma (drawn at Baseline, Week 20, and Flare or Week 60 Visits only, except limit blood draw to 8 mL)
- Future Use: Plasma (drawn at Weeks 4, 8, 12, 16, 24, 32, 40, 48, and Week 60 only if the subject experienced a flare while on study)

Should the subject have been experiencing moderate-severe anemia (hemoglobin 8-9 g/dL), the blood draw limit is 50 mL and the priority of samples to collect is as follows:

- Safety draws: chemistries, hematologies, anti-dsDNA, C3, C4 (10-13 mL, depending on visit)
- Serum for Cytokines/Chemokines/Antibodies to Sm, RNP, SSA/Ro, SSB/La (except limit blood drawn to approximately 5 mL)
- RNA Assays
- Future use: PBMCs & Plasma (drawn at Baseline, Week 20, and Flare or Week 60 Visits only, except limit blood draw to 24 mL)
- Future Use: Plasma (drawn at Weeks 4, 8, 12, 16, 24, 32, 40, 48, and Week 60 only if the subject experienced a flare while on study)

Subjects with hemoglobin above 9.0 mg/dL may have blood draws as scheduled.

Exceptions to Blood Drawing Limits:

- In any patient whose clinical condition might be adversely affected by removal of the volumes stated above, for example, patients with significant anemia or compromised cardiac output, investigators should consider further limiting the volume of blood withdrawn for research purposes.

6.4 Evaluations by Study Visit

Refer to Table 6.1, *Schedule of Evaluations* for a complete listing of evaluations by study visit.

Note: all subjective assessments completed by the subject (FACIT, SF-36®, Lupus QoL©) **must** be done at the beginning of a visit, prior to **any** other study related procedures.

Study physicians must enroll in the MMF REMS program and send a copy of the completed Prescriber Training Confirmation form to the sponsor.

6.4.1 Screening Period

Unless otherwise specified, the screening evaluations must be performed within 28 days prior to the Baseline/Randomization Visit.

This study will be explained in lay language to each potential participant. Each participant will sign an informed consent form before committing to study screening procedures.

The following labs, procedures, and assessments will determine subject eligibility:

- Demographics
- Medical history assessment, including Family History of Autoimmune Disease
- Physical examination
- Vitals, including height & weight
- Physician's global assessment
- m-SLEDAI

- Medications assessment
- PPD or QuantiFERON®-TB Gold In-Tube Test (QFT-G-IT): unless performed within 12 weeks prior to screening and documented as negative in the subject's records, or unless subject is known to have a positive or indeterminate test and has documentation of appropriate therapy.
- Chemistries (albumin, alkaline phosphatase [ALP], alanine transaminase [ALT], aspartate transaminase [AST], blood urea nitrogen [BUN], creatinine, glucose, phosphorus, potassium, bilirubin, total protein)
- Hematologies (hemoglobin, mean corpuscular volume [MCV], platelet count, red cell distribution width [RDW], WBC, lymphocytes, monocytes, neutrophils)
- Hematology: lymphocyte subset, *only if*
  - the subject was on a B cell depleting agent in the past 3 years

  and
  - a test result documenting detectable B cells was not done within 12 weeks prior to screening.
- Infectious disease screen including HIV antibody, hepatitis B surface antigen, hepatitis C virus (HCV) antibody with HCV RNA (PCR) if antibody positive (unless documented as negative within 12 weeks prior to the Screening visit)
- Urinalysis including dipstick, microscopic analysis, spot protein/creatinine
- Pregnancy test, for women of child-bearing potential *only*
  - Review acceptable contraceptive methods per MMF REMS guidelines (See Appendix L).

6.4.2 **Baseline/Randomization Visit**

The baseline evaluations must be performed on Day 0 and within 28 days of the Screening visit.

- Randomization
- FACIT
- SF-36®
- Lupus QoL©
- Physical examination
- Vitals, including weight
- Physician's global assessment
- SELENA-SLEDAI*
- SLICC/DI*
- BILAG*
- Medications assessment
- AE assessment
- Anti-dsDNA, C3, C4
- Serum creatinine

  - *Note: When a chemistry panel is not done, serum creatinine and Anti-dsDNA, C3, C4 will be run from the same blood tube.*
- Hematologies (hemoglobin, MCV, platelet count, RDW, WBC, lymphocytes, monocytes, neutrophils)
- Urinalysis including dipstick, microscopic analysis, spot protein/creatinine
- Serum for Cytokines/Chemokines/Antibodies to Sm, RNP, SSA/Ro, SSB/La – 10 mL
- RNA Assays – 5 mL
- Future Use: PBMCs & Plasma – 40 mL
- Future Use: Urine – 10 mL
- Dispense MMF to all subjects

6.4.3 Treatment Period

6.4.3.1 Week 4 (± 7 days)

- Physical examination
- Vitals, including weight
- Physician's global assessment
- SELENA-SLEDAI*
- BILAG*
- Medications assessment
- AE assessment
- Anti-dsDNA, C3, C4
- Serum creatinine
- Hematologies (hemoglobin, MCV, platelet count, RDW, WBC, lymphocytes, monocytes, neutrophils)
- Urinalysis including dipstick, microscopic analysis, spot protein/creatinine
- Serum for Cytokine/Chemokine Assays – 10 mL
- RNA Assays – 5 mL
- Future Use: Plasma – 8.5 mL
- Assess MMF compliance for all subjects
- Dispense MMF to all subjects

6.4.3.2 Week 8 (± 7 days)

- Physical examination
- Physical examination by a blinded investigator
- Vitals, including weight
- Physician's global assessment
- SELENA-SLEDAI*
- SELENA-SLEDAI* & treatment questionnaire by a blinded investigator
- BILAG*

- Medications assessment
- AE assessment
- Anti-dsDNA, C3, C4
- Serum creatinine
- Hematologies (hemoglobin, MCV, platelet count, RDW, WBC, lymphocytes, monocytes, neutrophils)
- Urinalysis including dipstick, microscopic analysis, spot protein/creatinine
- Serum for Cytokine/Chemokine Assays – 10 mL
- RNA Assays – 5 mL
- Future Use: Plasma – 8.5 mL
- Assess MMF compliance for all subjects
- Dispense MMF to all subjects

6.4.3.3 **Week 12 (± 7 days)**

- Physical examination
- Physical examination by a blinded investigator
- Vitals, including weight
- Physician's global assessment
- SELENA-SLEDAI*
- SELENA-SLEDAI* & treatment questionnaire by a blinded investigator
- BILAG*
- Medications assessment
- AE assessment
- Chemistries (albumin, ALP, ALT, AST, BUN, creatinine, glucose, phosphorus, potassium, bilirubin, total protein)
- Anti-dsDNA, C3, C4
- Hematologies (hemoglobin, MCV, platelet count, RDW, WBC, lymphocytes, monocytes, neutrophils)
- Urinalysis including dipstick, microscopic analysis, spot protein/creatinine
- Serum for Cytokine/Chemokine Assays – 10 mL
- RNA Assays – 5 mL
- Future Use: Plasma – 8.5 mL
- Assess MMF compliance for all subjects
- Dispense MMF to *only* subjects in the MMF maintenance arm
- Pregnancy test, for women on MMF and of child-bearing potential *only*
    - Review acceptable contraceptive methods per MMF REMS guidelines (See Appendix L).

6.4.3.4 **Week 16 (± 7 days)**

- Physical examination
- Physical examination by a blinded investigator
- Vitals, including weight

- Physician's global assessment
- SELENA-SLEDAI*
- SELENA-SLEDAI* & treatment questionnaire by a blinded investigator
- BILAG*
- Medications assessment
- AE assessment
- Anti-dsDNA, C3, C4
- Serum creatinine
- Hematologies (hemoglobin, MCV, platelet count, RDW, WBC, lymphocytes, monocytes, neutrophils)
- Urinalysis including dipstick, microscopic analysis, spot protein/creatinine
- Serum for Cytokine/Chemokine Assays – 10 mL
- RNA Assays – 5 mL
- Future Use: Plasma – 8.5 mL
- Assess MMF compliance for *only* subjects in the MMF maintenance arm
- Dispense MMF to *only* subjects in the MMF maintenance arm

6.4.3.5 **Week 20 (± 7 days)**

- Physical examination
- Physical examination by a blinded investigator
- Vitals, including weight
- Physician's global assessment
- SELENA-SLEDAI*
- SELENA-SLEDAI* & treatment questionnaire by a blinded investigator
- BILAG*
- Medications assessment
- AE assessment
- Anti-dsDNA, C3, C4
- Serum creatinine
- Hematologies (hemoglobin, MCV, platelet count, RDW, WBC, lymphocytes, monocytes, neutrophils)
- Urinalysis including dipstick, microscopic analysis, spot protein/creatinine
- Serum for Cytokine/Chemokine Assays – 10 mL
- RNA Assays – 5 mL
- Future Use: PBMCs & Plasma – 40 mL
- Future Use: Urine – 10 mL
- Assess MMF compliance for *only* subjects in the MMF maintenance arm
- Dispense MMF to *only* subjects in the MMF maintenance arm

6.4.3.6 **Week 24 (± 7 days)**

- FACIT
- SF-36®

- Lupus QoL©
- Physical examination
- Physical examination by a blinded investigator – *only* if at Week 20, the subject is being monitored for flare
- Vitals, including weight
- Physician's global assessment
- SELENA-SLEDAI*
- SELENA-SLEDAI* & treatment questionnaire by a blinded investigator – *only* if at Week 20, the subject is being monitored for flare
- SLICC/DI*
- BILAG*
- Medications assessment
- AE assessment
- Chemistries (albumin, ALP, ALT, AST, BUN, creatinine, glucose, phosphorus, potassium, bilirubin, protein)
- Anti-dsDNA, C3, C4
- Hematologies (hemoglobin, MCV, platelet count, RDW, WBC, lymphocytes, monocytes, neutrophils)
- Urinalysis including dipstick, microscopic analysis, spot protein/creatinine
- Serum for Cytokine/Chemokine Assays – 10 mL
- RNA Assays – 5 mL
- Future Use: Plasma – 8.5 mL
- Assess MMF compliance for *only* subjects in the MMF maintenance arm
- Dispense MMF to *only* subjects in the MMF maintenance arm
- Pregnancy test, for women on MMF and of child-bearing potential *only*
  - Review acceptable contraceptive methods per MMF REMS guidelines (See Appendix L).

6.4.3.7 **Week 32 (± 7 days)**

- Physical examination
- Vitals, including weight
- Physician's global assessment
- SELENA-SLEDAI*
- BILAG*
- Medications assessment
- AE assessment
- Chemistries (albumin, ALP, ALT, AST, BUN, creatinine, glucose, phosphorus, potassium, bilirubin, protein)
- Anti-dsDNA, C3, C4
- Hematologies (hemoglobin, MCV, platelet count, RDW, WBC, lymphocytes, monocytes, neutrophils)
- Urinalysis including dipstick, microscopic analysis, spot protein/creatinine
- Serum for Cytokine/Chemokine Assays – 10 mL

- RNA Assays – 5 mL
- Future Use: Plasma – 8.5 mL
- Assess MMF compliance for *only* subjects in the MMF maintenance arm
- Dispense MMF to *only* subjects in the MMF maintenance arm

6.4.3.8 **Week 40 (± 7 days)**

- Physical examination
- Vitals, including weight
- Physician's global assessment
- SELENA-SLEDAI*
- BILAG*
- Medications assessment
- AE assessment
- Chemistries (albumin, ALP, ALT, AST, BUN, creatinine, glucose, phosphorus, potassium, bilirubin, protein)
- Anti-dsDNA, C3, C4
- Hematologies (hemoglobin, MCV, platelet count, RDW, WBC, lymphocytes, monocytes, neutrophils)
- Urinalysis including dipstick, microscopic analysis, spot protein/creatinine
- Serum for Cytokine/Chemokine Assays – 10 mL
- RNA Assays – 5 mL
- Future Use: Plasma – 8.5 mL
- Assess MMF compliance for *only* subjects in the MMF maintenance arm
- Dispense MMF to *only* subjects in the MMF maintenance arm
- Pregnancy test, for women on MMF and of child-bearing potential *only*
  - Review acceptable contraceptive methods per MMF REMS guidelines (See Appendix L).

6.4.3.9 **Week 48 (± 7 days)**

- FACIT
- SF-36®
- Lupus QoL©
- Physical examination
- Vitals, including weight
- Physician's global assessment
- SELENA-SLEDAI*
- SLICC/DI*
- BILAG*
- Medications assessment
- AE assessment
- Chemistries (albumin, ALP, ALT, AST, BUN, creatinine, glucose, phosphorus, potassium, bilirubin, protein)

- Anti-dsDNA, C3, C4
- Hematologies (hemoglobin, MCV, platelet count, RDW, WBC, lymphocytes, monocytes, neutrophils)
- Urinalysis including dipstick, microscopic analysis, spot protein/creatinine
- Serum for Cytokine/Chemokine Assays – 10 mL
- RNA Assays – 5 mL
- Future Use: Plasma – 8.5 mL
- Assess MMF compliance for *only* subjects in the MMF maintenance arm
- Dispense MMF to *only* subjects in the MMF maintenance arm

6.4.3.10 **Week 60 (± 7 days)**

- FACIT
- SF-36®
- Lupus QoL©
- Physical examination
- Vitals, including weight
- Physician's global assessment
- SELENA-SLEDAI*
- SLICC/DI*
- BILAG*
- Medications assessment
- AE assessment
- Chemistries (albumin, ALP, ALT, AST, BUN, creatinine, glucose, phosphorus, potassium, bilirubin, protein)
- Anti-dsDNA, C3, C4
- Hematologies (hemoglobin, MCV, platelet count, RDW, WBC, lymphocytes, monocytes, neutrophils)
- Urinalysis including dipstick, microscopic analysis, spot protein/creatinine
- Serum for Cytokines/Chemokines/Antibodies to Sm, RNP, SSA/Ro, SSB/La – 10 mL
- RNA Assays – 5 mL
- Future Use: Urine – 10 mL, if the subject did not experience a flare while on study
- Either
    - Future Use: Plasma – 8.5 mL, if Future Use: PBMCs & Plasma have been previously collected for a flare while on study
    - Future Use: PBMCs & Plasma – 40 mL, if the subject did not experience a flare requiring increased prednisone or immunomodulatory medication while on study
- Assess MMF compliance for *only* subjects in the MMF maintenance arm
- Pregnancy test, for women on MMF and of child-bearing potential *only*
    - Review acceptable contraceptive methods per MMF REMS guidelines (See Appendix L).

6.4.4 As Needed Visits

6.4.4.1 Flare Visit

A flare visit is to occur when a subject experiences a flare and may coincide with a regularly scheduled or unscheduled study visit.

- FACIT
- SF-36®
- Lupus QoL©
- Physical examination
- Vitals, including weight
- Physician's global assessment
- SELENA-SLEDAI*
- SLICC/DI*
- BILAG*
- Medications assessment
- AE assessment
- Chemistries (albumin, ALP, ALT, AST, BUN, creatinine, glucose, phosphorus, potassium, bilirubin, total protein)
- Anti-dsDNA, C3, C4
- Hematologies (hemoglobin, MCV, platelet count, RDW, WBC, lymphocytes, monocytes, neutrophils)
- Urinalysis including dipstick, microscopic analysis, spot protein/creatinine

Collect the following specimens prior to beginning or increasing treatment with an increased dose of prednisone or immunomodulatory medications.

- Serum for Cytokines/Chemokines/Antibodies to Sm, RNP, SSA/Ro, SSB/La – 10 mL
- RNA Assays – 5 mL
- Future Use: PBMCs & Plasma – 40 mL, only for qualifying Flare visits. See Section 6.3.4: *Future Use Assays.*
- Future Use: Urine – 10 mL

6.4.4.2 Endpoint Visit

An endpoint visit is to occur when a site needs to determine if a subject has met the primary endpoint, as described in Section 3.2, *Description of Primary Endpoint* and may coincide with a regularly scheduled study visit. An endpoint visit will consist of all Week 60 assessments, see Section 6.4.3.15, *Week 60*.

6.4.4.3 **Unscheduled Visits**

If concerns arise between regularly scheduled visits, subjects should be instructed to contact study personnel to come in for an "unscheduled" visit. The following evaluations will be performed at each unscheduled visit:

- Physical examination
- Vitals, including weight
- Medications assessment
- AE assessment

Additional evaluations may be performed according to investigator discretion.

Note: if during the unscheduled visit, the investigator suspects a flare is occurring, the site must conduct a Flare Visit with all its assessments.

6.4.4.4 **Early Withdrawal Visit**

Subjects who withdraw early from the study will be asked to complete an Early Withdrawal Visit. All scheduled exams, procedures, and laboratory tests scheduled for the Week 60 visit will be performed at this visit. Data from subjects who do not complete all study visits will still be included in the Intent-to-Treat and safety analyses.

6.4.5 **Visit Windows**

All study procedures should be performed within the designated visit window (i.e., ± 7 days) for each scheduled visit (see Table 6.1, *Schedule of Events)*. Whenever possible, a rescheduled visit should remain within the designated visit window. The coordinating center should be notified if the study procedures for any scheduled visit cannot be performed within the designated window.

Table 6.1, Schedule of Events													As Needed		
Visit Name	Screen-ing	Base-line	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 40	Week 48	Week 60[1]	Flare[2]	End-point[3]	Unsched-uled[4]
Unless otherwise noted, all assessments are to be done by unblinded personnel.			M1	M2	M3	M4	M5	M6	M8	M10	M12	M15			
Visit Window *(days)*	-28 to -1	0	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	n/a	n/a	n/a
Central Clinical Draw *(mL, approximate)*	18.5	10	10	10	13	10	10	13	13	13	13	13	13	13	0
Central Research Draw *(mL)*	0	55	23.5	23.5	23.5	23.5	55	23.5	23.5	23.5	23.5	55	55	23.5	0
Visit Draw Total *(mL, approximate)*	18.5	65	33.5	33.5	36.5	33.5	65	36.5	36.5	36.5	36.5	68	68	36.5	0
Physician Requirements															
REMS Program Enrollment	X														
General Assessment															
Randomization		X													
Informed Consent	X														
Demographics	X														
Medical History, including Family History of Autoimmune Disease	X														
Physical Examination[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[6] by a blinded investigator				X	X	X	X	X[17]							
Vitals, including weight (& height at Screening)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician's Global Assessment (0-3 VAS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
m-SLEDAI[13]	X														
SELENA-SLEDAI*[13]		X	X	X	X	X	X	X	X	X	X	X	X	X	
SELENA-SLEDAI*[13] & treatment questionnaire by a blinded investigator				X	X	X	X	X[17]							
SLICC/DI*[13]		X						X			X	X	X	X	
BILAG*[13]		X	X	X	X	X	X	X	X	X	X	X	X	X	
FACIT[7]		X						X			X	X	X	X	
SF-36®[7]		X						X			X	X	X	X	
Lupus QoL©[7]		X						X			X	X	X	X	
Medications Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug															
Treatment Period[12]		60 weeks													
Dispense Study Drug		X	X	X	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]				
Assess Study Drug Compliance			X	X	X	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]			
Local Laboratory Assessments[8]															
Urinalysis: dipstick, microscopic, & spot protein-creatinine	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test, if applicable[11]	X				X			X		X		X			
PPD, if applicable[5]	X														
Central Laboratory Assessments[8]															
QuantiFERON®-TB Gold In-Tube Test (QFT-G IT), if applicable[5] (~3 mL)	X														
Infectious Disease Screen (~8.5 mL): HIV antibody, hepatitis B surface antigen, HCV antibody with HCV RNA (PCR) if antibody positive[10]	X														
Chemistries (~3 mL) – albumin, ALP, ALT, AST, BUN, creatinine, glucose, phosphorus, potassium, bilirubin, total protein	X				X			X	X	X	X	X	X	X	
Serum creatinine		X[19]	X[19]	X[19]		X[19]	X[19]								
Anti-dsDNA,C3, C4 (~6 mL)		X[19]	X[19]	X[19]	X	X[19]	X[19]	X	X	X	X	X	X	X	

Table 6.1, Schedule of Events													As Needed		
Visit Name	Screen-ing	Base-line	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 40	Week 48	Week 60[1]	Flare[2]	End-point[3]	Unsched-uled[4]
Unless otherwise noted, all assessments are to be done by unblinded personnel.			M1	M2	M3	M4	M5	M6	M8	M10	M12	M15			
Visit Window *(days)*	-28 to -1	0	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	n/a	n/a	n/a
Hematologies (~4 mL): hemoglobin, MCV, platelet count, RDW, WBC, lymphocytes, monocytes, neutrophils	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology (6 mL): lymphocyte subset, if applicable[9]	X														
Central Mechanistic Specimens															
Serum for Cytokine/Chemokines/Antibodies[18] to Sm, RNP, SSA/Ro, SSB/La (10 mL)		X[18]	X	X	X	X	X	X	X	X	X	X[18]	X[18]	X	
RNA Assays (5 mL)		X	X	X	X	X	X	X	X	X	X	X	X	X	
Future Use: PBMCs & Plasma (40 mL)		X					X					X[15]	X		
Future Use: Plasma (8.5 mL)			X	X	X	X		X	X	X	X	X[16]		X[16]	
Future Use: Urine (10 mL)		X					X					X[20]	X[21]	X	

1. Week 60: should a subject withdraw early, he/she should complete all assessments listed under the Week 60 visit.
2. Flare visits: should occur when a subject experiences a flare and may coincide with a regularly scheduled study visit.
3. Endpoint visits: should occur when a subject reaches primary endpoint, as described in Section 3.2, *Description of Primary Endpoint* and may coincide with a regularly scheduled study visit.
4. Unscheduled visits: all noted assessments must be done, but any additional assessments that the investigator feels should be done should be collected. Note: if during the unscheduled visit, the investigator suspects a flare is occurring, the site must conduct a Flare Visit.
5. PPD or QuantiFERON®-TB Gold In-Tube Test (QFT-G-IT): unless performed within 12 weeks prior to screening and documented as negative in the subject's records, or unless subject is known to have a positive or indeterminate test and has documentation of appropriate therapy.
6. 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.
7. Subjective assessments must be done at the beginning of the visit, prior to any other study assessments (except for informed consent at Screening).
8. Local & Central Laboratory Assessments: see Section 6.3.6, *Blood Draw Prioritization*
9. Lymphocyte subset: *only* if the subject was on a B cell depleting agent in the past 3 years and the test was not done within 12 weeks prior to screening documenting detectable B cells
10. Infectious disease screen: unless documented as negative within 12 weeks prior to the Screening visit.
11. Pregnancy tests: for women on MMF and of childbearing potential *only*. Additional pregnancy tests should also be done when clinically indicated.
12. Treatment Period: will end if a subject meets primary endpoint. While visits & assessments will occur as scheduled, ALE06 will no longer provide any more MMF. Any treatment medications chosen by the investigator will be documented on the concomitant medications log.
13. ALE06 will typically use a spot urinalysis rather than a 24-hour urine assessment for the BILAG*, mSLEDAI, SELENA-SLEDAI*, and SLICC/DI*. However, if indicated, results from a 24-hour urine collection may be used.
14. For subjects randomized to MMF maintenance arm only.
15. Future Use: PBMCs & Plasma will be drawn at Week 60 *only* if the subject did not experience a mild/moderate flare requiring an increase in prednisone or a severe flare requiring increased immunomodulatory medication while on study.
16. Future Use: Plasma will be drawn at Week 60 or Endpoint *only* if the subject did experience a flare while on study.
17. At Week 24, a blinded physical exam and SELENA-SLEDAI* should only be conducted if the subject is being monitored for flare at the Week 20 visit.
18. Antibodies to Sm, RNP, SSA/Ro, and SSB/La will only be assessed at the Baseline, Week 60, and if needed, the flare visit.
19. Serum creatinine will be run off the Baseline, Weeks 4, 8, 16, and 20 Anti-dsDNA, C3, C4 blood draw.
20. FutureUse:Urine will be collected at Week 60 *only* if the subject did not experience a flare while on study.
21. FutureUse:Urine will be collected at any (and all) Flare Visits where increased predisone or immunomodulatory medication is prescribed

7 SAFETY MONITORING AND REPORTING

7.1 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 that data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per Section 7.5, *Reporting of Adverse Events*) and appropriately to the sponsor (DAIT/NIAID), principal investigators in the trial, and Institutional Review Boards (IRBs). Information in this section complies with *ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice,* and applies the standards set forth in the National Cancer Institute (NCI), *Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0*: http://ctep.cancer.gov/reporting/ctc.html.

7.2 Definitions

7.2.1 Adverse Event (or Adverse Experience)

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice)." [From OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" <http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm>

7.2.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

Suspected adverse reaction (SAR) means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction 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)).

7.2.3 Unexpected Adverse Reaction

A SAR is considered "unexpected" if it is not listed in the MMF package insert or is not listed at the specificity or severity that has been observed.

7.2.4 Serious Adverse Event

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)):

1. Death
2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or DAIT/NIAID, its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. Congenital anomaly or birth defect

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 subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

7.3 Collection and Recording of Adverse Events

7.3.1 Investigational Product

The primary investigational product in this protocol is MMF. In addition, subjects in this protocol are required to receive hydroxychloroquine or chloroquine. For purposes of reporting safety information, these drugs will be considered concurrent study mandated therapy.

7.3.2 Collection Period

Adverse events will be collected from the time the subject signs the informed consent until he/she initiates study intervention or until he/she is determined to be ineligible to receive study intervention, if the investigator determines that the adverse event is related to a study-mandated procedure, treatment, or change in treatment.

Regardless of whether the above is applicable, for all participants: Adverse events will be collected from the time of initiation of study intervention (i.e., the administration of the first dose of study-supplied MMF as defined in Section 6.4.2, *Baseline/Randomization Visit*) until he/she completes study participation or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study.

7.3.3 Collecting Adverse Events

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

- Observing the subject.

- Questioning the subject in an objective manner.
- Receiving an unsolicited complaint from the subject.
- In addition, an abnormal value or result from a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, or an electrocardiogram) can also indicate an adverse event, as defined in Section 7.4, *Grading and Attribution of Adverse Events*.

7.3.4 Recording Adverse Events

Throughout the study, the investigator will record and grade adverse events NCI-CTCAE grade 2 and above on the appropriate AE electronic case report form (AE eCRF) regardless of their severity or relation to study medication or study procedure.

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

7.3.5 Recording Serious Adverse Events

Serious AEs will be recorded on the appropriate AE eCRF and on the SAE eCRF. All requested information on the AE eCRF and SAE eCRF should be provided, if available, for submission to the Statistical and Clinical Coordinating Center (SACCC) and DAIT/NIAID.

If a site investigator discovers a new serious adverse event within 30 days after the end of study participation, the SAE will be reported.

Once recorded, an SAE will be followed until it resolves with or without sequelae.

7.4 Grading and Attribution of Adverse Events

7.4.1 Grading Criteria

The study site will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute's *Common Terminology Criteria for Adverse Events Version (CTCAE) 4.0*. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the Protocol Chair(s) and has been deemed appropriate for the subject population to be studied in this protocol.

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

Grade 1 = mild adverse event, not recorded.

Grade 2 = moderate adverse event.

Grade 3 = severe and undesirable adverse event.

Grade 4 = life-threatening or disabling adverse event.

Grade 5 = death.

If NCI-CTCAE criteria are defined for grading an abnormal value or result from a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, or an electrocardiogram), then a treatment-emergent adverse event is defined as an increase in grade from Baseline (Day 0) or from the last post-baseline value that doesn't meet grading criteria. Changes in grade from screening to Baseline (Day 0) will also be recorded as outlined in Section 7.3.2, *Collection Period*. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented.

Adverse events that are related to disease activity will be graded according to the plan outlined above. However, an increase in disease activity leading to an adverse event should also be reflected in standard measures of disease activity (BILAG* 2004 and SELENA-SLEDAI) measured at regularly scheduled visits as well as at flare and endpoint visits.

To facilitate identification of a safety signal associated with increased disease activity, the modified BILAG* 2004 and SELENA-SLEDAI* tools will be used throughout the study to monitor changes in disease activity over time. The DSMB will receive reports on these assessments for each treatment arm at regularly scheduled reviews.

7.4.2 Attribution Definitions

The relation, or attribution, of an adverse event to an investigational product will initially be determined by the site investigator. The site investigator will also record the initial determination of attribution on the appropriate AE eCRF. The relation of an adverse event to the study intervention will be determined using the descriptors and definitions provided in Table 7.1, *NCI-CTCAE attribution of adverse events*. Final determination of attribution for safety reporting will be decided by DAIT/NIAID.

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 7.1 NCI-CTCAE attribution of adverse events

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy)
Unrelated Categories		
1	Unrelated	The adverse event is clearly not related.
2	Unlikely	The adverse event is unlikely related.
Related Categories		
3	Possible	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
4	Probable	The adverse event is likely related.
5	Definite	The adverse event is clearly related.

7.5 Reporting of Adverse Events

7.5.1 Reporting of Adverse Events to DAIT/NIAID

This section describes the responsibilities of the site investigator to report adverse events to the SACCC. Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines. For this study, adverse events of NCI-CTCAE Grade 2 and higher will be reported.

7.5.1.1 Procedure for Adverse Events Requiring 24 Hour Reporting

The adverse events that are bulleted below must be reported by site investigators to the SACCC regardless of relationship or expectedness to study intervention within a 24 hour period of discovering the adverse event:

- All SAEs per 21 CFR 312.32 definitions (see Section 7.2.4, *Serious Adverse Event*).
- All BILAG* A flares.
- All severe SELENA-SLEDAI* flares.

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.

The following process for reporting of the adverse events bulleted above ensures compliance with the ICH guidelines and the Food and Drug Administration (FDA) CFR regulations. When an investigator identifies such an adverse event, he or she must notify the SACCC within 24 hours of discovering the adverse event, and complete and submit the AE/SAE eCRF within one business day following initial notification. The SACCC is responsible for notifying DAIT/NIAID upon receipt of the site's notification of the adverse event and sending a SAE report form to DAIT/NIAID within two business days after receipt of the AE/SAE eCRF from the site.

7.5.1.2 Procedure for Standard Adverse Event Reporting

All other adverse events (Section 7.3.3, *Collecting Adverse Events*) must be recorded by the site on the appropriate AE eCRF within five business days of the site learning of the adverse event(s).

BILAG* A and severe SELENA-SLEDAI* flares will be reported as described above in Section 7.5.1.1, *Procedure for Adverse Events Requiring 24 Hour Reporting*; all other BILAG* and SELENA-SLEDAI* flares will be reported using standard AE reporting timelines.

7.5.2 DAIT/NIAID Reporting to the Health Authority

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).

7.5.3 Reporting of Adverse Events to IRBs

All investigators must report adverse events in a timely fashion to their respective IRBs in accordance with applicable regulations and local reporting guidelines.

7.6 Pregnancy Reporting

This study includes pregnancy information as safety data. Information about any pregnancy should be reported promptly to the SACCC on the same timeline as an SAE (Section 7.5.1.1, *Procedure for Adverse Events Requiring 24 Hour Reporting*).

All pregnancies identified during the study must be followed to conclusion and the outcome of each must be reported. The investigator should be informed immediately of any pregnancy in a study subject or a partner of a study subject. A pregnant subject should be instructed to stop taking study medication. The investigator should report to the SACCC all pregnancies within 1 business day (as described in Section 7.5.1.1, *Procedure for Adverse Events Requiring 24 Hour Reporting*) using the Pregnancy eCRF. The investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant subject should continue until the conclusion of the pregnancy, and a follow-up Pregnancy eCRF detailing the outcome of the pregnancy should be submitted to the SACCC. When possible, similar information should be obtained for a pregnancy occurring in a partner of a study subject.

Information requested about the delivery will include:

- Subject's enrollment ID
- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at one minute, five minutes, and 24 hours after birth, if available

- Any abnormalities

Should the pregnancy result in a congenital abnormality or birth defect, an SAE must be submitted to the SACCC using the SAE reporting procedures described above.

7.6.1 Mycophenolate REMS Program

ALE06 investigators are required to enroll in the FDA's Mycophenolate Risk Evaluation and Mitigation Strategy (REMS) program (www.mycophenolaterems.com). An investigator will be required to report any pregnancy occurring in an ALE06 female subject 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. Subjects will be encouraged to participate in MMF REMS program as well.

7.7 Reporting of Other Safety Information

An investigator should promptly notify the SACCC when an "unanticipated problem involving risks to subjects or others" is identified, which is not otherwise reportable as an adverse event.

7.8 Review of Safety Information

7.8.1 Medical Monitor Review

The DAIT Medical Monitor will receive monthly reports from the SACCC compiling new and accumulating information on AEs, SAEs, and pregnancies recorded by the sites on appropriate eCRFs.

In addition, the Medical Monitor will receive SAE and pregnancy reports for review and triage after the SACCC is made aware of these events (see Sections 7.5.1, *Reporting of Adverse Events to DAIT/NIAID*, and 7.6, *Pregnancy Reporting*).

7.8.2 DSMB Review

The Data and Safety Monitoring Board (DSMB) will review accumulating 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. To ensure patient safety between Data Review Meetings, the DSMB will be informed of all Expedited Safety Reports in a timely manner.

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for ad hoc reviews or emergency meetings (see Section 5.10.3, *Safety Stopping Guidance*). The DSMB will have discretion to recommend actions regarding study conduct and continuation as a consequence of any planned or unplanned monitoring activity.

8 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Sample Size and Power

Sample size justification will focus on the primary endpoint of disease reactivation by Week 60. We anticipate that the risk of disease reactivation will likely increase with MMF withdrawal, and recognize that the acceptable level of increased risk will be highly variable among clinicians and their patients. The planned analyses are designed to provide information to help clinicians make decisions for individual patients with varied levels of risk tolerance. To this end, we will provide the estimated risk of disease reactivation in each arm, but more importantly we will provide the % confidence that the increased risk with MMF withdrawal $\leq \boldsymbol{a}$, where $\boldsymbol{a}$ is a specific value for acceptable increase in risk. To facilitate decisions for individual patients, we will provide a table and/or plot showing the confidence levels over a range of values for $\boldsymbol{a}$.

In deriving an appropriate sample size, we assumed most physicians would want at least 85% confidence that the increase in risk with MMF withdrawal $\leq \boldsymbol{a}$, for whatever value of $\boldsymbol{a}$ is selected for an individual patient. As such, we computed, under a variety of scenarios, the probability that the study would yield estimates where the confidence was at least 85% that the increase in risk with MMF withdrawal $\leq \boldsymbol{a}$ (the acceptable increase in risk). Since this probability is analogous to power for a study designed to test a hypothesis, the term "power" will be used in this discussion.

In addition to the study size and the selected value of $\boldsymbol{a}$, power depends on two unknowns: the risk of disease reactivation for patients in the MMF maintenance arm and the increase in risk for patients upon withdrawal of MMF. With respect to the former, a preliminary analysis was conducted on observational data from a subset of 49 patients in the Johns Hopkins Lupus Cohort who were on MMF for a minimum of one year. Based on these results, the probability of experiencing disease reactivation (defined for the preliminary analysis as at least one SELENA-SLEDAI-defined flare requiring additional treatment) by month 16 was estimated at 0.10 (95% CI 0.02-0.19) for subjects remaining on MMF. For the sample size and power calculations, we assumed the risk of disease reactivation in the MMF maintenance arm would be on the range of 0.05 to 0.15. There is no preliminary data on the increase in risk with MMF withdrawal, but since patients/clinicians would be more likely to consider withdrawal if the increased risk were low, we evaluated potential increases ranging from 0.05 to 0.15.

Table 8.1 presents power estimates based on simulations for a sample size of 120 eligible subjects randomized in a 1:1 to MMF maintenance or withdrawal. If all other factors are constant, power improves as $\boldsymbol{a}$, the acceptable level of increased risk, increases. However, the relevance of the study results in clinical practice decreases with increasing $\boldsymbol{a}$. For example, the statement, "We are 85% confident that the increased risk with withdrawal of MMF is $< \boldsymbol{a} = 0.20$" would be useful for those patients willing to accept an increase in risk of $\boldsymbol{a} \geq 0.20$, but would not be of value for a more risk-averse patient willing to accept, say, an increase in risk of only $\boldsymbol{a} = 0.10$. Unfortunately, the sample size required to achieve 80%

power when $\alpha = 0.10$ (or below) are not feasible for this study. For example, if $\alpha = 0.10$, then under a best case scenario, if the risk of flare is 0.05 in the MMF maintenance arm and the increase in risk with withdrawal is 0.05 (i.e. the risk with MMF withdrawal = 0.10), then the number of patients required for 80% power is 390.

The sample size of 120 was selected to achieve reasonable power for values of $\alpha \geq 0.15$. The study will have the best chance of impacting a wide range of patients if both the risk of disease reactivation in the MMF maintenance arm and the increased risk with withdrawal are low. Table 8.1 shows that if the risk in the MMF maintenance arm is 0.05 and the increase in risk with withdrawal is 0.05, then there is a least 85% power for $\alpha \geq 0.15$. If either the risk in the MMF maintenance arm or the increase in risk with withdrawal is larger than 0.05, then the acceptable increase in risk (α) will have to be ≥ 0.20 in order to maintain power above 80%.

Table 8.1: Power results for 120 subjects (1:1 MMF maintenance: MMF withdrawal)

Power = the probability that a random sample will yield estimates with at least 85% confidence that the increase in risk with MMF withdrawal $\leq \alpha$

Risk in the MMF maintenance arm	Increase in risk with MMF withdrawal	Acceptable risk increase α =… 0.15	0.2	0.25	0.3
0.05	0.05	85%	98%	100%	100%
0.05	0.10	45%	79%	96%	100%
0.05	0.15		42%	74%	93%
0.15	0.05	66%	87%	97%	99%
0.15	0.10	36%	63%	85%	96%
0.15	0.15		35%	61%	83%

8.2 Analysis Populations

8.2.1 Safety Population

The safety population (SP), which will be used for all safety analysis, will include all subjects for whom study intervention is initiated.

8.2.2 Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) population will include all randomized subjects who begin ALE06-provided MMF and meet study entry criteria. Randomized subjects who withdraw from the trial prior to starting ALE06-provided MMF will be excluded from the mITT analysis set. The analyses for disease activity endpoints will be based on the mITT

population. Subjects who, for whatever reason, do not complete their assigned therapy will be included in the mITT population in the groups to which they were randomized.

8.2.3 Per Protocol Population

The Per Protocol (PP) population will be defined as those subjects who adequately comply with the assigned treatment protocol with no serious protocol deviations impacting the primary disease reactivation endpoint or mechanistic outcomes of the study. A masked data review panel will evaluate deviations from the protocol including, for example, departures from assigned treatment regimen, modification 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 subjects from the PP population. The panel may exclude subjects with serious protocol deviations from the PP population.

8.3 Description of the Analyses

In presenting data from this trial, continuous data will be summarized in tables listing the mean, standard deviation or standard error, median, and number of subjects in a group. Categorical data will be summarized in tables listing the frequency and the percentage of subjects in a group. These summaries will be presented separately for subjects on the two treatment arms.

8.3.1 Safety Analysis

All safety analyses will be performed using the Safety Population.

AEs including changes in laboratory values will be graded according to the National Cancer Institute's *Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0* (http://ctep.cancer.gov/reporting/ctc.html). The frequency of AEs will be summarized by system organ class, preferred term, severity (grade), and relationship to study treatment. Relationship to study treatment will be categorized as either treatment related (possibly, probably, or definitely related to study medication) or unrelated (unlikely related or unrelated). Similar analyses will be performed for SAEs. To account for differential duration of study participation among subjects, the summaries will include the event rate (i.e. number of events per person-time) in addition to the number and percent of events and subjects experiencing events.

For each key safety endpoint defined in Section 3.3.2, *Secondary Safety Endpoints* the proportion of subjects experiencing at least one event in each treatment group will be reported and the treatment groups compared based on Fisher's Exact Test. In addition, event rates in the two arms will be compared using Poisson regression.

Laboratory parameters will be summarized both overall and by treatment group using appropriate descriptive statistics. For each lab parameter, the number and percent of subjects that have an increase, decrease, or no change from baseline to Week 60 will be displayed for each treatment group and pooled across treatment arms. For parameters with an explicit NCI-CTCAE grading criterion, change from baseline will be indicated by a change in grade. For

parameters that do not have an explicit NCI-CTCAE, observed values will be categorized as 'high' (defined as >ULN) and 'normal' (defined as ≤ ULN). Then, a change from baseline will be indicated as a change in category

All safety comparisons and associated p-values are considered exploratory, not as formal tests of hypothesis. As such, no adjustments will be made for multiple comparisons and all p-values must be interpreted cautiously.

8.3.2 Analysis of Disease Activity Endpoints

8.3.2.1 Primary Endpoint Analysis

The hope is that this study will provide physicians with some rationale for medical decision making. It is important to note that in practice the decision to withdraw from MMF is multifactorial; one has to weigh the increased risk of disease reactivation against decreased risk of lymphoproliferative disease, hematological derangements, and infections as well as the impact of chronic medication use on quality of life and plans for pregnancy. How the risks and benefits should be weighed is highly individual. For example, for one patient, an acceptable increase in risk with MMF withdrawal might be 0.20, but for another, it might be 0.05, where risk is the probability of disease reactivation on a 0 to 1 scale. Acceptable risk varies according to physician and patient circumstances and preferences, so a pre-specified margin of non-inferiority cannot be defined. Hence, a study designed to test a non-inferiority hypothesis with a single pre-specified risk margin that may or may not be relevant for any particular patient would have limited utility. As such, the planned analyses for this study are designed to maximize the information available for medical decision making.

The first step will be to report effect estimates and 95% confidence intervals for the risk of disease reactivation by Week 60 in each arm as well as the estimated risk difference (i.e. $risk_{\_MMFwithdrawal} - risk_{\_MMF\ maintenance}$), which we assume will be a positive increase in risk with MMF withdrawal. Next, to aid physicians and patients in making decisions based on individualized assessments of acceptable risk, the observed risk estimates will be used to compute the "% Confidence that the true increase is ≤ $\boldsymbol{\alpha}$" as a function of values for the "Acceptable increase in risk with withdrawal of MMF ($\boldsymbol{\alpha}$)". This information can be plotted with values for "Acceptable increase in risk with withdrawal of MMF ($\boldsymbol{\alpha}$)" on the x axis and estimates for "% Confidence that the true increase is ≤ $\boldsymbol{\alpha}$" on the y axis. Our study will generate a single curve based on the observed risk estimates for the two arms. Figure 8.1 shows examples of what this plot might look like given a few possible scenarios for the observed risk estimates. Physicians with their patients could decide on an acceptable level of increased risk ($\boldsymbol{\alpha}$) then read from the plot the % confidence that this selected value of $\boldsymbol{\alpha}$ would not be exceeded with withdrawal of MMF. Depending on the level of confidence, they may or may not decide to withdraw MMF.

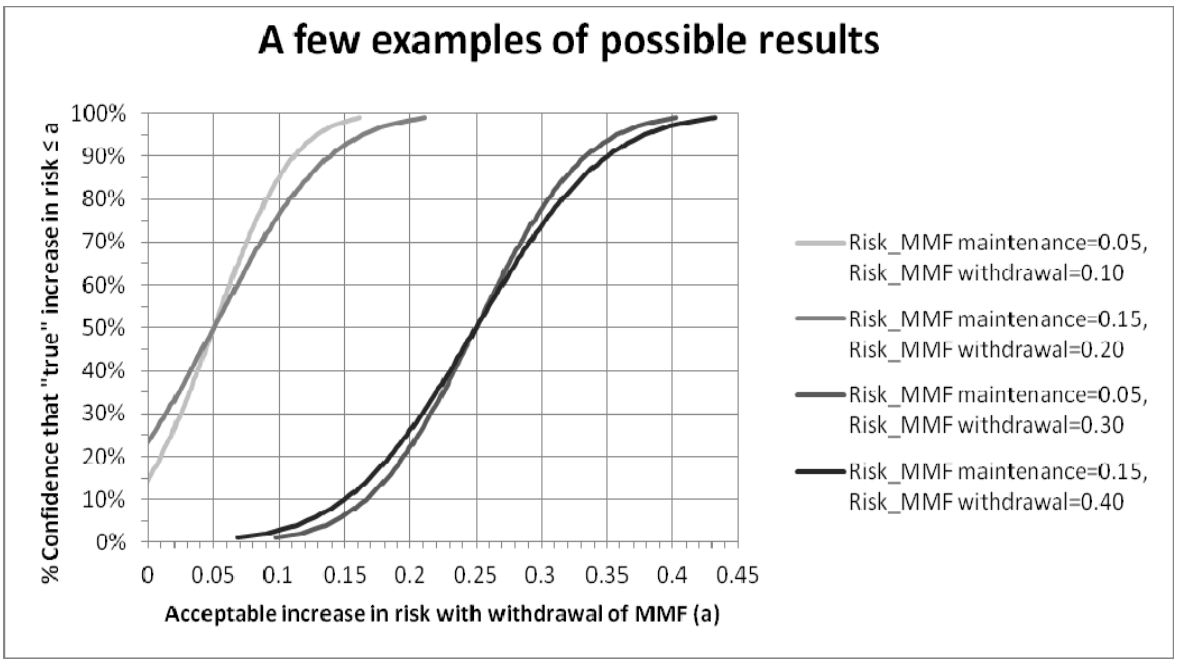


Figure 8.1

The motivation for the curve in Figure 8.1 comes from the test of non-inferiority with the following hypotheses:

*H_0: the increase in risk with withdrawal of MMF (**T**) ≥ **a**, and*
*H_A: the increase in risk with withdrawal of MMF (**T**) < **a**,*
*where **a** is some value for the acceptable increase in risk.*

The H_0 hypothesis would be rejected in favor of H_A if the upper (1-α) % confident limit about the estimated risk difference (i.e. $risk_{\_MMFwithdrawal} - risk_{\_MMF\ maintenance}$) is less than ***a***. Then, we could conclude that ***T < a*** with (1-α)% confidence. Physicians and patients who are comfortable with both a risk increase of no more than ***a*** and a confidence level of (1-α)% could conclude that withdrawal from MMF is "not unacceptably worse" than maintenance on MMF.

Recognizing that the appropriate value of ***a*** will be highly variable among physicians and patients, a single hypothesis is not defined for this study. Alternatively the upper 1-sided (1-α)% confidence limit (UCL) for the observed risk difference will be computed for values of α ranging from 0.01 to 0.99. Note that for a given value of α, the computed UCL equals the value of ***a***, at which a null hypothesis could be rejected with a Type I error rate of α. Results of these computations will be tabulated and plotted as shown in Figure 8.1.

These analyses will be completed on the mITT population.

8.3.2.2 **Secondary Analyses**

All secondary analyses will be conducted in an exploratory fashion with p-values and confidence intervals presented as descriptive statistics with no adjustments for multiple comparisons. Interval estimates will be generated at the 95% confidence level. Analyses will be conducted on the mITT population and the per protocol population.

Analyses described for the primary analysis of the primary endpoint will be repeated using the per protocol population.

In addition, analysis will be conducted in a similar fashion for the secondary endpoints that are probability of experiencing an event including: any SELENA-SLEDAI* flare by Week 60, any severe SELENA-SLEDAI* flare by Week 60, any BILAG* A flare by Week 60, a BILAG* Renal A flare (for subjects with renal manifestations) by Week 60, and addition of aggressive adjunctive therapy to MMF or a change in MMF therapy to cytotoxic drug due to flare. These analyses will be conducted on the mITT and PP populations.

For the time to event endpoints (time to clinically significant disease reactivation, time to first SELENA-SLEDAI* flare and time to first severe SELENA-SLEDAI* flare), graphical summaries of time to event will be generated using Kaplan-Meier survival curves. The Greenwood method will be used to compute confidence intervals.

Descriptive statistics (mean, standard deviation or standard error, median, minimum, maximum and number of subjects in a group) and 95% confidence intervals will be reported for the difference between the treatment groups in cumulative steroid dose at Week 60; change in FACIT fatigue score from baseline to Weeks 24, 48, and 60; change in SF-36® PF and PCS domains from baseline to Weeks 24, 48, and 60; change in LupusQoL-US© from baseline to Weeks 24, 48, and 60, and change in SLICC/DI* from baseline to Weeks 24, 48, and 60.

For subjects who meet the primary endpoint of clinically significant disease reactivation, the time to improvement in BILAG* from maximum level during flare, time to recovery to BILAG* C and time to return to pre-flare steroid dose will be analyzed using Kaplan-Meier curves. Descriptive statistics (mean, standard deviation or standard error, median, minimum, maximum) and 95% confidence intervals will be reported for the difference between the treatment groups in cumulative excess steroid dose from the time of clinically significant disease reactivation until return to pre-flare dose (or end of study participation). It is likely that some subjects will meet the primary endpoint close to the end of follow-up and will therefore be censored at the end of study follow-up for some or all of these endpoints. If one treatment group tends to flare earlier than the other does so that they are more likely to be censored, then censoring will be informative. Estimates of effect will therefore be biased.

8.3.3 **Mechanism/Immunological Analysis**

Descriptive statistics and plots (including, but not limited to, those described subsequently) will be used to gain an understanding of the data prior to developing any statistical models. Means, medians, standard deviations, minimums, and maximums will be computed for each

continuous biomarker at each time point for treatment groups and separately for subjects who do/do not experience clinically significant disease reactivation. For dichotomous biomarkers, frequencies and percents will be computed at each time point for treatment groups and separately for subjects who do/do not experience clinically significant disease reactivation. To gain a better understanding of trends over time, summary statistics (e.g., means, medians, or percents) will be plotted versus time at the relevant time points. Plots for individual subjects may also be useful.

8.4 Interim Analysis

Interim study results will be reported to the DSMB for planned Data Review Meetings. Reports prepared for these meetings will focus on study conduct and subject safety and may include information on enrollment, randomization, site activation status, protocol deviations, subject status and demographics, and safety analyses. In particular, at each DSMB review, disease reactivation rates in each arm and the risk difference (i.e. $risk_{\_MMFwithdrawal} - risk_{\_MMF\ maintenance}$) will be reported along with the 2-sided 95% confidence interval. If the lower 95% confidence limit about the risk difference exceeds 0.40, the DSMB should consider whether or not the study should be stopped for safety concerns. In order to trigger the guidance, the number of disease reactivations in the MMF withdrawal arm must exceed the number in the MMF maintenance arm, but the magnitude of the excess depends on the sample size. Some examples of observed scenarios that would trigger the guidance are as follows:

# Subjects per arm	Minimum # excess reactivations in the MMF withdrawal arm*
10	7
20	13
30	18
40	23
50	27
60	32

* The excess needed to trigger the guidance also depends on the # of reactivations in the MMF maintenance arm.

In addition, if ≤ 10% of the first 80 subjects experience disease reactivation after accruing 60 weeks of post-randomization time and the study is still accruing subjects, then the pooled estimate of the disease reactivation rate may be used to re-estimate the required sample size. The pooled observed rate (and the 2-sided 95% CI) will be used to reconsider the maximum potential difference between the arms. If power is at least 85% under scenarios where the assumed rate in the maintenance arm is ≤ 5% with an acceptable risk difference of 0.15, then the study team may consider reducing the sample size.

8.5 Other Statistical Considerations

8.5.1 Covariates

Covariates that may be considered include, but are not limited to:

- Age
- Race/ethnicity
- SLE duration
- MMF dose at baseline
- MMF use (cumulative mg-year)
- HCQ use (cumulative mg-year)
- Historical organ involvement
- Serological activity at entry (depletion of C3 or C4, presence of dsDNA antibodies)
- Steroid dose at entry
- Disease activity at entry (m-SLEDAI)
- Disease damage at entry, SLICC/ACR Damage Index (SDI)

8.5.2 Multicenter Studies

Because the analyses for this study are largely descriptive, no special consideration of site effects is planned.

8.5.3 Multiple Comparisons and Multiplicity

The primary and secondary analyses for this trial are considered to be descriptive with p-values and confidence intervals presented as descriptive measures of strength of evidence rather than formal statistical inference. Therefore, no multiplicity adjustments are needed for this study.

8.5.4 Examination of Subgroups

To support and further explain findings from the primary and secondary analyses, additional analyses may be conducted for the following subgroups:

- Age
- Race/ethnicity
- Disease manifestation (renal disease/extra-renal disease)
- SLE duration (< 5 years / ≥ 5 years)
- Baseline MMF dosing group (<2000 mg per day / ≥ 2000 mg per day)

8.5.5 Missing Data

Standard procedures will be used to ensure that data are as complete and accurate as possible. In analyses, a full accounting will be made for all data items. Generally, missing data will be treated as randomly missing with no data imputation. Deviations from this approach will be specified in the Statistical Analysis Plan (SAP). If data are missing for the primary endpoint, sensitivity analyses will be conducted to assess whether conclusions are robust to alternative

analytic approaches for handling these data. If data are missing for other key endpoints, sensitivity analyses could also be conducted, if deemed appropriate. Details of the sensitivity analyses will be provided in the SAP.

8.5.6 Changes to the Statistical Analysis Plan

A detailed description of the planned analyses will be provided in a SAP to be completed and signed off prior to the completion of the trial. Major changes from this protocol will be noted in the SAP. If there is sufficient reason to do so, revised plans may be issued during the course of the study. Changes to the SAP that are made subsequent to database lock will be documented in the clinical study report.

9 ACCESS TO SOURCE DATA AND DOCUMENTS

Each participating site will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from subjects participating in this clinical trial. Medical and research records should be maintained at each site in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of an investigation, each site must permit authorized representatives of the sponsor, the SACCC, and health authorities to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. Unless required by the laws permitting copying of records, only the coded identity associated with documents or other subject data may be copied (obscuring any personally identifying information). Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals. Participating sites will normally be notified in advance of auditing visits.

All subject records and study documentation will be kept after the protocol is completed. This will include all documentation of AEs, records of study drug receipt and dispensation, and all IRB correspondence. All study records will be kept for at least two years after the investigation is completed.

10 DATA COLLECTION, QUALITY CONTROL AND QUALITY ASSURANCE

The investigator is required to keep accurate records to ensure the conduct of the study is fully documented. 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.

The investigator will report all protocol deviations to DAIT and the SACCC per the instructions in the ACE Manual of Procedures. The SACCC will forward reports of protocol deviations to the responsible DAIT/NIAID medical officer for review as specified in the ACE Manual of Procedures.

The SACCC is 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.

Data will be obtained from a variety of sources including, but not limited to laboratory notebooks, automated instrument output files, and clinical subject charts. Data from these source materials will be transmitted to the SACCC via one of two mechanisms. Data collected electronically at central laboratories will be transferred electronically directly from the laboratory to the SACCC using standard secure data transfer procedures. Data collected at the clinical sites will be transmitted to the SACCC using an internet-based remote data entry system. Clinical site personnel use an internet browser to key data into e-CRFs; 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.

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

Data collected by the SACCC will be held in the strictest confidence, and are protected from access that could reveal personally identifying information about any subject in the trial.

11 ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

The study will be conducted according to Good Clinical Practice (GCP) guidelines, U.S. 21 CFR Part 50 – Protection of Human Subjects, and Part 56 – Institutional Review Boards.

11.1 Compliance with Good Clinical Practices

This trial will be conducted in compliance with the protocol, current GCPs recommended by the International Conference on Harmonization (ICH) and the applicable regulatory requirements for participating institutions. These include the tenets of the Declaration of Helsinki and review and approval by the appropriate ethics review committee or IRBs of participating organizations. The SACCC will assure compliance through a program of quality assurance audits performed both at participating sites and within the SACCC for data quality

and adherence to protocol requirements. The SACCC is operated by Rho Federal Systems Division, Inc. (RhoFED), Chapel Hill, North Carolina under a contract from NIAID.

11.2 Institutional Review Board (IRB)

Each participating institution must provide for the review and approval of this protocol and associated informed consent documents by an appropriate ethics review committee or IRB. Any amendments to the protocol or consent materials must be approved by the IRB before they are placed into use. In both the United States and in other countries, only institutions holding a current Federal Wide Assurance issued by the Office of Human Research Protection (OHRP) at the Department of Health and Human Services (DHHS) may participate.

The investigator will inform the IRB of serious or unexpected AEs that might occur during the study and are likely to affect the safety of the subjects, or the conduct of the study. The investigators will comply fully with all IRB requirements for both the reporting of AEs, protocol, or consent form changes, as well as any new information pertaining to the use of the study medication that might affect the conduct of the study.

11.3 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki, as well as compliance with all IRB requirements, will be implemented in the study, before any protocol-specified procedures are carried out. A standard consent form for subject participation will be provided with the protocol to each institution. Any modifications to the standard information in the template will require review and approval by DAIT/NIAID. Informed consent will be obtained in accordance with 21 CFR 50.52. Information may be given to subjects in oral, written, or video form by the investigator. All prospective subjects will be given ample time to read the consent form, and ask questions, before signing.

If subjects are to be enrolled who do not speak and read English, the consent materials must be translated into the language appropriate for the enrolling subject. Translated documents must be certified to contain the complete descriptions provided in the English version of the document. If an interpreter is used to provide or assist in describing the consent materials to an enrolling subject, the interpreter must also sign the consent materials certifying their involvement with the consent process.

After completion, a copy of the signed consent form will be given to the subject. The original signed consent form will be kept on file in the subject's study chart, available for inspection by regulatory authorities, both federal and institutional.

11.4 Data and Safety Monitoring Board

The responsibility for reviewing the ethical conduct of the study and for monitoring reports of evidence of adverse or beneficial effect is assigned to the DAIT Autoimmunity DSMB. The DSMB is an independent group composed of biomedical ethic experts, physicians, and other scientists who are responsible for continuing review of study information. The DSMB

makes recommendations to DAIT/NIAID on issues affecting the course and conduct of this clinical study.

12 FINANCING AND INSURANCE

Participating institutions must comply with their institution's policies on compensation, insurance, and indemnity. Institutions must have adequate liability insurance coverage to satisfy their local and national requirements for study participation.

13 PUBLICATION POLICY

The Autoimmunity Centers of Excellence (ACE) policy on publication of study results will apply to this study. Authorized participants may find details regarding the policy statement on the ACE internet website at http://www.rhoworld.com. Study investigators are encouraged to communicate and publish study results with prior notification of DAIT, NIAID.

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15 APPENDICES

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  - *ALE06 will typically use a spot proteinuria assessment, rather than a 24-hour urine proteinuria assessment However, if indicated, results from a 24-hour urine collection may be used.*
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  - *ALE06 will typically use a spot urinalysis rather than a 24-hour urine assessment. However, if indicated, results from a 24-hour urine collection may be used.*
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15.1 Appendix A: Definition of Mild Disease

Guidelines for Defining Mild SLE for ALE06 **Note: all timeframes are measured from ALE06 randomization.*		
Severe SLEDAI Manifestations		
	Acceptable	**Exclusionary**
Seizure	• Only if it is definitely not attributable to active lupus (e.g. changes in seizure medications)	• Within 12 months, if due to active lupus
Pyschosis		• Within 12 months
Organic Brain Syndrome		• Within 12 months
Visual Disturbance		• Within 6 months
Cranial Nerve Disorder		• Within 6 months
Lupus Headache	• Migraines	• Within 6 months
CVA	• None	• Within 12 months
Vasculitis	• Minor splinter hemorrhages • Mild digital vasculitis	
Arthritis	• Arthralgias • Joint tenderness without swelling	
Moderate/Chronic SLEDAI Manifestations		
	Acceptable	**Exclusionary if within last 6 months**
Myositis/Myalgia	• Weakness due to steroids or deconditioning • Non-specific myalgia without CPK elevation	• CK elevations associated with clinical evidence of myositis (weakness, myalgia)
Urinary Casts	• None	• RBC casts
Hematuria, Pyuria	• None due to active SLE	• Abnormal urinary sediment as defined in SLEDAI, indicative of ongoing, active lupus nephritis
Proteinuria	• ≤ 1 g/day for 6 months	• > 1 g/day
Rash	• Minor malar flush • Very small chronic discoid lesions • Damage	• Ulcerating lesions • New or widespread, inflammatory SLE rashes not due to acute sun exposure
Alopecia	• Chronic (> 1 year) diffuse alopecia • Scarred alopecia from prior disease	• New patches larger than 2 cm

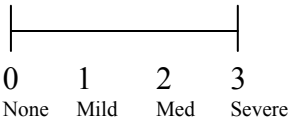
Guidelines for Defining Mild SLE for ALE06 **Note: all timeframes are measured from ALE06 randomization.*		
Mucosal Ulcers	• History of mild ulcers (not interfering with eating) within 1 month • History of mucosal ulcers of an unlikely relationship to SLE based on location	• Active ulcers at Screening
Pleurisy	• History of mild pleuritic chest pain (lasting < 1 hour or ascribed to non-serositis causes) that didn't require immunosuppressive treatment (i.e. steroids) within 1 month	• Pleural rubs or effusions on CXR requiring treatment
Pericarditis		• Clinical picture consistent with pericarditis via rub, EKC, or echocardiograph
Low Complement Level	• Yes	
dsDNA antibodies	• Yes	
Fever		• If due to active lupus
Thrombocytopenia		• Platelets ≤ 100,000/μL (equivalent to 100 $x10^9$/L
Leukopenia		• < 2.0 $x10^9$/L
Other Manifestations		
	Acceptable	**Exclusionary if within last 6 months**
Fatigue	• Yes	
Weight Loss	• If intentional • If < 5 % of body weight in 6 months	• More than 5% body weight felt to be due to SLE.
Anorexia	• Yes	
Lymphadenopathy		• Palpable nodes > 1 cm at Screening
Raynauds		• Digital ulcers
Livedo	• Yes	
Sicca Symptoms	• Yes	
Chilblains	• If chronic and stable	

15.2 Appendix B: ACR Criteria for SLE [32]

To be enrolled in this study, at least 4 of the following 11 ACR/SLE criteria must have been present at SLE diagnosis.			
	Criteria	**Description**	**Present**
1	**Malar rash**	Fixed malar erythema, flat or raised	☐
2	**Discoid rash**	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions	☐
3	**Photosensitivity**	Skin rash as an unusual reaction to sunlight, by patient history or physician observation	☐
4	**Oral ulcers**	Oral and nasopharyngeal ulcers, usually painless, observed by physician	☐
5	**Arthritis**	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion	☐
6	**Serositis**	a. Pleuritis (convincing history of pleuritic pain or rub heard by physician or evidence of pleural effusion) OR b. Pericarditis (documented by ECG or rub or evidence of pericardial effusion)	☐
7	**Renal disorder**	a. Persistent proteinuria > 0.5 protein:creatinine ratio or > 3+ if quantification not performed OR b. Cellular casts, may be red cell, hemoglobin, granular, tubular, or mixed	☐
8	**Neurologic disorder**	a. Seizures - in the absence of offending drugs or known metabolic derangements: e.g., uremia, ketoacidosis, or electrolyte imbalance OR b. Psychosis - in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance	☐
9	**Hematologic disorder**	a. Hemolytic anemia – with reticulocytosis OR b. Leukopenia (< 4000/mm^3 [equivalent to 4 x10^9/L] total on two or more occasions). OR c. Lymphopenia (< 1500/mm^3 [equivalent to 1.5 x10^9/L] on two or more occasions) OR d. Thrombocytopenia (< 100,000/mm^3 [equivalent to 100 x10^9/L] in the absence of offending drugs)	☐
10	**Immunologic disorder**	a. Anti-ds DNA: antibody to native DNA in abnormal titer OR b. Anti-Sm: presence of antibody to Sm nuclear antigen OR c. Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, (2) a positive test for lupus coagulant using a standard method, or (3) a false positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test	☐
11	**Antinuclear antibodies**	An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug induced lupus" syndrome	☐

15.3 Appendix C: SELENA-SLEDAI*

PHYSICIANS GLOBAL ASSESSMENT:
(3cm)



Length of line (from 0 to vertical assessment line) _____ cm

SLEDAI SCORE				
Check "Present" if descriptor is present at the time of visit or in the preceding 10 days.				
#	**Descriptor**	**Definition**	**Present**	**Weight**
1	**Seizure**	Recent onset (last 10 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 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.	☐	**8**
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 nonresponsive 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 2 joints with pain and signs of inflammation (i.e., tenderness, swelling, or effusion).	☐	**4**

SLEDAI SCORE				
Check "Present" if descriptor is present at the time of visit or in the preceding 10 days.				
#	**Descriptor**	**Definition**	**Present**	**Weight**
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 per high power field. Exclude stone, infection, or other causes.	☐	**4**
13	**Proteinuria**	> 0.5 protein:creatinine ratio. New onset or recent increase of more than 0.5 on the protein:creatinine ratio. *Note: ALE06 will typically use a spot urine protein:creatinine ratio.* If only the 24-hour urine is available, then proteinuria is defined as: " >0.5 gm/24 hours. New onset or recent increase of more than 0.5 gm/24 hours."	☐	**4**
14	**Pyuria**	> 5 white blood cells per 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 confirmation.	☐	**2**
20	**Low complement**	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.	☐	**2**
21	**Increased DNA binding**	> 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/mm^3 [equivalent to 100 x10^9/L]	☐	**1**
24	**Leukopenia**	< 3,000 white blood cells/mm^3 [equivalent to 3 x10^9/L] Exclude drug causes.	☐	**1**

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

MILD OR MODERATE FLARE	
☐	Change in SLEDAI > 3 points
☐	New/Worse • Discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus • Nasopharyngeal ulcers • Pleuritis • Pericarditis • Arthritis • Fever attributable to SLE
☐	Increase in prednisone, but not to > 0.5 mg/kg/day
☐	Added NSAID or Plaquenil
☐	≥ 1.0 increase in Physician's Global Assessment (PhGA), but not to more than 2.5 (on a 3.0 indexed VAS scale—refer to the Physican's Global Assessment located on the Modified SLEDAI Source Document)
SEVERE FLARE	
☐	Change in SLEDAI > 12
☐	New/Worse • CNS-SLE • Vasculitis • Nephritis • Myositis • Platelet Count < 60,000/ mm^3 [equivalent to 60 $x10^9$/L] • Hemolytic anemia with hemoglobin < 7% OR Decrease in hemoglobin > 3% *Requiring: doubling of prednisone, prednisone > 0.5 mg/kg/day, and/or hospitalization
☐	Prednisone > 0.5 mg/kg/day
☐	New Cyclophosphamide (Cytoxan), Azathioprine, Methotrexate, Mycophenolate Mofetil, or hospitalization attributable to SLE
☐	Increase in Physician's Global Assessment (PhGA) to > 2.5 (on a 3.0 indexed VAS scale—refer to the Physican's Global Assessment located on the Modified SLEDAI Source Document)

15.4 Appendix D: SLICC/DI* [39]

System Lupus International Collaborating Clinics/ACR Damage Index for SLE (SLICC/DI*)				
Check "Present" if descriptor is present at the time of visit (and circle 2 if applicable)				
*Damage (nonreversible change, not related to active inflammation) occurring since onset of lupus, ascertained by clinical assessment and present for at least **6 months** unless otherwise stated. Repeat episodes must occur 6 months apart to score 2. The same lesion cannot be scored twice.*				
	Descriptor	**Definition**	**Present**	**Score**
1	**Ocular** (either eye, by clinical assessment)	Any cataract ever	☐	1
		Retinal change or optic atropy	☐	1
2	**Neuropsychiatric**	Cognitive impairment (e.g. memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance levels) or major psychosis	☐	1
		Seizures requiring therapy for 6 months	☐	1
		Cerebrovascular accident ever (score 2> 1)	☐	1 (2)
		Cranial or peripheral neuropathy (excluding optic)	☐	1
		Transverse myelitis	☐	1
3	**Renal**	Estimated or measured glomerular filtration rate < 50%	☐	1
		Proteinuria ≥ 3.5 g/24hours *Note: ALE06 will use a spot proteinuria assessment.*	☐	1
		End-stage renal disease (regardless of dialysis or transplantation)	☐	3
4	**Pulmonary**	Pulmonary hypertension (right ventricular prominence, or loud P2)	☐	1
		Pulmonary fibrosis (physical and radiograph)	☐	1
		Shrinking lung (radiograph)	☐	1
		Pleural fibrosis (radiograph)	☐	1
		Pulmonary infarction (radiograph)	☐	1
5	**Cardiovascular**	Angina or coronary artery bupass	☐	1
		Myocardial infarction ever (score 2 if > 1)	☐	1 (2)
		Cardiomyopathy (ventricular dysfunction)	☐	1
		Valvular disease (diastolic murmur, or systolic murmur > 3/6)	☐	1
		Pericarditis for 6 months, or pericardiectomy	☐	1

System Lupus International Collaborating Clinics/ACR Damage Index for SLE (SLICC/DI*)				
Check "Present" if descriptor is present at the time of visit (and circle 2 if applicable)				
*Damage (nonreversible change, not related to active inflammation) occurring since onset of lupus, ascertained by clinical assessment and present for at least **6 months** unless otherwise stated. Repeat episodes must occur 6 months apart to score 2. The same lesion cannot be scored twice.*				
	Descriptor	**Definition**	**Present**	**Score**
6	**Peripheral vascular**	Claudication for 6 months	☐	1
		Minor tissue loss (pulp sauce)	☐	1
		Significant tissue loss ever (e.g. loss of digit or limb) (score 2 if > 1 site)	☐	1 (2)
		Venous thrombosis with swelling, ulceration, or venous stasis	☐	1
7	**Gastrointestinal**	Infarction or resection of bowel below duodenum spleen, liver, or gall bladed ever, for cause any (score 2 if > 1 site)		1 (2)
		Mesenteric insufficiency		1
		Chronic peritonitis		1
		Stricture or upper gastrointestinal tract surgery ever	☐	1
8	**Musculoskeletal**	Muscle atrophy or weakness	☐	1
		Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	☐	1
		Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	☐	1
		Avascular necrosis (score 2 if > 1)	☐	1 (2)
		Osteomyelitis	☐	1
9	**Skin**	Scarring chronic alopecia	☐	1
		Extensive scarring or panniculum other than scalp and pulp space	☐	1
		Skin ulceration (excluding thrombosis) for > 6 months	☐	1
10	Premature gonadal failure		☐	1
11	Diabetes (regardless of treatment)		☐	1
12	Malignancy (exclude dysplasia) (score 2 if > 1 site)		☐	1 (2)
Total Score (sum of scores next to descriptors marked present)**:**				

15.5 Appendix E: BILAG* 2004 (2007 Revision)

Note: ALE06 will typically use a spot urinalysis rather than a 24-hour urine assessment. However, if indicated, results from a 24-hour urine collection may be used.

BILAG2004 INDEX Centre: Date: Initials/Hosp No:

Only record 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 ♦♦

Scoring: **ND Not Done**
1 Improving
2 Same
3 Worse
4 New
Yes/No OR Value (where indicated)
❑ indicate if not due to SLE activity
(default is 0 = not present)

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 ( )

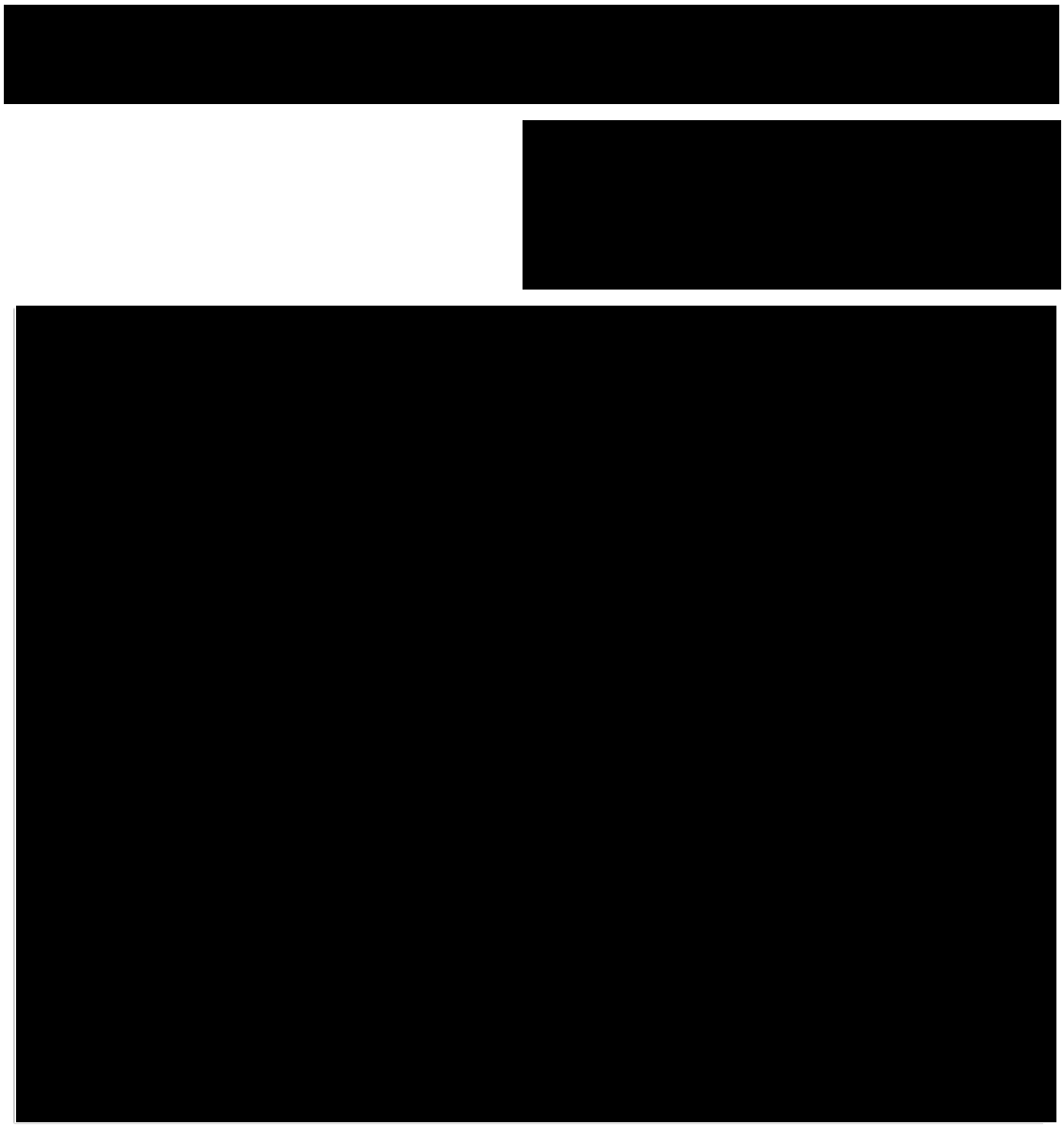
RENAL
78. Systolic blood pressure (mm Hg) value ( ) ❑
79. Diastolic blood pressure (mm Hg) value ( ) ❑
80. Accelerated hypertension Yes/No ( )
81. Urine dipstick protein (+=1, ++=2, +++=3) ( ) ❑
82. Urine albumin-creatinine ratio mg/mmol ( ) ❑
83. Urine protein-creatinine ratio mg/mmol ( ) ❑
84. 24 hour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

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

Revision: 12/Jan/2007

15.6 Appendix F: SF-36® [40]

[redacted]



4. [redacted]

[redacted]

[redacted]

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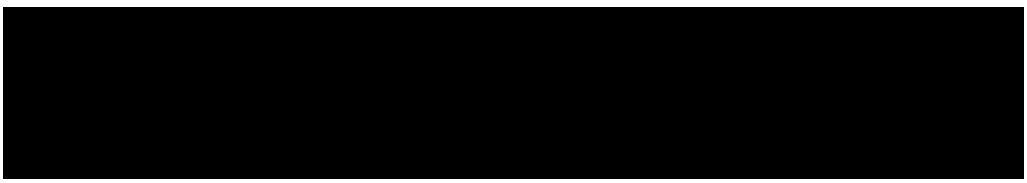
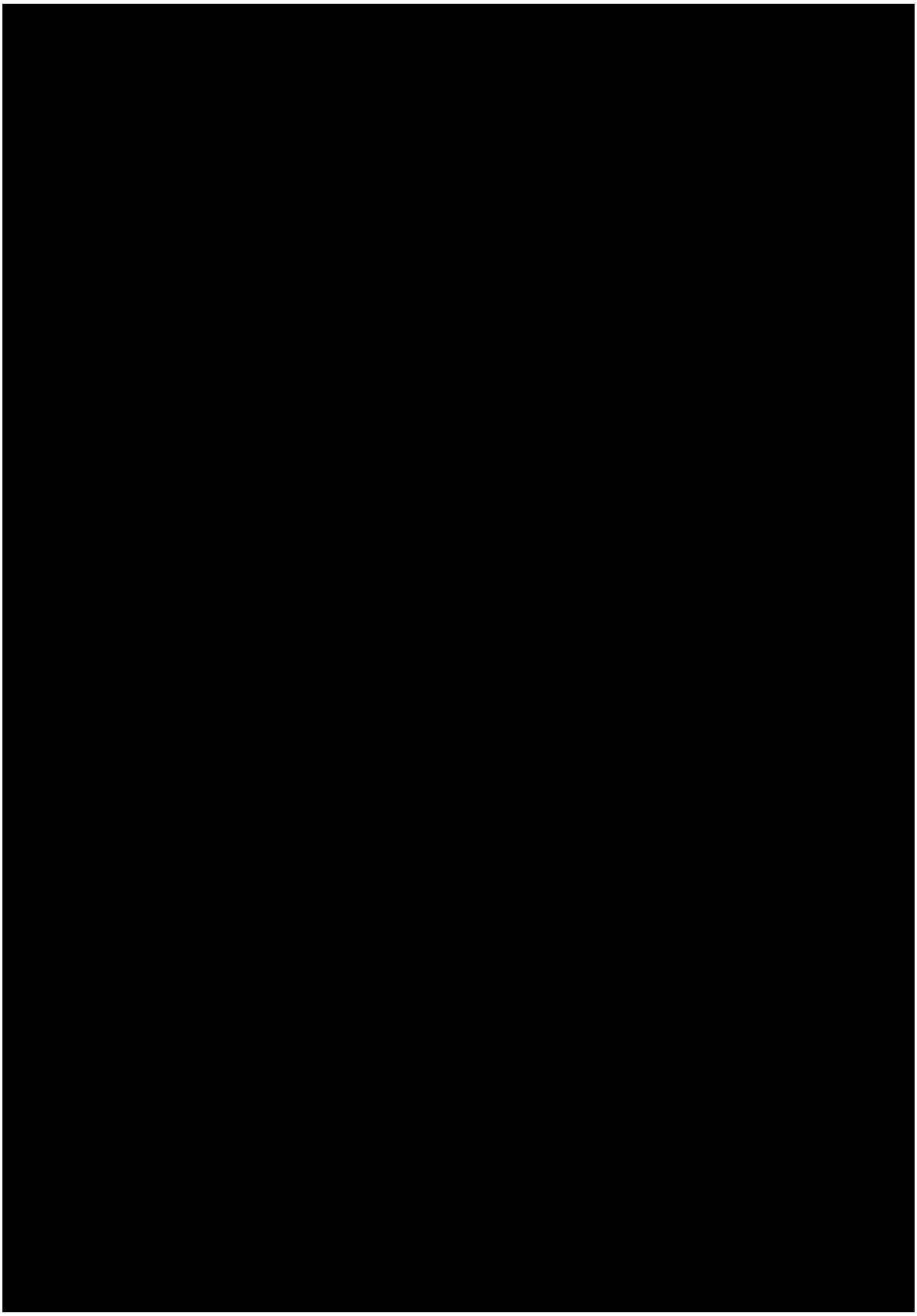
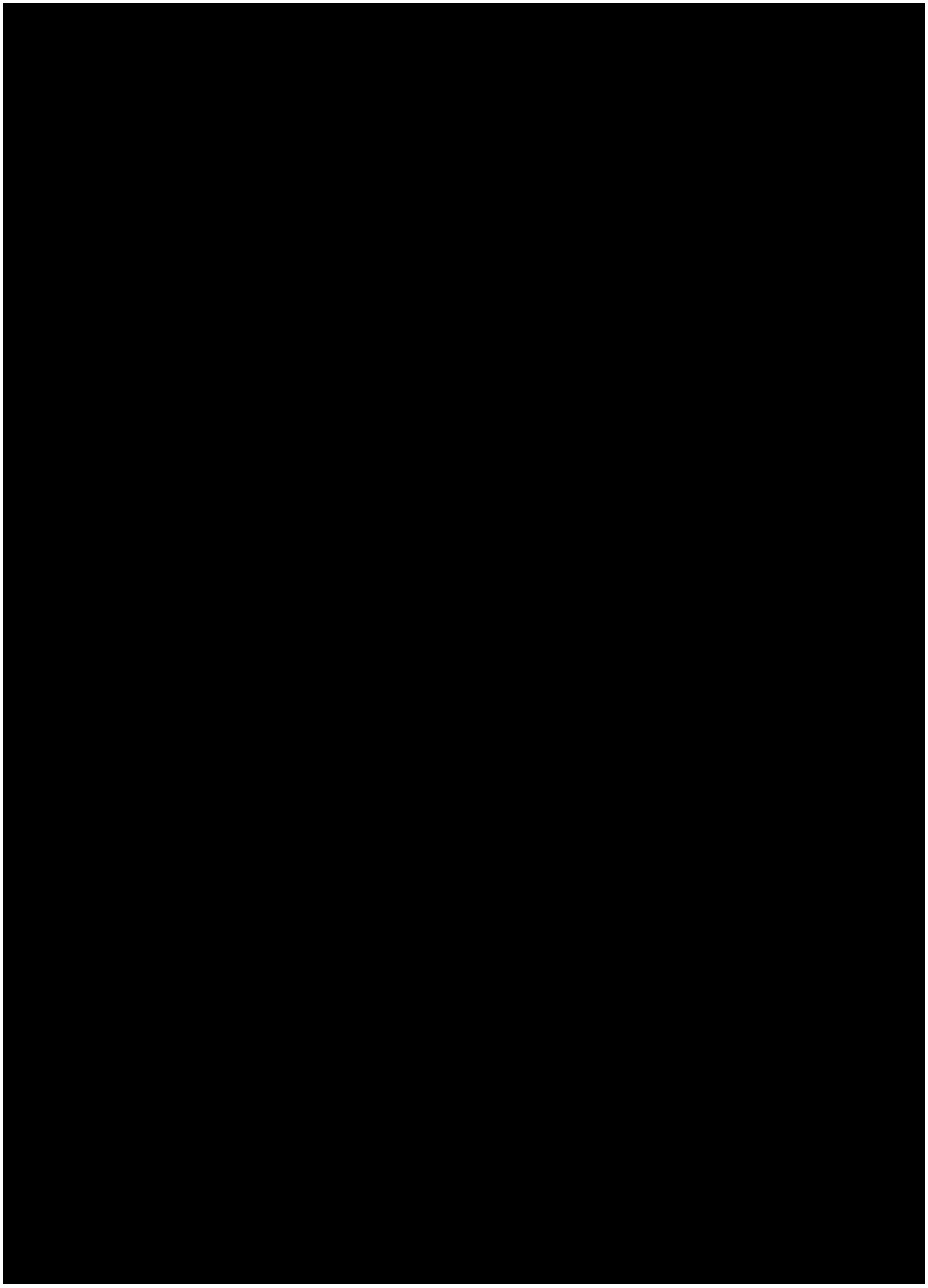
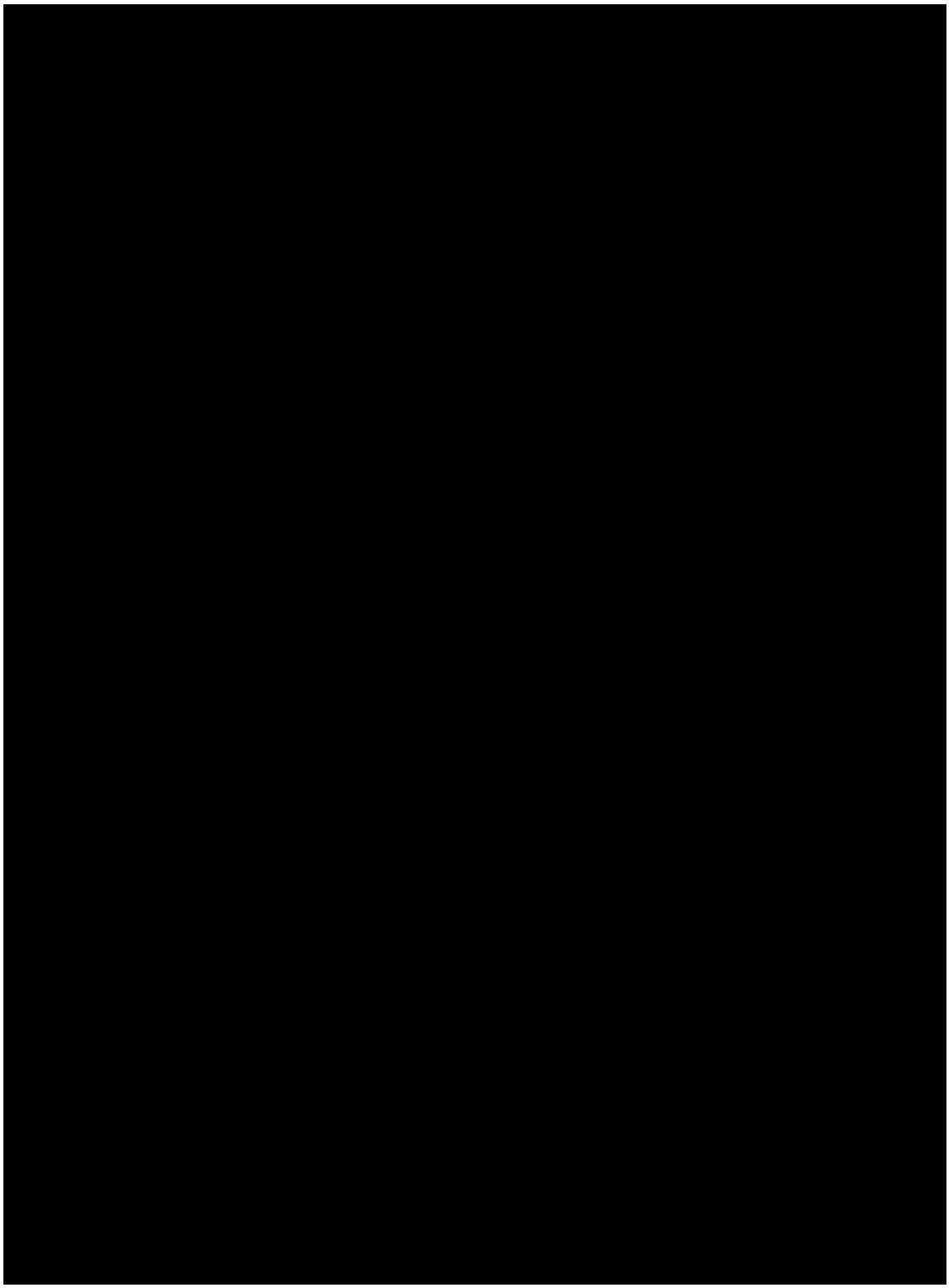
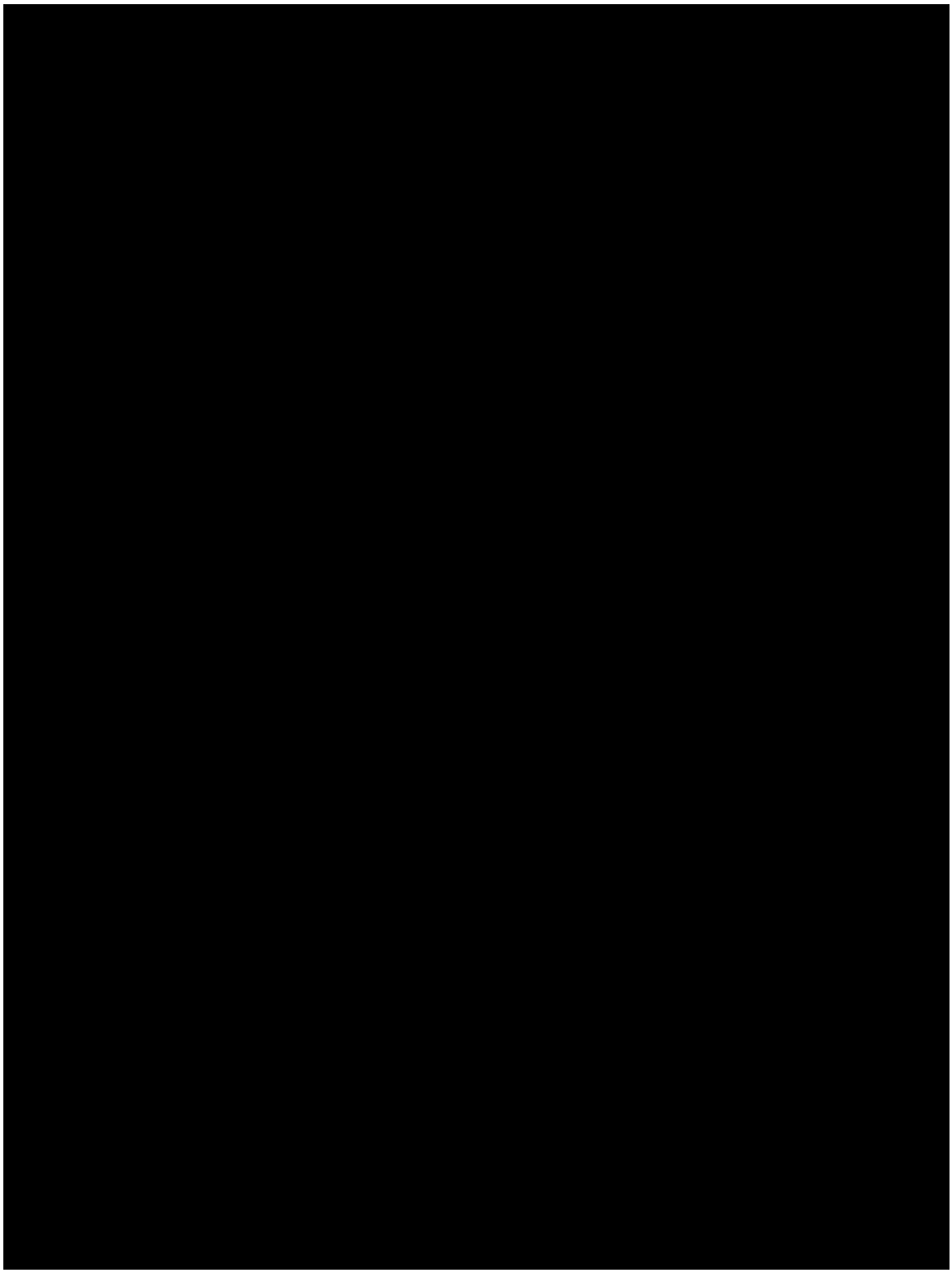


15.7 Appendix G: SF-36® (Spanish version) [40]









15.8 Appendix H: FACIT [41]

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

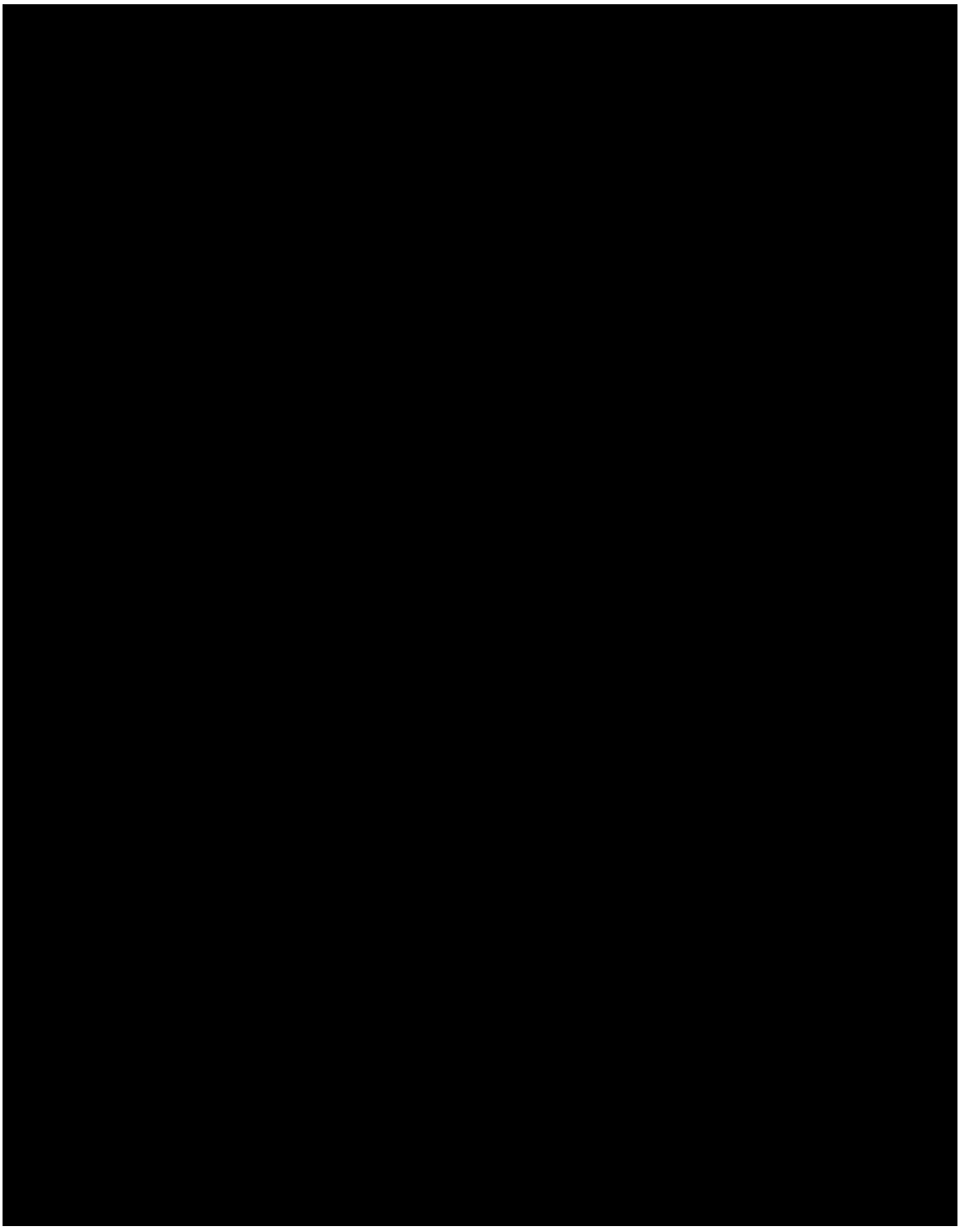
15.9 Appendix I: FACIT [41] (Spanish version)

Escala FACIT de fatiga (Versión 4)

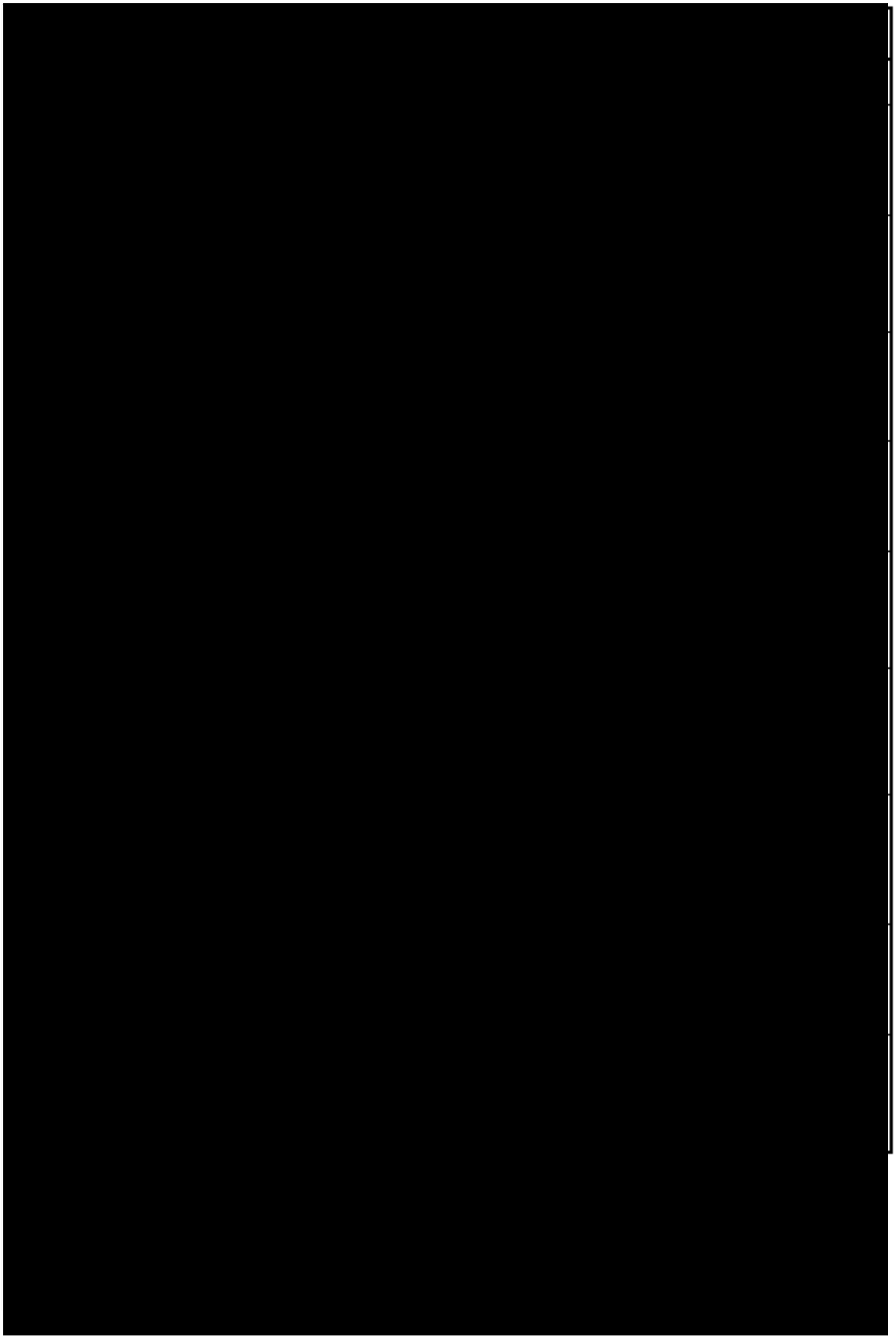
A continuación encontrará una lista de afirmaciones que otras personas con su misma enfermedad consideran importantes. **Marque un solo número por línea para indicar la respuesta que corresponde a los últimos 7 días.**

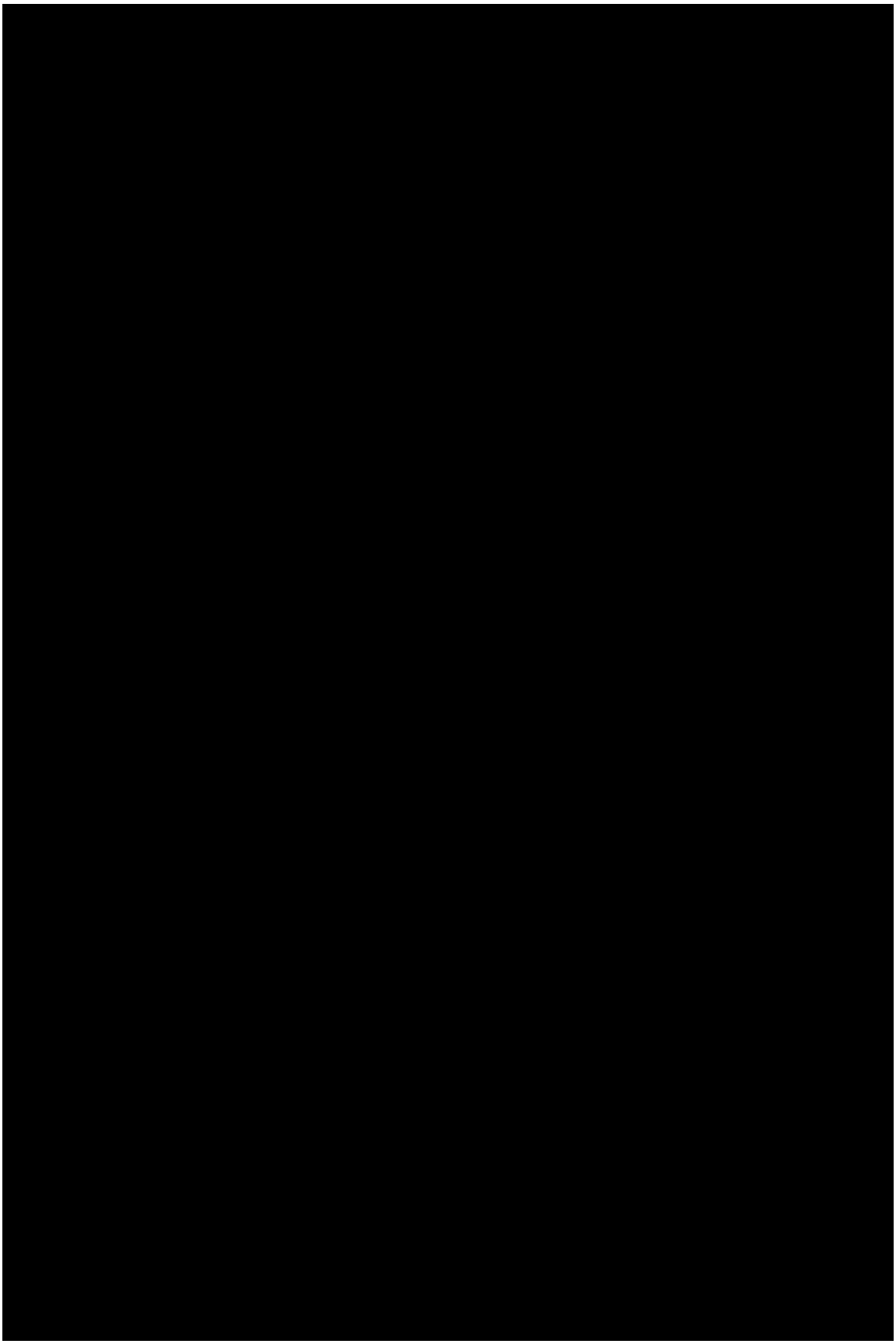
		Nada	Un poco	Algo	Mucho	Muchí-simo
H07	Me siento agotado(a)	0	1	2	3	4
H11 12	Siento debilidad en todo el cuerpo	0	1	2	3	4
An1	Me siento decaído(a)	0	1	2	3	4
An2	Me siento cansado(a)	0	1	2	3	4
An3	Tengo dificultad para comenzar las cosas porque estoy cansado(a)	0	1	2	3	4
An4	Tengo dificultad para terminar las cosas porque estoy cansado(a)	0	1	2	3	4
An5	Tengo energía	0	1	2	3	4
An7	Soy capaz de hacer mis actividades habituales (trabajar, ir a la escuela, hacer las compras)	0	1	2	3	4
An8	Necesito dormir durante el día	0	1	2	3	4
An 12	Estoy demasiado cansado(a) para comer	0	1	2	3	4
An 14	Necesito ayuda para hacer mis actividades habituales	0	1	2	3	4
An 15	Estoy frustrado(a) porque estoy demasiado cansado(a) para hacer las cosas que quiero hacer	0	1	2	3	4
An 16	Tengo que limitar mis actividades sociales debido al cansancio	0	1	2	3	4

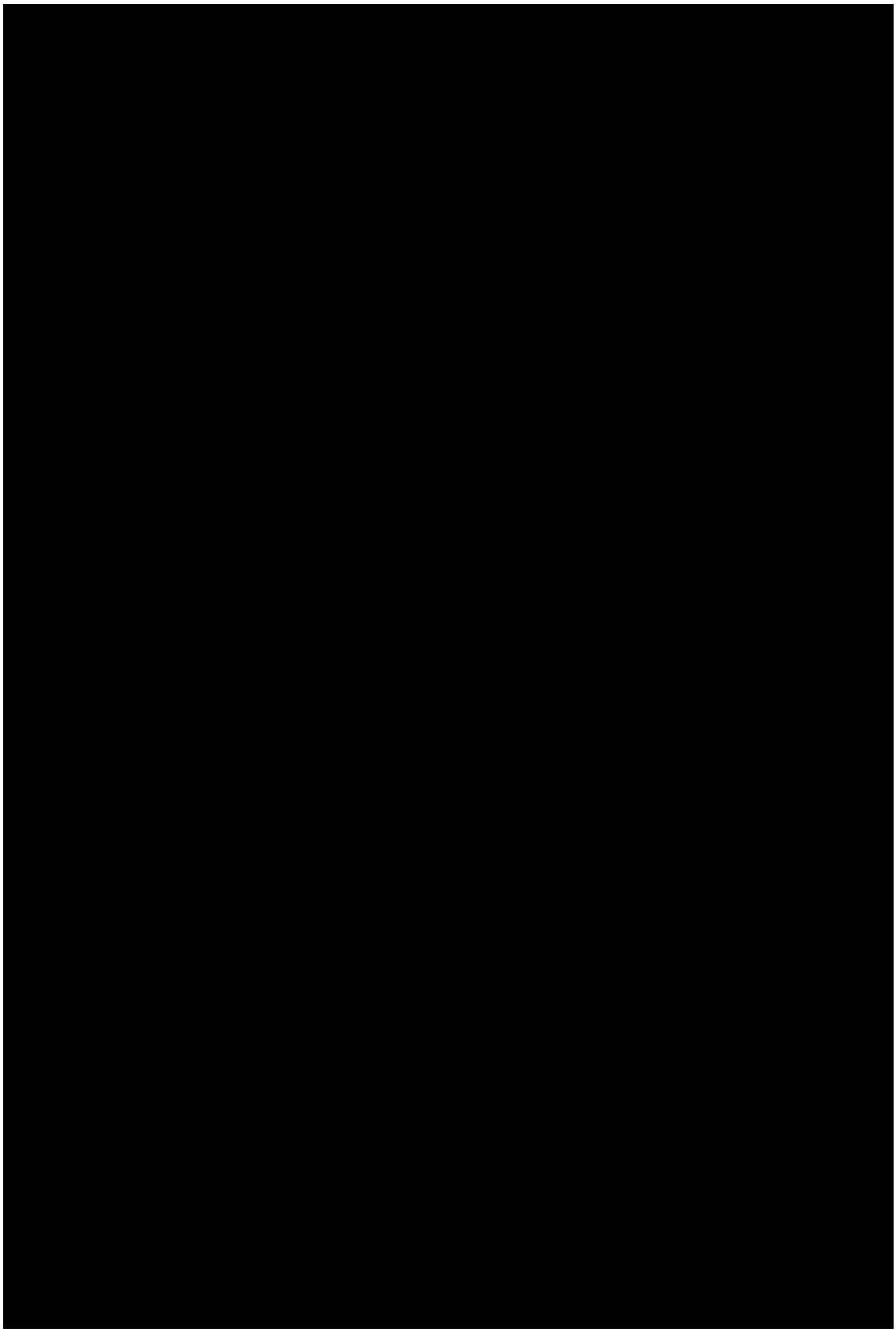
15.10 Appendix J: Lupus QoL© [42]



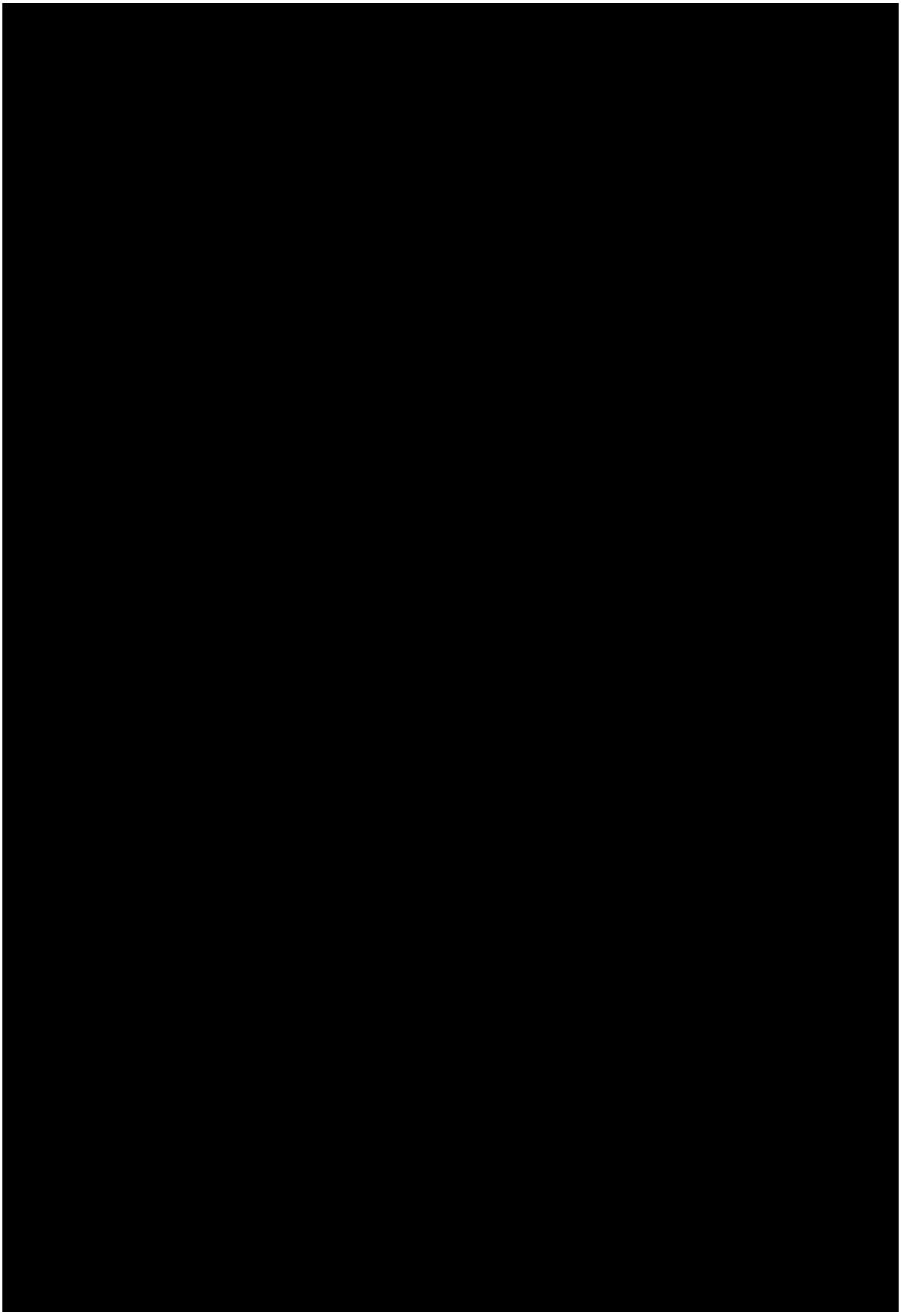
English for USA

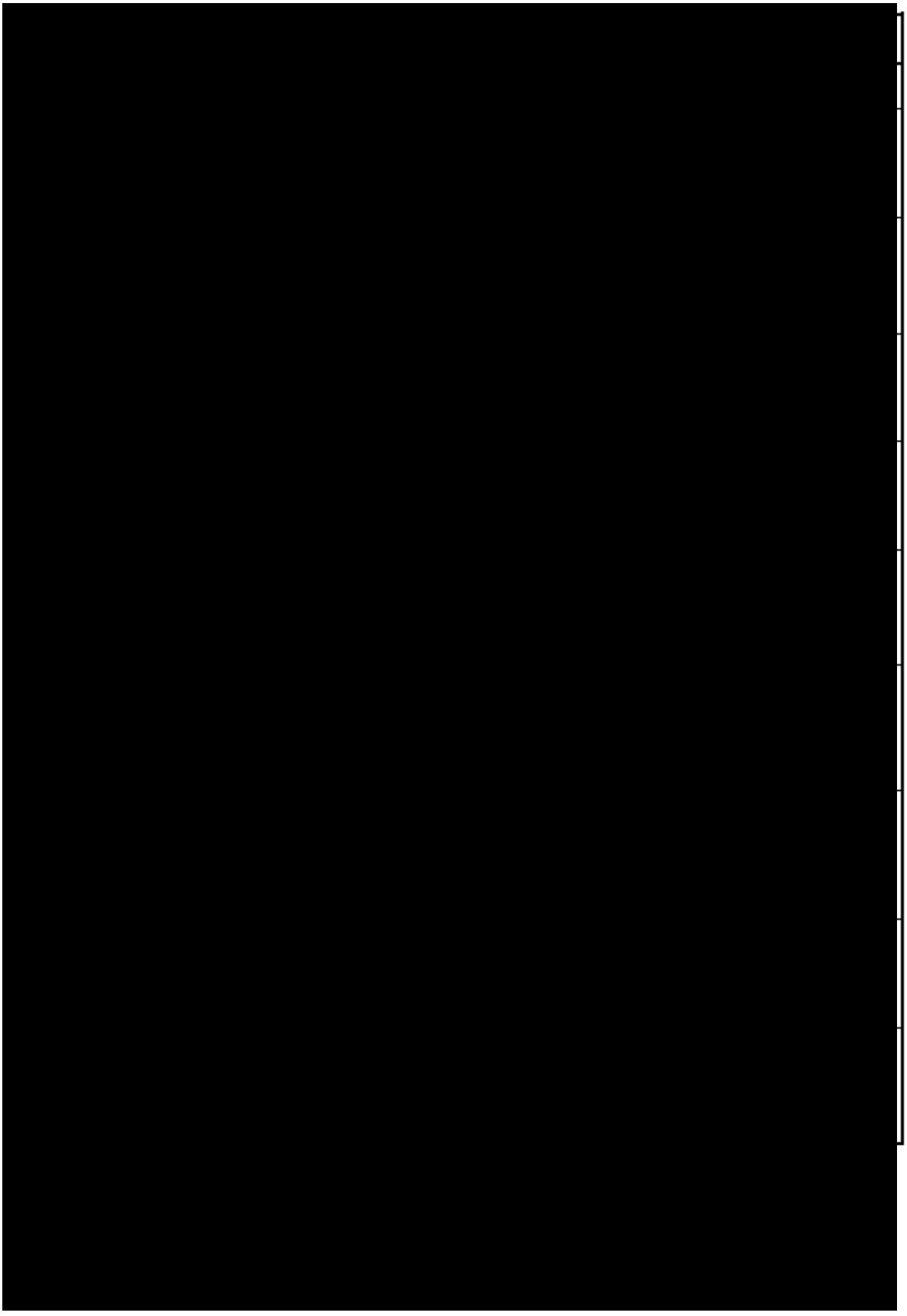


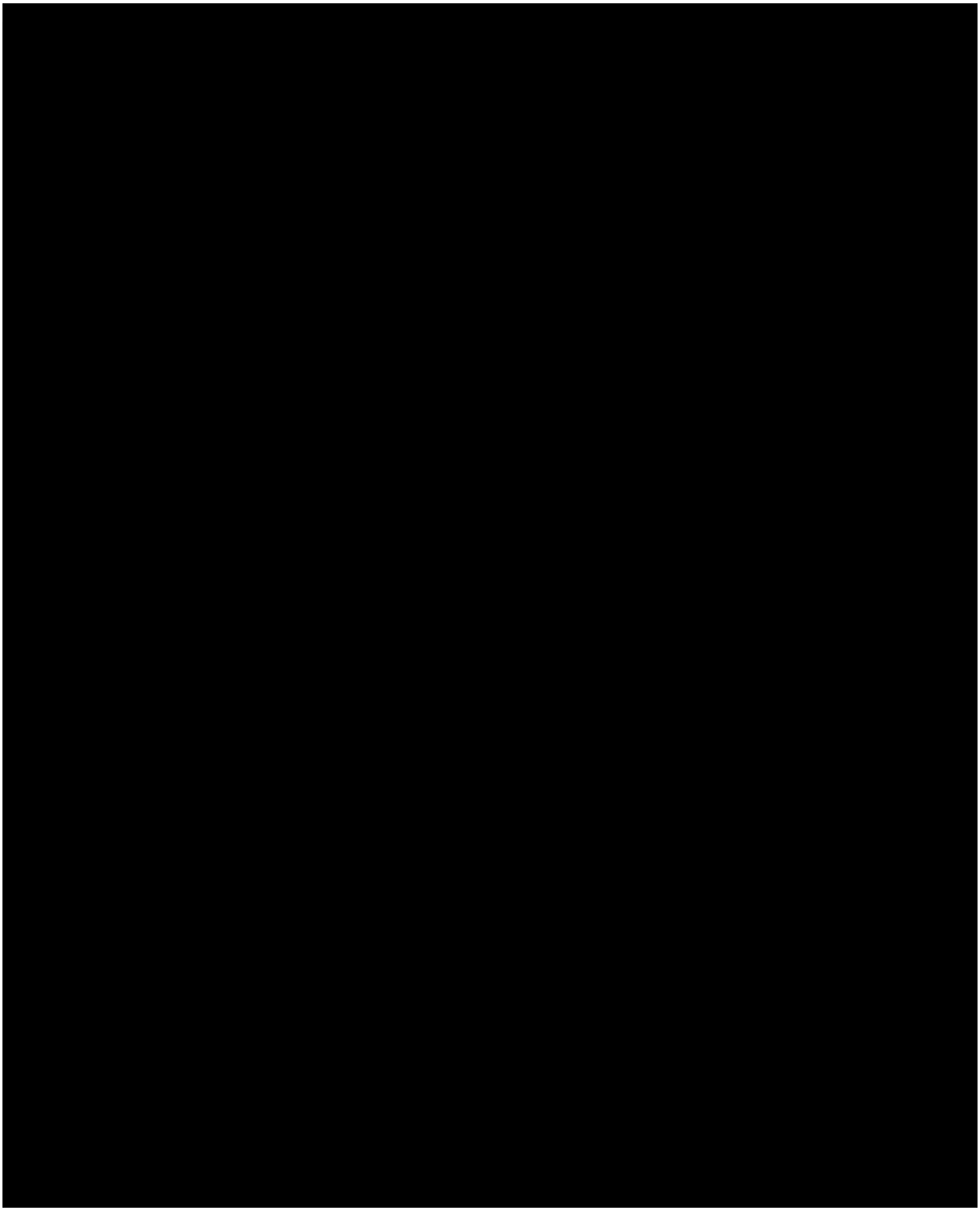




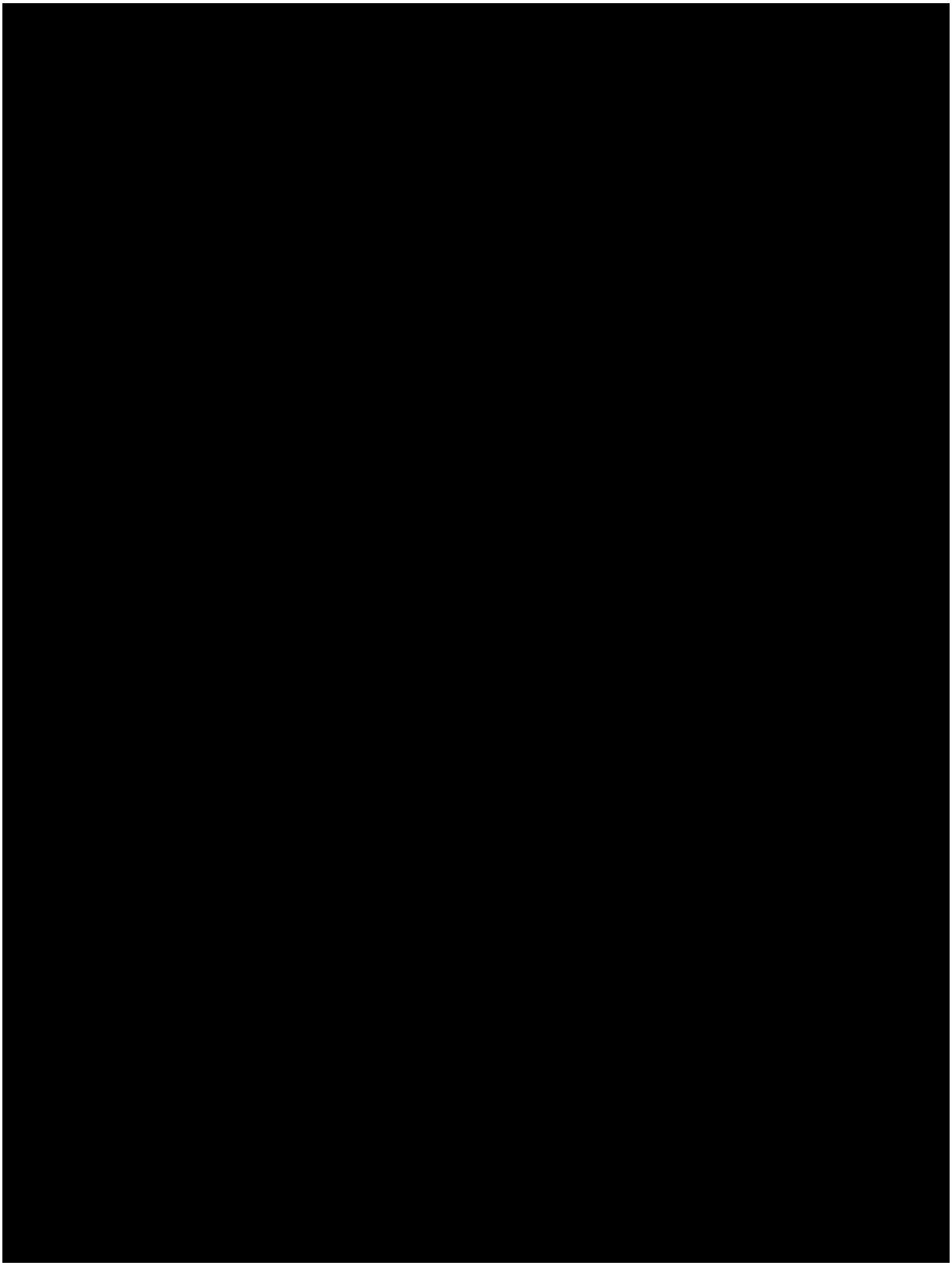
15.11 Appendix K: Lupus QoL© [42] (Spanish version)







Spanish for Puerto Rico/USA



Spanish for Puerto Rico/USA

15.12 Appendix L: 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
• Patient’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.