# DAIT/Rho STATISTICAL ANALYSIS PLAN
# 14 November 2019

**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

**VERSION:** 1.0

**DATE:** 14 November 2019

**SPONSOR:**
Division of Allergy, Immunology, and Transplantation
National Institute of Allergy and Infectious Diseases – NIH
5601 Fishers Lane
Rockville, MD 20852
Telephone: (301) 496-5717
Fax: (301) 402-3573

**PREPARED BY:**
Rho
2635 E NC Hwy 54
Durham, NC 27713
Telephone: (919) 408-8000
Fax: (919) 408-0999

# DAIT/Rho STATISTICAL ANALYSIS PLAN ACKNOWLEDGMENT AND SIGNATURE SHEET

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

Approved: _____ Date: _____
Eliza Chakravarty, MD
Protocol Chair

Approved: _____ Date: _____
Ellen Goldmuntz, MD, PhD
NIAID Medical Monitor

Approved: _____ Date: _____
Bill Barry, PhD
Rho Scientist

Approved: _____ Date: _____
Ashley Pinckney, MS
Rho Statistician

## Document History

| Version | Date | Change(s) | Author |
|---|---|---|---|
| 0.1 | 28June2019 | Initial Draft | Ashley Pinckney |
| 1.0 | 14Nov2019 | Final | Ashley Pinckney |

# Table of Contents

# 1. 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.

**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)

**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 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

**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)

**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.

**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 ≤ ***a***" as a function of values for the "Acceptable increase in risk with withdrawal of MMF (***a***)". 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.

**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:

**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)

- 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 11$^{th}$ 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 11$^{th}$ 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 11$^{th}$ 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. $risk_{\_MMF\,withdrawal} - risk_{\_MMF\ maintenance}$) and consider whether or not the trial should be stopped for safety concerns. (See Section 8.4 *Interim Analysis* for details.)

## 2. INTRODUCTION

This statistical analysis plan includes pre-planned analyses related to the study objectives outlined in the protocol.

# 3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following analyses and reporting conventions will be used:

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form "n (%)." Percentages will be rounded to one decimal place.

- Numeric variables will be summarized using n, mean, standard deviation (SD), median, minimum (min), maximum (max). The min/max will be reported at the same level of significance as original data. The mean and median will be reported at one more significant digit than the precision of the data, and SD will be reported at two more significant digits than the precision of the data.

- The median will be reported as the average of the two middle numbers if the dataset contains an even number of observations.

- Test statistics including *t* and *z* test statistics will be reported to two decimal places.

- *P*-values will be reported to three decimal places if greater than or equal to 0.001. If less than 0.001, the value will be reported as "<0.001." A *p*-value can be reported as "1.000" only if it is exactly 1.000 without rounding. A *p*-value can be reported as "0.000" only if it is exactly 0.000 without rounding.

If departures from these general conventions are present in the specific evaluations section of this SAP, then those conventions will take precedence over these general conventions.

# 4. ANALYSIS SAMPLES

## 4.1. Safety Population

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

## 4.2. 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.

## 4.3. 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 (including <80% compliance over the subject's treatment period, as defined in Section 6.2, *Treatment Adherence*), 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.

# 5. STUDY SUBJECTS

## 5.1. Disposition of Subjects

The disposition of all enrolled subjects will be summarized in tables and listed.

The numbers and percentages of subjects randomized, in each analysis sample, and completing selected study weeks (Weeks 12 and 60), as well as reasons for early termination from the study will be presented overall and by treatment arm. For subjects discontinuing ALE06-provided MMF early, the reasons for discontinuing early will also be presented.

## 5.2. Demographic and Other Baseline Characteristics

Summary descriptive statistics for baseline and demographic characteristics will be reported for all analysis samples overall and by treatment arm. Characteristics to be summarized include age, race, ethnicity, sex, duration of SLE, renal vs. non-renal disease, MMF dose, MMF dose (< 2000 mg per day versus ≥ 2000 mg per day), duration of MMF treatment at the baseline dose, hydroxychloroquine dose, SLEDAI score, creatinine, GFR, C3, C4, anti-double stranded DNA, hemoglobin, height, and weight. A listing of demographic and baseline characteristics will also be provided.

No hypothesis tests will be used to compare treatment arms with respect to demographic or baseline characteristics.

# 6. STUDY OPERATIONS

## 6.1. Protocol Deviations

Major protocol deviations will be listed by site with information such as type of deviation, whether notification to the IRB was required, date of occurrence, and the reason for the deviation. Protocol deviations will be summarized in tabular format by type of deviation. No protocol deviation will exclude a subject from the mITT, or safety populations.

## 6.2. Treatment Adherence

Subjects will be randomized 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

Prescribed MMF doses for subjects in the study will be collected on the *Study Drug Dose Log* CRF page. Information on this page includes dates of dose changes, prescribed doses (including a "zero" dose when a subject completes tapering), and reasons for dose changes. Bottles of MMF dispensed along with pill counts will be collected on the *Study Drug Accounting Log* CRF page. This page includes information on the number of bottles dispensed, number of pills in the bottle, dates dispensed and returned, pills returned, and pills lost.

For both treatment arms, the total number of expected pills to be taken will be derived based on a subject's prescribed MMF dose, taken from the *Study Drug Dose Log* CRF page, and duration of time in the study.

The actual number of pills taken will be derived based on data on the *Study Drug Accounting Log* CRF page. Given then number of bottles dispensed and number of pills in the bottles, actual pills counts will be derived based on the number of pills returned and number of pills lost. It will be assumed that any pills not returned or reported as lost by a subject will have been taken by the subject. Compliance will be calculated over the 12 week taper period for the Withdrawal arm and over the 60 week study period for the Maintenance arm.

Compliance will be calculated as:

$$\%\, Compliance = \frac{Total\ Number\ of\ Actual\ Pills\ Taken}{Expected\ Number\ of\ Pills\ Taken} \times 100$$

For subjects who terminate early from the study or who discontinued study-provided MMF early, compliance will only be calculated for the time in which the subject is taking study-provided MMF.

# 7. ENDPOINT EVALUATION

## 7.1. Overview of Efficacy Analysis Methods

### 7.1.1. Multicenter Studies

Study subjects were recruited from 19 study sites. Because the endpoint evaluations for this study are largely descriptive, clinical site will not be included as a covariate in the analyses.

### 7.1.2. Assessment Time Windows

Allowable visit windows for all scheduled visits are provided in Table 7-1.

**Table 7-1 Visit Windows**

| Visit | Window |
|---|---|
| Screening | -28 to -1 |
| Baseline | 0 |
| Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48, 60 | ± 7 days |

Unscheduled, Flare, and Endpoint visits may also occur throughout the study. All data will be included in analyses, regardless of time of assessment.

## 7.2. Primary Endpoint

### 7.2.1. Computation of the 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 in the withdrawal arm 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.*

**SELENA-SLEDAI:**

The SELENA-SLEDAI instrument will be completed at baseline and every follow-up visit, including any Flare or Endpoint visits, during the course of the 60 week study period for all subjects. Data for this assessment will be collected on the *Physician's Global Assessment*, *SLEDAI*, and *SELENA Flare & Endpoint Assessment* CRF pages. The SELENA-SLEDAI assesses SLE disease activity and flares based on changes in the SLEDAI score, the Physician's Global Assessment (PGA), medication use (prednisone, NSAIDS, Plaquenil, major immunosuppressives), other disease activity criteria, and hospitalization due to SLE.

Study investigators complete the SLEDAI scale by indicating of presence of 24 SLE disease manifestations during the preceding 10 days. The original SLEDAI instrument includes 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. Each of the 24 disease manifestations has an assigned weight (see Appendix 14.3). The SLEDAI total score will be computed as the sum of the weights for the items indicated as present. If a component of the SLEDAI (urinalysis or hematological labs only) was missed at a visit, then the missing data will be imputed by using the last observation carried forward approach. If a component of the SLEDAI is missed over consecutive visits, then the subsequent components will not be imputed. If an entire visit was missed, the score will not be imputed.

Mild/moderate and severe SELENA-SLEDAI flares will be defined per the table below. If one or more criteria for a mild/moderate or severe flare have been met, a subject will be considered as having a mild/moderate or severe flare at that study visit.

| | |
|---|---|
| **MILD OR MODERATE FLARE** | |
| ☐ | Change in SLEDAI > 3 points |
| ☐ | New/Worse<br>Discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus<br>Nasopharyngeal ulcers<br>Pleuritis<br>Pericarditis<br>Arthritis<br>Fever attributable to SLE |
| ☐ | Increase in prednisone, but not to > 0.5 mg/kg/day[1] |
| ☐ | 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<br>CNS-SLE<br>Vasculitis<br>Nephritis<br>Myositis<br>Platelet Count < 60,000/ $mm^3$ [equivalent to 60 $x10^9$/L] |

| | |
|---|---|
| | Hemolytic anemia with hemoglobin < 7% OR Decrease in hemoglobin > 3%<br>*Requiring: doubling of prednisone, prednisone > 0.5 mg/kg/day, and/or hospitalization |
| ☐ | Prednisone > 0.5 mg/kg/day[1] |
| ☐ | New Cyclophosphamide (Cytoxan), Azathioprine, Methotrexate, Mycophenolate Mofetil, or hospitalization attributable to SLE |
| ☐ | Increase in Physician's Global Assessment (PhGA) to > 2.5<br>(on a 3.0 indexed VAS scale—refer to the Physican's Global Assessment located on the Modified SLEDAI Source Document) |

[1] For ALE06, prednisone > 0.5 mg/kg/day is categorized as a severe SELENA-SLEDAI flare if the duration is >2 weeks. Increases in prednisone >0.5 mg/kg/day but for ≤2 weeks will be categorized as mild/moderate SELENA-SLEDAI flares.

**Increased immunosuppressive therapy:**

Increased steroid therapy, as defined by 2a and 2b in the definition of clinically significant SLE reactivation, will be taken from the *SELENA Flare & Endpoint Assessment* and *Prior/Concomitant Medications* CRF pages. To differentiate from any doses of steroids taken for non-SLE related causes, only records marked as "Yes" to the question "Is this medication a corticosteroid or immunosuppressant prescribed after Day 0 due to increased SLE activity?" will be analyzed. Prednisone started ≤10 days post-visit for a flare will be included as increased therapy.

Increase/resumption of MMF therapy or the addition of major immunosuppressive therapy, as defined by 2c in the definition of clinically significant SLE reactivation, will be taken from the *SELENA Flare & Endpoint Assessment* CRF page.

**Endpoint:**

For each subject, a yes/no variable will be assigned to indicate whether a subject has met the primary endpoint of clinically significant disease reactivation between Day 0 and Week 60, as defined above.

Subjects who terminate early from the study, and who had not previously met primary endpoint, will be handled as follows:

1. Subjects who do not have a mild/moderate or severe SELENA-SLEDAI flare at their last study visit will be categorized as not experiencing clinically significant disease reactivation.

2. Subjects who have a mild/moderate or severe SELENA-SLEDAI flare at their last study visit:

    a. Subjects will be categorized as experiencing clinically significant disease reactivation for the following three scenarios:

        i. Subject has a SELENA-SLEDAI mild/moderate or severe flare at the time of early termination, and a steroid increase/burst to ≥ 15 mg/day prednisone that is sustained through end of study.

        ii. Subject previously experienced a flare requiring either intra-articular, intra-muscular or IV steroids, or an increase/burst of steroids that was successfully tapered to < 15 mg/day within four

weeks, and is experiencing a severe flare at the time of early termination.

iii. Subject has a SELENA-SLEDAI severe flare based on the following clinical components: SLEDAI score; New/Worse disease, and Increase in PhGA without considering prednisone or other treatments

b. Subjects experiencing flare at the time of early termination, but who do not met the criteria in 2.a. above, will be classified as not experiencing clinically significant disease reactivation.

These cases will be re-categorized under sensitivity analyses for the primary endpoint (see 7.2.3).

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 for clinically significant SLE reactivation. The time-to-event will be defined as the interval: date of disease reactivation – date of Day 0 visit. Subjects who do not experience clinically significant disease will be censored at the last visit date on study.

The probability, or risk, of disease reactivation by Week 60 (on a 0 to 1 scale) in each arm will be derived using the Kaplan-Meier product-limit estimator for the cumulative incidence of disease reactivation. Standard errors and confidence intervals for the cumulative incidence will be obtained using Greenwood's formula.

### 7.2.2. Primary Analysis of the Primary Endpoint

The planned analyses for this study are designed to maximize the information available for medical decision-making. The planned analyses are as follows:

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) and 95% confidence intervals around the risk difference will be reported using the Kaplan-Meier product-limit estimator.

The observed risk estimates will be used to compute the "% Confidence that the true increase is ≤ a" as a function of values for the "Acceptable increase in risk with withdrawal of MMF (a)". This information will be plotted with values for "Acceptable increase in risk with withdrawal of MMF (a)" on the x axis and estimates for "% Confidence that the true increase is ≤ a" on the y axis. The study will generate a single curve based on the observed risk estimates for the two arms. Physicians with their patients could decide on an acceptable level of increased risk (a) then read from the plot the % confidence that this selected value of a would not be exceeded with withdrawal of MMF. Depending on the level of confidence, they may or may not decide to withdraw MMF.

The motivation for the curve 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. $risk_{\_MMF\ withdrawal}$ - $risk_{\_MMF\ maintenance}$) 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 to 0.99, in 0.01 increments. 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.

The primary analyses of the primary endpoint will be performed on the mITT population.

### 7.2.3. Sensitivity and Additional Analyses of the Primary Endpoint

Sensitivity and additional analyses on the primary endpoint will include the following:

1. Analyses analogous to the primary will be run on the PP population.

2. Sensitivity analyses will be performed to assess the robustness of the conclusions under different assumptions for missing data for subjects who terminated early from the study. All subjects who have a mild/moderate or severe SELENA-SLEDAI flare at their last study visit will be re-categorized as experiencing clinically significant disease reactivation. Additional sensitivity analyses may be performed including single and multiple imputation methods.

3. A sensitivity analysis will be run to assess the impact of new or increased major immunosuppressive medications as the only cause of flare and therefore meeting primary endpoint. Subjects who re-start or increase a major immunosuppressive, but have no other disease activity that would categorize them as having a mild/moderate or severe flare will be categorized as not meeting primary endpoint (which requires both a SELENA-SLEDAI flare and increased immunosuppressive activity). Analyses analogous to the primary will be run for this sensitivity analysis.

## 7.3. Secondary Clinical Disease Activity Endpoints

All secondary analyses will be conducted in an exploratory fashion with any 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 PP population.

### 7.3.1. Time to Clinically Significant Disease Reactivation

**Endpoint**: See Section 7.2.1, *Computation of the Primary Endpoint*, for details on the definition of clinically significant SLE reactivation.

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 for clinically significant SLE reactivation. The time-to-event will be defined as the interval: date of disease reactivation – date of Day 0 visit. Subjects who do not experience clinically significant disease will be censored at the last visit date on study.

**Analysis**: Time to disease reactivation will be summarized by treatment group. Kaplan-Meier curves will be created for each treatment arm and will include 95% confidence intervals based on the Greenwood method. Estimated percent probability of disease reactivation will be calculated at Weeks 12, 24, 36, 48 and 60. Analyses will be conducted on the mITT population and the PP population.

### 7.3.2. Probability of Experiencing a SELENA-SLEDAI Flare

**Endpoint**: The SELENA-SLEDAI instrument will be completed at baseline and every follow-up visit, including any Flare or Endpoint visits, during the course of the 60 week study period for all subjects. The SELENA-SLEDAI assesses SLE disease activity and flares based on changes in the SLEDAI score, the Physician's Global Assessment (PGA), medication use (prednisone, NSAIDS, Plaquenil, major immunosuppressives), other disease activity criteria, and hospitalization due to SLE. See Section 7.2.1., *Computation of the Primary Endpoint*, for more information on scoring of the SELENA-SLEDAI flare assessment.

For each subject, a yes/no variable will be created to indicate whether a subject had at least one mild/moderate or severe SELENA-SLEDAI flare by Week 60 and separately whether the subject had at least one severe SELENA-SLEDAI flare by Week 60. Subjects who terminate early from the study prior to experiencing any SELENA-SLEDAI flare will be categorized as not experiencing any SELENA-SLEDAI flare by Week 60.

Additionally, for each subject, the total number of visits with mild/moderate or severe SELENA-SLEDAI flares will be tabulated, including categorizing number of flare visits for a subject into 0, 1, or >1 flare.

The probability of experiencing any SELENA-SLEDAI flare and the probability of experiencing any severe SELENA-SLEDAI flare by Week 60 will be calculated 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).

**Analysis**: Analyses analogous to those specified for the primary endpoint (effect estimates and 95% confidence intervals, risk difference, and summaries of increased risk ($\alpha$) vs.% confidence the "true" risk is ≤ $\alpha$) will be performed for the probability of experiencing any SELENA-SLEDAI flare and any severe SELENA-SLEDAI flare by Week 60, including analyses within subgroups for disease manifestation and baseline MMF dose. See Section 7.2.2, *Primary Analysis of the Primary Endpoint*, for more details on the analyses.

The total number of visits that a subject has with a SELENA-SLEDAI flare will be summarized by treatment group and overall. Summary tables detailing the reasons for mild/moderate or severe flares, along with reason for new or increased major immunosuppressives will be provided. Additionally, sensitivity analysis may be run to assess the impact of new or increased major immunosuppressives as the only cause of severe flare. Subjects who re-start

or increase major immunosuppressives, but have no other disease activity that would categorize them as having a severe flare, will be categorized as not having a severe SELENA-SLEDAI flare and analyses would be replicated using this definition of a severe flare.

The study day of flare, type (mild/moderate or severe), and number of flares for each subject will also be shown graphically over time by subject and treatment group.

### 7.3.3. Time to First SELENA-SLEDAI Flare

**Endpoint**: The SELENA-SLEDAI instrument will be completed at baseline and every follow-up visit during the course of the 60 week study period for all subjects. The SELENA-SLEDAI assesses flares based on changes in the SLEDAI score, the Physician's Global Assessment (PGA), medication use (prednisone, NSAIDS, Plaquenil, major immunosuppressives), other disease activity criteria, and hospitalization due to SLE. See Section 7.2.1., *Computation of the Primary Endpoint*, for more information on scoring of the SELENA-SLEDAI flare assessment.

For each subject, time from Day 0 to first SELENA-SLEDAI flare and time to first severe SELENA-SLEDAI flare will be calculated in study days as: date of first flare – date of Day 0 visit. Subjects who do not experience SELENA-SLEDAI flare will be censored at their last visit date on study.

**Analysis**: Analyses analogous to those specified in Section 7.3.1, *Time to Clinically Significant Disease Reactivation*, will be performed for time to SELENA-SLEDAI flare. Additionally, sensitivity analysis may be run to assess the impact of new or increased major immunosuppressives as the only cause of severe flare. Subjects who re-start or increase major immunosuppressives, but have no other disease activity that would categorize them as having a severe flare, will be categorized as not having a severe SELENA-SLEDAI flare (i.e. categorized as a mild/moderate flare) and analyses would be replicated using this definition of a severe flare.

### 7.3.4. Probability of Experiencing a BILAG A Flare

**Endpoint**: The British Isles Lupus Assessment Group (BILAG) 2004 (2007 Revision) instrument will be completed at baseline and every follow-up visit, including any Flare or Endpoint visits, during the course of the 60 week study period for all subjects. Data for this assessment will be collected on the *Modified BILAG: Constitutional*, *Modified BILAG: Mucocutaneous*, *Modified BILAG: Neuropsychiatric*, *Modified BILAG: Musculoskeletal*, *Modified BILAG: Cardiorespiratory*, *Modified BILAG: Gastrointestinal*, *Modified BILAG: Ophthalmic*, *Modified BILAG: Renal*, and *Modified BILAG: Hematological* CRF pages.

The rules for scoring the BILAG 2004 are in Appendix 14.4 *BILAG 2004 Index Scoring*. In each of the nine body system categories (constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal, and hematological) subjects are assessed on a variety of disease activity criteria. Each category is then scored as an A, B, C, or D/E, where A indicates most severe disease activity and D/E indicates inactive/no disease activity. For this study the following additional scoring rules are applied:

1. According to the scoring algorithm, D means "Inactive disease but previously affected", and E means "System never involved". Since we may not know whether the subject has ever experienced involvement in a particular system prior to starting the study, we will not attempt to distinguish between D and E. Subjects will be assigned the score "D/E" if they did not meet the criteria for A, B, or C at the particular visit.

2. In the Renal category, some of the scoring rules require looking at previous measurements to assess change (e.g., 24 hour protein > 1g that has not decreased (improved) by >=25%). At Screening the BILAG is not collected as it is not required for eligibility purposes. As such, no previous BILAG assessment is available to refer to for applying such rules at the Day 0 visit and therefore subjects will not have a renal score assigned at Day 0.

3. In the Renal category, the original instrument includes 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.

For each subject, a yes/no variable will be created to indicate whether a subject had at least one BILAG A flare, in any body system, by Week 60. Subjects who terminate early from the study prior to experiencing a BILAG A flare will be categorized as not experiencing a BILAG A flare by Week 60.

The probability of experiencing any BILAG A flare will be calculated for each study arm.

Additionally, for each subject, the total number of visits with BILAG A flare will be tabulated.

**Analysis**: Analyses analogous to those specified for the primary endpoint (effect estimates and 95% confidence intervals, risk difference, and summaries of increased risk ($\alpha$) vs.% confidence the "true" risk is ≤ $\alpha$) will be performed for the probability of experiencing a BILAG A flare by Week 60. See Section 7.2.2, *Primary Analysis of the Primary Endpoint*, for more details on the analyses. The total number of visits that a subject has with a BILAG A flare will be summarized by treatment group and overall. Summary tables for BILAG A scoring by body system will be provided.

### 7.3.5. Subjects in the Renal Subgroup with BILAG Renal A Flares

**Endpoint**: The BILAG instrument will be completed at baseline and every follow-up visit during the course of the 60 week study period for all subjects. See Section 7.3.4, *Probability of Experiencing a BILAG A Flare*, for more information on the BILAG and its scoring. The renal disease subgroup includes subjects who presently have renal disease as well as those who have had renal manifestations in the past, as specified by the site at randomization.

For each subject in the renal subgroup, a yes/no variable will be created to indicate whether a subject had at least one BILAG A flare in the renal body system by Week 60. Subjects in the renal subgroup, who terminate early from the study prior to experiencing a BILAG A renal flare, will be categorized as not experiencing a BILAG A flare by Week 60.

The proportion of subjects in the renal subgroup with at least one BILAG A flare in the renal body system by Week 60 will be calculated for each study arm.

**Analysis**: Analyses analogous to those specified for the primary endpoint (effect estimates and 95% confidence intervals, risk difference, and summaries of increased risk ($\alpha$) vs.% confidence the "true" risk is ≤ $\alpha$) will be performed for the probability of experiencing a BILAG A renal flare by Week 60 in the renal subgroup. See Section 7.2.2, *Primary Analysis of the Primary Endpoint*, for more details on the analyses.

### 7.3.6. Probability of Experiencing a BILAG A or B Flare

**Endpoint**: The BILAG instrument will be completed at baseline and every follow-up visit, including any Flare or Endpoint visits, during the course of the 60 week study period for all subjects. See Section 7.3.4, *Probability of Experiencing a BILAG A Flare*, for more details on the BILAG assessment.

For each subject, a yes/no variable will be created to indicate whether a subject had at least one BILAG A or B flare, in any body system, by Week 60. Subjects who terminate early from the study prior to experiencing a BILAG A or B flare will be categorized as not experiencing a BILAG A or B flare by Week 60.

The probability of experiencing any BILAG A or B flare will be calculated for each study arm by each body system and overall.

Additionally, for each subject, the total number of visits with a BILAG A or B flare will be tabulated by arm for each body system and overall.

**Analysis**: Analyses analogous to those specified for the primary endpoint (effect estimates and 95% confidence intervals, risk difference, and summaries of increased risk ($\alpha$) vs.% confidence the "true" risk is ≤ $\alpha$) will be performed for the probability of experiencing a BILAG A flare by Week 60. See Section 7.2.2, *Primary Analysis of the Primary Endpoint*, for more details on the analyses. Summary tables for BILAG scoring by body system will be provided. The total number of visits that a subject has with a BILAG A or B flare will be summarized by treatment group and overall.

The study day of flare, type (A or B), body system, and number of flares for each subject will also be shown graphically over time by subject and treatment group.

### 7.3.7. Changes in the SLICC/DI

**Endpoint**: The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Disease Damage Index for Systemic Lupus Erythematosus (SLICC/DI) will be assessed at Baseline, Weeks 24, 48 and 60, and any Flare or Endpoint visits that occur during the course of the trial. Data for the SLICC/DI will be captured on the *SLICC/ACR Damage Index for Systemic Lupus Erythematosus* CRF page.

The SLICC/DI measures accumulated damage that has occurred since the onset of SLE, regardless of cause, in 12 organ systems. SLE damage is defined as an irreversible change in an organ or system that has been present for at least 6 months. The original SLICC/DI instrument includes an evaluation of proteinuria based on a 24-hour urine assessment. 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.

The SLICC/DI includes 39 areas of damage in 12 domains, where each item is rated as present or absent; if evidence of damage is present for a particular item, it is given a score of 1. Some items are scored with 2 or 3 points in the case of recurring events or end stage renal disease. The SLICC/DI total score will be computed as the sum of all scores for items indicated as present; scores can range from 0 to 45. Higher scores indicate more damage. Missing scores will not be imputed.

Change from baseline in the SLICC/DI score at Weeks 24, 48, and 60 will be computed for each subject.

**Analysis**: 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 in the change from baseline in the SLICC/DI score between the treatment groups at each specified time point. The SLICC/DI score and change from baseline in will be shown graphically by treatment arm. Spaghetti plots and summary statistics including 25$^{th}$ percentile, mean, median, and 75$^{th}$ percentile will be plotted for each visit by treatment group.

### 7.3.8. The Addition of Aggressive Adjunctive Therapy to MMF or Change in MMF Therapy to Cytotoxic Drug Due to Flare

**Endpoint**: Medications are assessed at each study visit throughout the duration of the study and are collected on the *Prior/Concomitant Medications* CRF page.

For both the maintenance and withdrawal arms, the addition of aggressive adjunctive therapy can include IV immunoglobulin or rituximab at any point during the subject's participation in the study. A change in therapy to cytotoxic drug due to flare can include drugs such as cyclophosphamide, etc. A blinded list of study medications will be reviewed to identify the addition of aggressive adjunctive therapy or cytotoxic drugs.

For each subject, a yes/no variable will be created to indicate whether a subject added aggressive adjunctive therapy to MMF or changed MMF therapy to cytotoxic drug due to flare by Week 60. Subjects off MMF in the withdrawal arm will be included in the endpoint if aggressive adjunctive therapy or cytotoxic drugs were added to treat a flare. Subjects who terminate early from the study prior to adding aggressive adjunctive therapy to MMF or changing MMF therapy to cytotoxic drug due to flare will be categorized as not meeting the endpoint.

The probability of adding aggressive adjunctive therapy to MMF or changing MMF therapy to cytotoxic drug due to flare will be calculated for each study arm.

**Analysis**: Analyses analogous to those specified for the primary endpoint (effect estimates and 95% confidence intervals, risk difference, and summaries of increased risk ($\alpha$) vs.% confidence the "true" risk is $\leq \alpha$) will be performed for adding aggressive adjunctive therapy to MMF or changing MMF therapy to cytotoxic drug due to flare by Week 60. See Section 7.2.2, *Primary Analysis of the Primary Endpoint*, for more details on the analyses. Additionally, type of new therapy will be summarized by treatment arm and overall.

### 7.3.9. Systemic Steroid Dose

**Endpoint**: Medications, including steroid use, are assessed at each study visit throughout the duration of the study and are collected on the *Prior/Concomitant Medications* CRF page.

Steroids include medications that code to a medication class which includes the terms "glucocorticoid" or "corticosteroid". Systemic steroids will include any of these steroids that are taken by mouth (PO), intravenous (IV), or intramuscular (IM).

Total cumulative systemic steroid dose, in milligrams, will be summarized over the 60 week study period, or until early study termination, for each subject. Total cumulative systemic steroid dose, in milligrams, given specifically to treat a SLE flare may also be summarized.

Additionally, the excess steroid dose given over the course of the 60 week study period, or until early study termination, will be calculated for each subject. Excess steroid dose will be

calculated based on the difference between expected steroid dose (extrapolated from baseline steroid dose) and actual total cumulative steroid dose given during the course of the study.

**Analysis**: Analyses analogous to those specified in Section 7.3.6, *Changes in the SLICC/DI*, will be performed on the total steroid dose and excess steroid dose at Week 60.

### 7.3.10. Changes in the FACIT Score

**Endpoint**: The Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale will be assessed at Baseline, Weeks 24, 48 and 60, and any Flare or Endpoint visits that occur during the course of the trial. Data for the FACIT fatigue scale will be captured on the *FACIT* CRF page.

The FACIT fatigue scale assesses fatigue in subjects with chronic illness. Thirteen fatigue-related questions are measured on a 4-point scale. The FACIT fatigue subscale scoring guide (see Appendix 14.5, *FACIT-Fatigue Subscale Scoring Guidelines*) identifies those items that must be reversed before being added to obtain subscale totals. Negatively stated items are reversed by subtracting the response from "4". After reversing proper items, all subscale items are summed to a total, which is the subscale score**.** High scores represent less fatigue and better quality of life.

If there are missing items, subscale scores can be prorated. This is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered. This can be done on the scoring guide or by using the formula below:

**Prorated subscale score =** [Sum of item scores] **x** [N of items in subscale] ÷ [N of items answered]

When there are missing data, prorating by subscale in this way is acceptable as long as more than 50% of the items were answered (e.g., a minimum of 7 of 13 items).

Change from baseline in the FACIT score at Weeks 24, 48, and 60 will be computed for each subject.

**Analysis**: Analyses analogous to those specified in Section 7.3.6, *Changes in the SLICC/DI*, will be performed on the FACIT score.

### 7.3.11. Changes in SF-36 Scores

**Endpoint**: The Short Form Health Survey (SF-36) will be assessed at Baseline, Weeks 24, 48 and 60, and any Flare or Endpoint visits that occur during the course of the trial. Data for the SF-36 will be captured on the *SF-36 Survey* CRF page.

The SF-36 is a 36-item, patient-reported survey of patient health. Higher scores indicate better outcomes while lower scores indicate more disability.

The following SF-36 scale scores will be calculated: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. From these scale scores, two summary scores that aggregate measures will be created. The Physical Component Score is comprised of the Physical Functioning Scale, the Role-Physical Scale, the Bodily Pain Scale, and the General Health Scale. The Mental Component Score is comprised of the Vitality Scale, the Social Functioning Scale, the Role-Emotional Scale, and the Mental Health Scale.

Norm-based scores will also be generated for the eight SF-36 scales and the two summary measures. All eight SF-36 scales and the two summary scores will be normalized to have a mean of 50 and a standard deviation of 10 for the 1998 general US population. The advantage of the standardization is that results for one scale can be meaningfully compared with the other scales, and the scores have a direct interpretation in relation to the distribution of scores in the 1998 general US population. Specifically, scores above or below 50 are above or below the average, respectively, for the 1998 general US population. Because the standard deviation is 10 for all 8 scales, each one point difference in scores is equivalent to one-tenth of a standard deviation unit or an effect size of 0.10. See Appendix 14.6, *Scoring the SF-36 Version 2*, of this SAP for details regarding calculation of these scores.

Change from baseline in the SF-36 Physical Functioning (PF) and Physical Component Summary (PCS) domains at Weeks 24, 48, and 60 will be computed for each subject.

**Analysis**: Analyses analogous to those specified in Section 7.3.6, *Changes in the SLICC/DI*, will be performed on the SF-36 PF and PCS.

### 7.3.12. Change in Lupus QoL Score

**Endpoint**: The Lupus Quality of Life (QoL) instrument will be assessed at Baseline, Weeks 24, 48 and 60, and any Flare or Endpoint visits that occur during the course of the trial. Data for the Lupus QoL will be captured on the *Lupus QoL* CRF page.

The Lupus QoL assessment is a 34 item questionnaire across 8 domains that is designed to find out how SLE affects a subject's life over the preceding 4 weeks. The physical health domain comprises item numbers 1–8, pain comprises 9–11, planning comprises 12–14, intimate relationships comprises 15 and 16, burden to others comprises 17–19, emotional health comprises 20– 25, body image comprises 26–30, and fatigue comprises 31–34. Each of the 34 questions are answered on a 5-point scale, where 0 = all of the time, 1 = most of the time, 2 = a good bit of the time, 3 = occasionally, and 4 = never.

Item response scores are totaled for each domain and the mean raw domain score is obtained by dividing the total score by the number of items in that domain. The mean raw domain score is transformed to scores ranging from 0 (worst QOL) to 100 (best QOL) by dividing by 4 (the number of Likert responses [5 responses] minus 1) and then multiplying by 100, as below:

$$\frac{\text{mean raw domain score}}{4} \times 100 = \text{transformed score for domain}$$

Transformed domain scores are obtainable when at least 50% of the items are answered. The mean raw domain score is then calculated by totaling the item response scores of the answered items and dividing by the number of answered items. A nonapplicable response is treated as unanswered and the domain score is calculated as above.

Change from baseline in the Lupus QoL scores at Weeks 24, 48, and 60 will be computed for each subject.

**Analysis**: Analyses analogous to those specified in Section 7.3.6, *Changes in the SLICC/DI*, will be performed on the Lupus QoL scores.

### 7.3.13. Recovery from Clinically Significant Disease Reactivation

The following endpoints will be assessed to describe the ability of subjects to recover from clinically significant disease reactivation.

#### 7.3.13.1. Time from clinically significant disease reactivation to improvement in BILAG from maximum level during flare

**Endpoint:** See Section 7.2.1, *Computation of the Primary Endpoint*, for details on the definition of clinically significant SLE reactivation, and Section 7.3.4, *Probability of Experiencing a BILAG A Flare*, for more information on the BILAG and its scoring.

For each subject who experiences disease reactivation, time from clinically significant disease reactivation to improvement in BILAG from maximum level (at least an A or B) during the flare will be calculated in study days as: date of clinically significant disease reactivation – date of BILAG improvement. If multiple body systems have a BILAG flare at the visit, then the body system with the most severe score will be tracked for improvement; if multiple body systems have the same score (at least an A or B), then just one needs to show improvement.

Subjects who do not experience improvement in the BILAG prior to the end of their study participation or if the subject doesn't experience an increase in their BILAG score to a B or higher will be censored at their last visit date on study.

**Analysis**: Kaplan-Meier curves will be created for each treatment arm and will include 95% confidence intervals based on the Greenwood method.

#### 7.3.13.2. Time from clinically significant disease reactivation to recovery to baseline BILAG scores or BILAG C, whichever is worse

**Endpoint:** See Section 7.2.1, *Computation of the Primary Endpoint*, for details on the definition of clinically significant SLE reactivation, and Section 7.3.4, *Probability of Experiencing a BILAG A Flare*, for more information on the BILAG and its scoring.

For each subject who experiences disease reactivation, time from clinically significant disease reactivation to recovery to baseline BILAG scores or BILAG C, whichever is worse, will be calculated in study days as: date of clinically significant disease reactivation – date of BILAG recovery.

If a subject does not recover to their baseline BILAG score or BILAG C, whichever is worse, prior to the end of their study participation, or if the subject doesn't experience an increase in their BILAG score, then their BILAG score will be censored at their last visit date on study.

**Analysis**: Kaplan-Meier curves will be created for each treatment arm and will include 95% confidence intervals based on the Greenwood method.

#### 7.3.13.3. Cumulative excess systemic steroid dose from time of clinically significant disease reactivation to return to pre-flare dose or end of trial participation

**Endpoint:** See Section 7.2.1, *Computation of the Primary Endpoint*, for details on the definition of clinically significant SLE reactivation, and Section 7.3.8., *Systemic Steroid Dose*, for details on the definition of systemic steroids.

For each subject who experiences disease reactivation, excess systemic steroid dose will be summed from the time of clinically significant disease reactivation until the dose returns to pre-flare levels or the end of study participation, whichever occurs first. Excess systemic steroid dose will be defined as the total dose given for the flare – a subject's pre-flare steroid dose.

Subjects who do not have an increase in their steroid use due to the flare will have their excess dose set to zero.

**Analysis**: 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 cumulative excess steroid dose in each treatment group.

#### 7.3.13.4. Time from clinically significant disease reactivation to return to pre-flare steroid dose.

**Endpoint:** See Section 7.2.1, *Computation of the Primary Endpoint*, for details on the definition of clinically significant SLE reactivation. Medications, including steroid use, are assessed at each study visit throughout the duration of the study and are collected on the *Prior/Concomitant Medications* CRF page.

For each subject who experiences disease reactivation, time from clinically significant disease reactivation to recovery to pre-flare steroid dose will be calculated in study days as: date of clinically significant disease reactivation – date of return to pre-flare steroid dose.

If a subject does not return to their pre-flare steroid dose prior to the end of their study participation, or if the subject does not have in increase in steroid dose due to their flare, then the variable will equal the duration of follow-up for that subject. Appropriate censor variables will be defined to indicate whether the time-to variable represents an event time or a censor time.

**Analysis**: Kaplan-Meier curves will be created for each treatment arm and will include 95% confidence intervals based on the Greenwood method.

## 7.4. Secondary Mechanistic Endpoints

### 7.4.1. C3, C4, and anti-dsDNA Levels

**Endpoint**: C3, C4, and anti-dsDNA are run at baseline and every follow-up visit, including any Flare or Endpoint visits, during the course of the 60 week study period and run by a central laboratory.

Specifically, levels of C3, C4, and anti-dsDNA at Baseline, Week 20, at the time of first flare, and immediately prior to first flare will be analyzed.

**Analysis**: Descriptive statistics (mean, standard deviation, median, minimum, maximum and number of subjects in a group) will be computed by treatment group and separately for subjects who do/do not experience clinically significant disease reactivation at each specified time point. Summary statistics will be plotted versus time at the relevant time points. Plots for individual subjects will also be created.

### 7.4.2. Changes in C3, C4, and anti-dsDNA Levels

**Endpoint**: C3, C4, and anti-dsDNA are run at baseline and every follow-up visit, including any Flare or Endpoint visits, during the course of the 60 week study period and run by a central laboratory. Change from baseline will be calculated for each test and time point.

Specifically, change from baseline in levels of C3, C4, and anti-dsDNA at Week 20, the time of first flare, and immediately prior to first flare will be analyzed.

**Analysis**: Descriptive statistics (mean, standard deviation, median, minimum, maximum and number of subjects in a group) will be computed by treatment group and separately for subjects who do/do not experience clinically significant disease reactivation at each specified time point. Summary statistics will be plotted versus time at the relevant time points. Plots for individual subjects will also be created.

### 7.4.3. Antibody Levels

**Endpoint**: Antibody levels, including, but not limited to Sm, ribonucleoprotein (RNP), SSA/Ro, & SSB/La are assessed at the Baseline, Week 60, and if needed, the flare visit and run by a central laboratory.

**Analysis**: Descriptive statistics (mean, standard deviation, median, minimum, maximum and number of subjects in a group) and/or a summary of categorical response (positive, negative, indeterminate, etc.) will be computed by treatment group for each antibody result. Summary statistics will be plotted versus time at the relevant time points as applicable.

## 7.5. Examination of Subgroups

Secondary analyses of the primary and secondary objectives may be conducted for the following subgroups, including, but not limited to:

- Age
- Race/ethnicity
- Disease manifestation (renal disease/extra-renal disease), as defined in Section 7.3.5.
- SLE duration (< 5 years / ≥ 5 years)
- Baseline MMF dosing group (<2000 mg per day / ≥ 2000 mg per day)
- Baseline autoantibody status

Additionally, exploratory analyses of subgroups defined through the mechanistic and immunological studies may also be conducted.

# 8. SAFETY EVALUATION

## 8.1. Overview of Safety Analysis Methods

All safety analyses will be carried out using the safety sample defined in Section 4.2 unless otherwise noted. Missing safety information will not be imputed. These analyses will not be stratified by site. 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.

Listings will be prepared for all safety measurements. All listings will be sorted in order of treatment, subject identifier (ID), and time of assessment (e.g., visit, time, and/or event).

## 8.2. Extent of Exposure

Extent of exposure during the trial will be described for MMF. Exposure will be measured as the total number of days on medication defined as last dose date – first dose date + 1 and the cumulative dose of that medication defined as the sum of the doses in mg taken up to the relevant cutoff date. Exposure will be summarized until a subject stops taking study provided MMF.

## 8.3. Adverse Events

All AEs will be classified by system organ class (SOC) and preferred term, according to a standardized thesaurus (Medical Dictionary for Regulatory Activities [MedDRA] version 16.1). The severity of AEs will be classified using the National Cancer Institute's (NCI's) Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. Each AE is entered on the electronic case report form (eCRF) once at the highest severity. As such, no additional data manipulation is needed to identify events.

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 AE is related to a study-mandated procedure, treatment, or change in treatment.

Regardless of whether the above is applicable, for all participants: AEs 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 Protocol 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.

Treatment-emergent AEs will be identified as those with an onset date on or after the first dose of study medication as well as those with onset before first dose but that continued and worsened in severity after first dose. If the start of the AE in relation to the start of study medication cannot be established (e.g., the start date for the AE is missing), then the AE will be considered treatment-emergent. All data tabulations will be of only treatment-emergent events while non-treatment-emergent AEs will be listed separately, unless otherwise noted.

Indicator variables will be derived for the following categories of AEs: infections, malignancies, BILAG A flares, and severe SELENA-SLEDAI flares. Yes/no questions for each of these types of events are included on the *Adverse Events* CRF page.

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).

An overall summary table will be developed to report the number of events and the number and percentage of subjects having at least one event in the following categories:

- AEs
- AEs indicated as serious
- AEs that lead to study drug discontinuation
- AEs with an outcome of death
- AEs that were reported as being related to MMF
- AEs that were reported as being related to SLE
- AEs reported by maximum severity
- AEs that are BILAG A flares
- AEs that are severe SELENA-SLEDAI flares

In addition, AEs classified by MedDRA SOC and preferred term will be summarized for each treatment group and overall for each of the following:

- All AEs
- AEs by maximum severity
- AEs by relationship to study drug

Summary tables will present the total number of events as well as the number and percentage of subjects experiencing the events. If a subject experiences the same AE on multiple occasions, the event will be counted once for each occurrence when reporting the number of AEs. When reporting the number of subjects experiencing the events, a subject will only be counted once if they experience an event within the particular SOC or preferred term. Percentages will be based on the number of subjects in the safety population. 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.

Separate data listings will be provided for treatment-related AEs and AEs leading to study drug discontinuation.

### 8.3.1. Secondary Safety Endpoints

Secondary safety endpoints include the following:

1. All Grade 3-5 adverse events, as defined by the NCI–CTCAE system, which are defined as possibly, probably, or definitely related to SLE.
2. All Grade 3-5 adverse events, as defined by the NCI-CTCAE system, which are defined as possibly, probably, or definitely related to MMF.
3. All NCI-CTCAE Grade 3-5 adverse events.
4. All serious adverse events.
5. All infection related events.
6. All malignancies.
7. All NCI-CTCAE Grade 3-5 hematological events.
8. Mortality possibly, probably, or definitely related to SLE.
9. All-cause mortality, defined as any death occurring at any time after randomization.

Serious adverse events will include only those events deemed serious per 21 CFR 312.32 (See Protocol Section 7.2.4). Events that require 24-hour reporting to the sponsor, such as BILAG A and severe SELENA-SLEDAI flares, will not be included unless they also meet SAE reporting criteria per 21 CFR 312.32; these events will be summarized separately.

Infections will include those events that are coded to the SOC of “Infections and infestations” along with any AE with an answer of Yes to the question “Was this AE an infection?” on the Adverse Events CRF page.

Malignancies will include those events that are coded to the SOC of “Neoplasms benign, malignant and unspecified (incl cysts and polyps)” along with any AE with an answer of Yes to the question “Was this AE a malignancy?” on the Adverse Events CRF page.

Hematological events will include AEs that are coded to the SOC of “Blood and lymphatic system disorders”.

For each of the safety endpoints listed above, the AEs, classified by MedDRA system organ class and preferred term, will be summarized for each treatment group and overall. 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.

The proportion of subjects experiencing at least one event specified aobve 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.

### 8.4. Deaths and Serious Adverse Events

Serious adverse events (SAEs) will be listed and summarized in a similar manner as described in Section 8.3. Separate displays listing and summarizing death, including time to death and cause of death, will also be created if a death occurs.

### 8.5. Clinical Laboratory Evaluation

Clinical laboratory measurements include serum chemistry, urinalysis, and hematology. Results will be converted to standardized units where possible. Chemistry and hematology panels are run by a central lab; as such, normal ranges will come from the central lab.

Laboratory data will be plotted to show patterns over time. Summary statistics including 25th percentile, median, and 75th percentile will be plotted for each visit by treatment group. Lines connecting individual subject results from subjects with grade 2 or higher values will be overlaid on each figure. For lab results that are not gradable, results from subjects with values outside of 2 *ULN or 0.5*LLN will be overlaid. Tests with qualitative results (such as "present" or "positive") will not be plotted.

### 8.6. Vital Signs, Physical Findings, and Other Observations Related to Safety

#### 8.6.1. Vital Signs

Vital sign information will be collected on the *Vital Signs* CRF page at every study visit. Data listings sorted by treatment group, subject, vital sign parameter, and time of assessment will be provided for vital signs measurements.

#### 8.6.2. Physical Examinations

Physical exam information will be collected on the *Physical Exam* CRF page at every study visit. Data listings will be provided for physical examination results and sorted by treatment group, subject, body system, and time of assessment.

## 9. PHARMACOKINETIC EVALUATION

No pharmacokinetic evaluations will be performed for ALE06.

# 10. OTHER ANALYSES

## 10.1. Use of Medications

Medications will be coded according to the World Health Organization (WHO) Drug Dictionary (version 2013.03). Medications reported on the CRF will be categorized for analysis as prior, concomitant, or after study treatment by comparing the medication start and stop dates with the first and last dose of study medication dates. Prior medications will have both the medication start and stop dates prior to the first dose of study medication date. After medications will have both the medication start and stop dates after the last dose of study medication date. All other medications will be classified as concomitant, indicating that use of the medication overlapped with use of the study medication by at least one day.

The number and percentage of subjects receiving prior, concomitant, and after medications will be presented overall and by medication class. When reporting the number of subjects receiving the medication, a subject will only be counted once if they ever received the medication within the medication class. Percentages will be based on the number of subjects in the analysis population.

# 11. INTERIM ANALYSES AND DATA MONITORING

The progress of the study will be monitored by the Data and Safety Monitoring Board (DSMB). The NIAID Autoimmune DSMB will be chartered to review safety data and to make recommendations regarding continuation, termination, or modification of the study. The DSMB will formally review the safety data at least yearly. The discontinuation of study treatment will also be periodically reported to the DSMB.

In addition, safety data will be reviewed by the DSMB when an event occurs that is of sufficient concern to the National Institute of Allergy and Infectious Diseases (NIAID) medical monitor or protocol chair to warrant review, or when an event occurs that could contribute to a predefined stopping rule specified in the protocol.

Findings will be reported to Institutional Review Boards (IRBs) and health authorities.

## 11.1. 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. $risk_{\_MMF\,withdrawal} - risk_{\_MMF\ maintenance}$) 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.

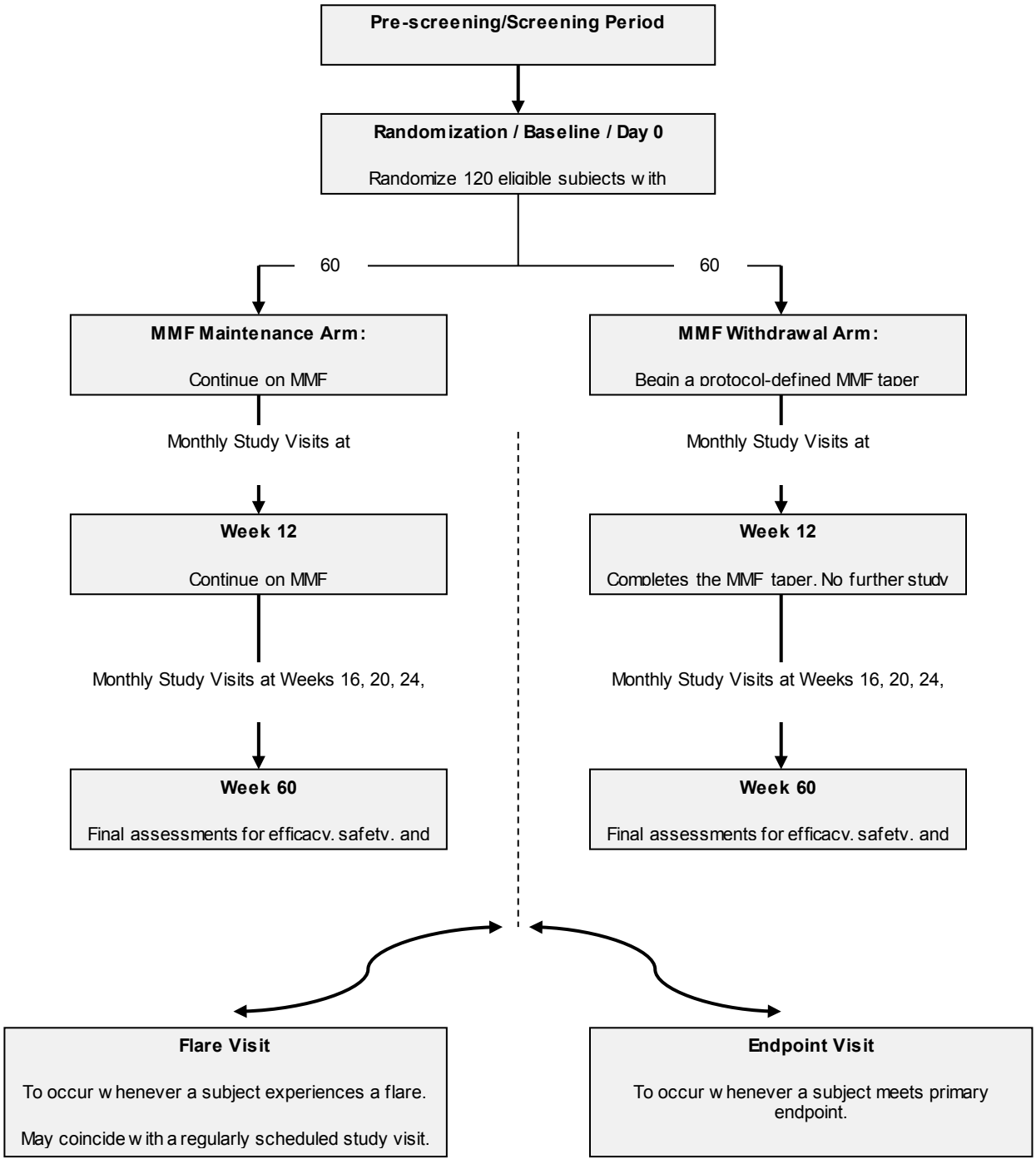
## 12. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

1. Section 7.2. Primary Endpoint. Statistical methods to obtain effect estimates and confidence intervals for the probability of observing clinically significant disease reactivation by 60 weeks have been changed from exact methods for complete data (proportions with Clopper Pearson intervals) to Kaplan-Meier predict-limit estimators to allow for censoring of subjects who terminated early without evidence of disease reactivation.
2. Section 7.3.3. Time to First SELENA-SLEDAI Flare: Time to first SELENA-SLEDAI flare has been changed from using withdrawal date to using Day 0 date. This allows us to calculate time to first SELENA-SLEDAI flare in both arms, since the Maintenance arm does not start withdrawal, and is consistent with the timing of the time to disease reactivation endpoint specified in Section 7.3.1.
3. Section 7.3.6. Probability of Experiencing a BILAG A or B Flare: This is a new endpoint was added to the SAP by the study team.
4. Section 11.1. Interim Analysis: The sample size re-estimation specified if ≤ 10% of the first 80 subjects experienced disease reactivation was not performed. We observed that after 60 weeks of post-randomization, 8 of the first 80 (10%) subjects experienced disease reactivation. Although the rate of disease reactivation was low, the team opted not to re-estimate the sample size. Rates of BILAG and SELENA-SLEDAI flares, which will also be important for evaluating the impact of MMF withdrawal, are higher than 10%. The larger sample size is necessary to improve precision for these important secondary endpoints and will strengthen the primary analysis.

# 13. REFERENCES

# 14. APPENDICES

## 14.1. Study Flow Chart



## 14.2. Schedule of Events

| 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] | | | | | | | | |

**Table 6.1, Schedule of Events**

| 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] | As Needed: Flare[2] | As Needed: End-point[3] | As Needed: 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 |
| Anti-dsDNA,C3, C4 (~6 mL) | | X[19] | X[19] | X[19] | X | X[19] | X[19] | X | X | X | X | X | X | X | |
| 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. Future Use: Urine will be collected at Week 60 *only* if the subject did not experience a flare while on study.
21. Future Use: Urine will be collected at any (and all) Flare Visits where increased predisone or immunomodulatory medication is prescribed

### 14.3. 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** |
| 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 x$10^9$/L] | ☐ | **1** |
| 24 | **Leukopenia** | < 3,000 white blood cells/$mm^3$ [equivalent to 3 x$10^9$/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<br>• Discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus<br>• Nasopharyngeal ulcers<br>• Pleuritis<br>• Pericarditis<br>• Arthritis<br>• 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<br>• CNS-SLE<br>• Vasculitis<br>• Nephritis<br>• Myositis<br>• Platelet Count < 60,000/ $mm^3$ [equivalent to 60 $x10^9$/L]<br>• Hemolytic anemia with hemoglobin < 7% OR Decrease in hemoglobin > 3%<br>*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<br>(on a 3.0 indexed VAS scale—refer to the Physican's Global Assessment located on the Modified SLEDAI Source Document) |

## 14.4. BILAG

*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*

## 14.5. FACIT

**FACIT-Fatigue Subscale Scoring Guidelines** (Version 4) – Page 1

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. **The higher the score, the better the QOL.**

| Subscale | Item Code | Reverse item? | | Item response | Item Score |
|---|---|---|---|---|---|
| **FATIGUE SUBSCALE** | HI7 | 4 | - | _____ | =_____ |
| | HI12 | 4 | - | _____ | =_____ |
| | An1 | 4 | - | _____ | =_____ |
| | An2 | 4 | - | _____ | =_____ |
| *Score range:* 0-52 | An3 | 4 | - | _____ | =_____ |
| | An4 | 4 | - | _____ | =_____ |
| | An5 | 0 | + | _____ | =_____ |
| | An7 | 0 | + | _____ | =_____ |
| | An8 | 4 | - | _____ | =_____ |
| | An12 | 4 | - | _____ | =_____ |
| | An14 | 4 | - | _____ | =_____ |
| | An15 | 4 | - | _____ | =_____ |
| | An16 | 4 | - | _____ | =_____ |

***Sum individual item scores:*** _____
***Multiply by 13:*** _____
***Divide by number of items answered:*** _____**=Fatigue Subscale score**

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

### 14.6. SF-36

Eight scale scores are derived from responses to the 36 items on the SF-36 questionnaire which are combined to produce the Physical Component Score and the Mental Component Score. The Physical Component Score is based upon the Physical Functioning Scale (10 items), the Role-Physical Scale (4 items), the Bodily Pain Scale (2 items), and the General Health Scale (5 items). The Mental Component Score is based upon the Vitality Scale (4 items), the Social Functioning Scale (2 items), the Role-Emotional Scale (3 items) and the Mental Health Scale (5 items). One item (self-reported health transition) is not used in the calculation of either component score. All methodology described below for scoring version 2 of the SF-36 (the version used in this study) is documented in How to Score Version 2 of the SF-36® Health Survey .

**Step 1:** Create numeric versions of the SF-36 questions (SF36. QUES1, QUES2, QUES3A, QUES3B, QUES3C, QUES3D, QUES3E, QUES3F, QUES3G, QUES3H, QUES3I, QUES3J, QUES4A, QUES4B, QUES4C, QUES4D, QUES5A, QUES5B, QUES5C, QUES6, QUES7, QUES8, QUES9A, QUES9B, QUES9C, QUES9D, QUES9E, QUES9F, QUES9G, QUES9H, QUES9I, QUES10, QUES11A, QUES11B, QUES11C, QUES11D).

**Step 2:** Recode the numeric values for certain questions as follows:

Question 1:
1 --> 5.0
2 --> 4.4
3 --> 3.4
4 --> 2.0
5 --> 1.0

Questions 6, 9a, 9d, 9e, 9h, 11b, 11d:
1 --> 5
2 --> 4
3 --> 3
4 --> 2
5 --> 1

Question 7:
1 --> 6.0
2 --> 5.4
3 --> 4.2
4 --> 3.1
5 --> 2.2
6 --> 1.0

Question 8:

Note that the (raw) numeric value is the answer to question 7 before recoding.

- If the numeric value of question 8=1 and the (raw) numeric value of question 7=1, then the recoded value=6

- If the numeric value of question 8=1 and (2 <= the (raw) numeric value of question 7 <= 6), then the recoded value=5
- If the numeric value of question 8=2 and (1 <= the (raw) numeric value of question 7 <= 6), then the recoded value=4
- If the numeric value of question 8=3 and (1 <= the (raw) numeric value of question 7 <= 6), then the recoded value=3
- If the numeric value of question 8=4 and (1 <= the (raw) numeric value of question 7 <= 6), then the recoded value=2
- If the numeric value of question 8=5 and (1 <= the (raw) numeric value of question 7 <= 6), then the recoded value=1
- If the (raw) numeric value of question 7 is missing, then recode as follows:
  1 --> 6.0
  2 --> 4.75
  3 --> 3.5
  4 --> 2.25
  5 --> 1.0

**Step 3:** Count the number of missing items for each scale for each subject and visit.

| | |
|---|---|
| Physical Functioning: | Questions 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j |
| Role-Physical: | Questions 4a, 4b, 4c, 4d |
| Bodily Pain: | Questions 7, 8 |
| General Health: | Questions 1, 11a, 11b, 11c, 11d |
| Vitality: | Questions 9a, 9e, 9g, 9i |
| Social Functioning: | Questions 6, 10 |
| Role-Emotional: | Questions 5a, 5b, 5c |
| Mental Health: | Questions 9b, 9c, 9d, 9f, 9h |

**Step 4:** Calculate the mean value of the non-missing items for each scale in Step 3.

**Step 5:** Use the mean values from Step 4 for imputation of any missing values if at least half of the scale items are non-missing.

For example, if subject 1 had a missing value for item 3b at Visit 1, and the mean of the other Physical Functioning items was 3.2 for that subject and visit, the missing value would be imputed as 3.2.

To impute a missing value,

- No more than 5 items can be missing on the Physical Functioning scale
- No more than 2 items can be missing on the Role-Physical scale
- No more than 1 item can be missing on the Bodily Pain scale
- No more than 2 items can be missing on the General Health scale
- No more than 2 items can be missing on the Vitality scale

- No more than 1 item can be missing on the Social Functioning scale
- No more than 1 item can be missing on the Role-Emotional scale
- No more than 2 items can be missing on the Mental Health scale

**Step 6:** Calculate the raw scale scores for each scale in step 3 on the recoded and imputed answers to the questions specified below.

PF_RAW = sum of Questions 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j

RP_RAW = sum of Questions 4a, 4b, 4c, 4d

BP_RAW = sum of Questions 7, 8

GH_RAW = sum of Questions 1, 11a, 11b, 11c, 11d

VT_RAW = sum of Questions 9a, 9e, 9g, 9i

SF_RAW = sum of Questions 6, 10

RE_RAW = sum of Questions 5a, 5b, 5c

MH_RAW = sum of Questions 9b, 9c, 9d, 9f, 9h

**Step 7:** Calculate transformed scale scores as the (actual raw score – lowest possible raw score) / (range of possible raw scores), and multiplying by 100.

PF_TRAN = 100*(PF_RAW-10) / 20

RP_TRAN = 100*(RP_RAW-4) / 16

BP_TRAN = 100*(BP_RAW-2) / 10

GH_TRAN = 100*(GH_RAW-5) / 20

VT_TRAN = 100*(VT_RAW-4) / 16

SF_TRAN = 100*(SF_RAW-2) / 8

RE_TRAN = 100*(RE_RAW-3) / 12

MH_TRAN = 100*(MH_RAW-5) / 20

**Step 8:** Calculate z-scores for each scale using the below formulas:

PF_Z = (PF_TRAN -83.29094) / 23.75883

RP_Z = (RP_TRAN -82.50964) / 25.52028

BP_Z = (BP_TRAN -71.32527) / 23.66224

GH_Z = (GH_TRAN -70.84570) / 20.97821

VT_Z = (VT_TRAN -58.31411) / 20.01923

SF_Z = (SF_TRAN -84.30250) / 22.91921

RE_Z = (RE_TRAN -87.39733) / 21.43778

MH_Z = (MH_TRAN -74.98685) / 17.75604

**Step 9:** Calculate norm-based scores by multiplying the z-score by 10 and adding 50. Use the following names: PF_NORM, RP_NORM, BP_NORM, GH_NORM, VT_NORM, SF_NORM, RE_NORM, MH_NORM.

**Step 10:** Calculate aggregate scores for Physical and Mental Component Scores using the following formulas:

AGG_PHYS = (PF_Z * .42402) + (RP_Z * .35119) + (BP_Z * .31754) + (GH_Z * .24954) + (VT_Z * .02877) + (SF_Z * -.00753) + (RE_Z * -.19206) + (MH_Z * -.22069)

AGG_MENT = (PF_Z * -.22999) + (RP_Z * -.12329) + (BP_Z * -.09731) + (GH_Z * -.01571) + (VT_Z * .23534) + (SF_Z * .26876) + (RE_Z * .43407) + (MH_Z * .48581)

**Step 11:** Calculate norm-based versions of the Physical and Mental Component Scores by multiplying by 10 and adding 50. Use the following names: PCS_NORM, MCS_NORM.