Clinical Trial Protocol

Clinical Trial Protocol Number	MS200527-0018
Title	A Phase II, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study To Evaluate the Safety and Efficacy of M2951 in Subjects with Systemic Lupus Erythematosus (SLE)
Phase	II
IND Number	CCI
EudraCT Number	2016-002950-19
Coordinating Investigator	PPD Telephone: PPD
Sponsor	For all countries except the USA, and Japan Merck KGaA Frankfurter Strasse 250 64293 Darmstadt Germany For Japan only: Merck Serono Co., Ltd. (Affiliate of Merck KGaA, Darmstadt, Germany) Arco Tower, 1-8-1 Shimomeguro Meguro-ku, Tokyo 153-8926, Japan And For the USA EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA 01821 USA Medical Responsible: PPD EMD Serono Research & Development Institute 45A Middlesex Turnpike Billerica MA 01821

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[redacted]

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List of Abbreviations

ACR	American College of Rheumatology
AE(s)	Adverse Event(s)
AIID(s)	Autoimmune And Inflammatory Disorders
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibody(ies)
CCI [redacted]	
Anti-La	An Antinuclear Antibody Associated With Autoimmune Diseases Including Sjögren Syndrome
Anti-Ro	An Antinuclear Antibody Associated With Autoimmune Diseases Including Sjögren Syndrome and Systemic Lupus Erythematosus
Anti-Sm	Anti-Smith Antibody, an Antinuclear Antibody Associated with Autoimmune Diseases Including Systemic Lupus Erythematosus
APRIL	A Proliferation-Inducing Ligand
AST	Aspartate Aminotransferase
β-hCG	Beta-Human Chorionic Gonadotropin
BICLA	BILAG-Based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BLyS	B Lymphocyte Stimulator (Also Called B Cell Activating Factor or BAFF)
BP	Blood pressure
CCI [redacted]	[redacted]
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLASI-A	CLASI Activity
CLASI-D	CLASI Damage
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRP	C-Reactive Protein
CS	Corticosteroid(s)
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol

CXR	Chest X-ray
DBPC	Double-Blind, Placebo-Controlled
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment
ePRO	Electronic Patient-Reported Outcome
EQ-5D-5L	EuroQoL 5 Dimension 5 Levels
FACIT	Functional Assessment of Chronic Illness Therapy
Fc	Fragment Crystallizable
FSH	Follicle-Stimulating Hormone
FWER	Family-Wise Type 1 Error Rate
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDA	High Disease Activity
HIV	Human Immunodeficiency Virus
HRQoL	Health Related Quality of Life
HRT	Hormone Replacement Therapy
HRU	Health Resource Utilization
IA	Interim Analysis
IAP	Integrated Analysis Plan
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product

IND	Investigational New Drug
INR	International Normalized Ratio
IPMP	Integrated Project Management Plan
IRB	Institutional Review Board
ITT	Intent-To-Treat
IWRS	Interactive Web Response System
LLN	Lower Limit of Normal
LTBI	Latent TB Infection
LTE	Long-Term Extension
LupusQoL	Lupus Quality of Life
MAD	Multiple Ascending Dose
MCS	Mental Component Summary
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary For Regulatory Activities
mITT	Modified Intent-To-Treat
MMF	Mycophenolate Mofetil
MPS	Mycophenolate Sodium
mRNA	messenger Ribonucleic Acid
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NK	Natural Killer
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
OCS	Oral Corticosteroids
OR	Odds Ratio
PCR	Polymerase chain reaction
PCS	Physical Component Summary
CCI	[redacted]
PGA	Physician's Global Assessment
PGIC	Patient Global Impression of Change
CCI	[redacted]
PI	Principal Investigator
CCI	CCI [redacted]

PP	Per-Protocol
PRO	Patient-Reported Outcome
PTT	Partial Thromboplastin Time
QoL	Quality of Life
RA	Rheumatoid Arthritis
RoW	Rest of the World
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-36v2®	Medical Outcomes Study 36-Item Short Form Health Survey
SFI	SLEDAI Flare Index
SLE	Systemic Lupus Erythematosus
SLEDAI-2K	SLE Disease Activity Index-2000
SLICC	Systemic Lupus International Collaborating Clinics
SMC	Safety Monitoring Committee
SOA	Schedule of Assessments
SoC	Standard of Care
SRI	SLE Responder Index
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
UPCR	Urine Protein to Creatinine Ratio
VAS	Visual Analog Scale

1 Synopsis

Clinical Trial Protocol Number	MS200527-0018
Title	A Phase II, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study To Evaluate the Safety and Efficacy of M2951 in Subjects with Systemic Lupus Erythematosus (SLE)
Trial Phase	II
IND Number	CCI [redacted]
FDA covered trial	☒ yes ☐ no
EudraCT Number	2016-002950-19
Coordinating Investigator	PPD [redacted] Telephone: PPD [redacted]
Sponsors	For all countries except the USA and Japan Merck KGaA Frankfurter Strasse 250 64293 Darmstadt Germany For Japan only: Merck Serono Co., Ltd. (Affiliate of Merck KGaA, Darmstadt, Germany) Arco Tower, 1-8-1 Shimomeguro Meguro-ku, Tokyo 153-8926, Japan And For the USA EMD Serono Research & Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA 01821 USA
Trial centers/countries	Approximately 180 sites / 20 countries
Planned Trial Period (first subject in-last subject out)	First subject in: Q4, 2016 Last subject out: Q3, 2022
Trial Registry	ClinicalTrials.gov, EudraCT, clinicaltrials.jp

Trial Objectives

Primary

- To evaluate the efficacy and dose response of evobrutinib (also referred to as M2951) compared to placebo in reducing disease activity in adult subjects with active, autoantibody-positive systemic lupus erythematosus (SLE) who are receiving standard of care (SoC) therapy based on SLE Responder Index (SRI)-4 response at Week 52 in all subjects, or on SRI-6 response at Week 52 in the High Disease Activity (HDA) subgroup, defined as SLE Disease Activity Index 2000 (SLEDAI-2K) $\geq$ 10
- To evaluate the safety of M2951 in subjects with SLE on SoC therapy.

Key Secondary

- To evaluate the efficacy and dose response of M2951 compared to placebo in delaying time to first severe flare during the Treatment Period, in subjects with SLE on SoC therapy, where a severe flare is defined as at least one British Isles Lupus Assessment Group (BILAG 2004) A in any organ system due to items that are new or worse, compared to the BILAG evaluation at the previous visit.
- To evaluate the efficacy and dose response of M2951 compared to placebo in reducing disease activity, based on the SRI-4 response at Week 52, in the serologically active subgroup, which is defined as subjects with positive anti-double-stranded deoxyribonucleic acid (anti-dsDNA) and/or low complement levels.

Secondary

- To evaluate the efficacy of M2951 compared to placebo on changes in disease activity over 52 weeks
- To evaluate the efficacy of M2951 compared to placebo on changes in organ-specific disease activity over 52 weeks
- To evaluate the effect of M2951 compared to placebo on the annualized flare rate
- To evaluate the impact of M2951 treatment compared to placebo on subject reported health related quality of life (HRQoL) over 52 weeks
- To evaluate the effect of M2951 on corticosteroid (CS) usage over 52 weeks.

Exploratory

CCI [redacted]

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Open-label Long-Term Extension (LTE) Period Objectives

The objective of the LTE Period is:

- To evaluate the long-term safety, efficacy, and HRQoL of M2951 at an initial dose of 50 mg twice daily or the eventual Phase III dose when decided for an additional two years.

Methodology

This is a Phase II, multicenter, international, randomized, double-blind, placebo-controlled (DBPC) parallel-arm study designed to determine the efficacy, dose response, and safety of M2951 in subjects with SLE, and to consider a dose to take forward into Phase III development.

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The study is composed of a Screening Period of four weeks, a DBPC Treatment Period of 52 weeks, an open-label LTE Period of 104 weeks, and a Safety Follow-Up Period of four weeks.

Planned number of subjects

Approximately 468 enrolled subjects (approximately 117 enrolled subjects per treatment group). To ensure enrollment of an adequate number of subjects with HDA, recruitment of subjects without HDA may be capped, depending on enrollment rates observed during the study of subjects with and without HDA.

Primary endpoints

- The co-primary efficacy endpoints are SRI-4 response at Week 52 in all subjects and SRI-6 response at Week 52 in a HDA subgroup.
- The primary safety endpoints are nature, severity, and incidence of adverse events (AEs), serious adverse events (SAEs); vital signs, electrocardiograms (ECGs); absolute values of and change from Baseline in serum total immunoglobulin (Ig) levels (IgG, IgA, IgM), total B cell counts, and clinical laboratory parameters.

Secondary endpoints

Key Secondary

- Time to first severe flare, where a severe flare is defined as at least one BILAG A score in any organ system due to items that are new or worse, compared to the BILAG evaluation at the previous visit, during the Treatment Period
- SRI-4 response at Week 52, in the serologically active subgroup, which is defined as subjects with positive anti-dsDNA and/or low complement levels.

Other Secondary

- SRI-6 response at Week 52, in the serologically active subgroup, which is defined as subjects with positive anti-dsDNA and/or low complement levels.
- SRI-4 Response at Week 52 with a Sustained Reduction of Oral Corticosteroids (OCS) Dose to 7.5 milligrams prednisone-equivalent per day or less (≤ 7.5 mg/day) and less than or equal to (≤) Day 1 dose during Week 41 Through Week 52, in all subjects.
- SRI-6 Response at Week 52 with a Sustained Reduction of OCS Dose to 7.5 milligrams prednisone-equivalent per day or less (≤ 7.5 mg/day) and less than or equal to (≤) Day 1 dose during Week 41 Through Week 52, in the HDA subgroup, defined as SLEDAI-2K ≥ 10 at Screening.
- SRI-4 Response at Week 52 with a Sustained Reduction of OCS Dose to 7.5 milligrams prednisone-equivalent per day or less (≤ 7.5 mg/day) and less than or equal to (≤) Day 1 dose during Week 41 Through Week 52, in the serologically active subgroup, which is defined as subjects with positive anti-dsDNA and/or low complement levels.
- Time to first flare, flare-free status at Week 52, and annualized flare rate, during the Treatment Period, will be analyzed separately, each assessed with flare defined as:
    - BILAG A Severe flare
    - BILAG A or 2B Moderate to Severe flare
    - SLEDAI Flare Index (SFI) Severe flare
- Disease activity over time, during the Treatment Period, as measured by:
    - Low disease activity status, defined by SLEDAI-2K ≤ 2, at Week 52
    - Low disease activity status, defined by clinical SLEDAI-2K (SLEDAI 2K excluding anti-dsDNA and low complement parameters) ≤ 2, at Week 52
    - Lupus low disease activity state (LLDAS), defined as meeting all of the following (Franklyn 2016):
        - SLEDAI-2K ≤ 4
        - No activity in any major organ systems (renal, central nervous system, cardiopulmonary, vasculitis, fever)
        - No new features of disease activity compared with the previous assessment

- Prednisone-equivalent ≤ 7.5 mg/day
- Unchanged background immunosuppressive therapy

  - Change from Baseline in SLEDAI-2K score by visit
  - Change from Baseline in Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity (CLASI-A) by visit
  - BILAG-based Composite Lupus Assessment (BICLA) response by visit
  - Change from Baseline in BILAG-2004 by visit
  - Change from Baseline in Physician's Global Assessment (PGA) by visit

- HRQoL over time, during the Treatment Period, as measured by:
  - Change from Baseline in Medical Outcomes Study 36-Item Short Form Health Survey (SF-36v2®) Physical Component Summary (PCS) and Mental Component Summary (MCS) score (and their components) by visit
  - Change from Baseline in EuroQoL 5 Dimension 5 Levels (EQ-5D-5L) score by visit
  - Change from Baseline in Lupus Quality of Life (LupusQoL) scores by visit
  - Patient Global Impression of Change (PGIC) score by visit
  - Change from Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score by visit
- Corticosteroid usage over time, during the Treatment Period, as measured by:
  - Reduction from Baseline in prednisone-equivalent CS dose by ≥ 25% to a dose of ≤ 7.5 mg/day, with no BILAG A or 2B flare in disease activity (at that visit)
  - Change from Baseline to Week 52 in prednisone-equivalent CS daily dose
  - Reduction from Baseline to Week 52 in prednisone-equivalent CS daily dose of zero to < 25%, 25% to 50%, > 50%, or an increase
  - Cumulative prednisone-equivalent CS dose from Baseline until completion of the Treatment Period
  - Clinically meaningful reduction in CS dose from Baseline, defined by:
    - A reduction of daily prednisone-equivalent CS dose ≥ 25% to a dose of ≤ 7.5 mg/day by Week 40 and sustained through Week 52

    And

    - No new BILAG A organ domain scores and no more than one new BILAG B organ domain score during Weeks 40 through 52.

Exploratory Endpoints

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[redacted]

Endpoints for Long-Term Extension Period

LTE Safety:

- Nature, severity, and incidence of AEs, SAEs, vital signs, ECGs, absolute values and change from Baseline in serum total Ig levels (IgG, IgA, IgM) and total B cell counts, and clinical laboratory parameters.

LTE Efficacy:

- The following LTE efficacy endpoints will be analyzed at Week 24, Week 52, and Week 104:
    - Changes over time in SRI response
    - Changes over time in Low Disease Activity status (LLDAS, SLEDAI-2K ≤ 2, clinical SLEDAI-2K ≤ 2).
    - Changes over time in CLASI-A, CLASI-D, and SLICC/ACR Damage Index organ damage scores
    - Changes over time in disease activity as measured by the BILAG, SLEDAI-2K, and PGA
    - Change over time in prednisone-equivalent CS dose
    - Changes over time in HRQoL
    - Changes over time in autoantibodies and complement levels
- Changes in HRU by visit, including but not limited to doctor/home/emergency visits, hospitalizations, paid assistance, and missed work
- Time to first flare; flare-free status at Weeks 24, 52, and 104; and annualized flare rate, will be analyzed separately, each assessed with flare defined as:
    - BILAG A Severe flare
    - BILAG A or 2B Moderate to Severe flare
    - SLEDAI Flare Index (SFI) Severe flare.

Schedule of visits and assessments

The study will be conducted on an outpatient basis. Subjects will attend clinic visits at regular intervals as indicated in the Schedule of Assessments (SOA).

Screening Period

The first visit will be a Screening Visit and will include a review of the inclusion/exclusion criteria. Subjects should undergo the Day 1 Visit as soon as possible after eligibility for the study has been confirmed. During the Screening Period, there will be no change in OCS dose.

Double-Blind, Placebo-Controlled Treatment Period

Duration of the Treatment Period will be 52 weeks starting at randomization (Day 1). The Day 1 Visit will be considered the Baseline for disease activity (e.g., BILAG 2004, SLEDAI-2K, PGA, and CLASI). Subject eligibility must be reviewed on Day 1 prior to randomization, and the first dose of the Investigational Medicinal Product (IMP) (M2951 or placebo) will be given while the subject is still on site for Day 1. Subjects must then return to the study site for study visits as indicated in the SOA. Subjects will receive the last dose of IMP at Week 52, which is the End of Treatment (EOT) for the study, unless they enter the LTE Period.

From Day 1 to the Week 4 Visit, corticosteroids may be increased, decreased, initiated (within the first two weeks of the treatment period), or remain unchanged. However, the corticosteroid dose must be ≤ 30 mg/day prednisone-equivalent by the end of Week 4. From Week 4 to the Week 8 Study Visit, OCS dose will be reduced to establish a Threshold Dose, the maximum dose allowed at any time in the study, other than for treatment of flares. Treatment decisions will be made by Investigator assessment for the purpose of subject management. Rescue therapy will be allowed for the treatment of flares.

Any subjects permanently withdrawn from IMP will be expected to complete the EOT/Early Withdrawal study visit within five days of IMP withdrawal, followed by the Safety Follow-Up Visit four weeks post last dose.

Optional Open-Label Long-Term Extension Period

Subjects who completed the 52-week DBPC Treatment period will be offered participation in the 104-week open-label, LTE Period of the study. The purpose of the LTE Period is to allow all the subjects with the opportunity to receive active treatment with M2951 and to collect long term safety and efficacy data. The Investigator should review the optional LTE Period with the subject prior to the DBPC Week 52 visit. Signed consent will be obtained prior to participation in the LTE Period. The DBPC Week 52/EOT Visit will be considered the LTE Day 1 Visit. The Safety Follow-Up Visit will be deferred until treatment is stopped in the LTE Period, due to either a subject's premature withdrawal/early termination from the LTE, termination of the study by the Sponsor, or completion of the LTE treatment period.

In some cases, due to Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, regulatory-specific, or other administrative delays, a subject may experience a treatment gap between the IMP last dose received in the DBPC Period (Week 52/EOT visit) and the start of the LTE IMP treatment. Upon Principal Investigator (PI) request, these subjects may still be able to enroll in the LTE with approval from Merck/EMD Serono, on a case-by-case basis. If the day of rollover to the LTE occurs after the DBPC Week 56/EOS visit, all assessments noted at the LTE Day 1 visit will need to be completed. For subjects that rollover after the Week 52/EOT visit but prior to their scheduled Week 56/EOS visit, concomitant medications and AEs will need to be reviewed and updated, and the PI will need to ensure that the subject remains eligible for the study. No other additional assessments other than dispensing of IMP will need to be completed.

Safety Follow-Up Period

The Safety Follow-Up/End of Study Visit is scheduled four weeks (+ 5 days) after the last administration of study treatment. For subjects who do not participate in the LTE Period, the Safety Follow-Up Visit is scheduled four weeks (+ 5 days) after the last administration of study treatment in the DBPC Period. For subjects who participate in the LTE Period, the Safety Follow-Up Visit is delayed until four weeks (+ 5 days) after the last administration of study treatment in the LTE Period. Subjects who are approved to rollover into LTE Period after they entered, or completed, the DBPC Safety Follow-Up Period, may have two Safety Follow-Up Visits. Additional details of the Safety Follow-Up/ End of Study Visit are provided in the SOA.

Assessment of Endpoints

During the study, efficacy endpoints will be evaluated using several disease activity indices, such as the BILAG 2004, SLEDAI-2K, PGA, and CLASI-A. As part of the efficacy assessment, the effects of treatment on HRQoL will be examined using Patient-Reported Outcome (PRO) measures including but not limited to: SF-36v2, EQ-5D-5L, LupusQoL, FACIT-Fatigue, and PGIC. Health Resource Utilization will also be collected as part of the efficacy assessment.

Safety will be evaluated through the nature, incidence, severity and outcome of AEs, and assessment of physical examination findings, ECGs, hematology and chemical laboratory assessments, vital signs, and change from Baseline in serum total Ig levels (IgG, IgA, and IgM) and total B cell counts.

Treatment decisions will be made by Investigator assessment for the purpose of subject management. Rescue therapy will be allowed for the treatment of flares.

Diagnosis and key inclusion and exclusion criteria

Eligible male and female subjects, aged 18 to 75 years (In Japan, if a subject is < 20 years of age, the written informed consent from the subject's parent or guardian will be required in addition to the subject's written consent); must have diagnosis of SLE with either the SLICC criteria for SLE, or at least four of the 11 ACR classification criteria for SLE, of at least six months duration prior to Screening; SLEDAI-2K total score ≥ 6 (including clinical SLEDAI ≥ 4) at Screening Visit; and have positive test results for anti-double-stranded DNA (anti-dsDNA) antibody and/or anti-nuclear antibody (human epithelial cell-2 ANA ≥ 1:80) at the time of Screening. Subjects are not eligible for this study if they have active, clinically significant interstitial lung disease or pulmonary arterial hypertension; proteinuria (urine protein to creatinine ratio [UPCR] > 4 mg/mg); acutely worsened renal function; central nervous system SLE; or within two weeks prior to Screening or during Screening: use of OCS > 30 mg daily prednisone-equivalent; use of injectable corticosteroids, or change in dose of corticosteroids.

Oral CS restrictions during study

Restrictions within two weeks prior to Screening or during Screening: included use of OCS > 30 mg daily prednisone-equivalent, use of injectable corticosteroids, or change in dose.

Restrictions and guidance for the use of OCS during the course of the study include prohibiting doses above 30 mg/day after Week 4 of the Treatment Period, prohibiting injectable CSs (outside limited exceptions), limits on when change in dose of CS may occur, recommendations to decrease CS dose within parameters allowed by the study, and limits on the use of CS during treatment of SLE flares.

Investigational Medicinal Product: dose/mode of administration/ dosing schedule

Subjects randomized into the study will receive one of three doses of M2951 (25 mg once daily, 75 mg once daily, or 50 mg twice daily) or placebo, taken orally for 52 weeks. To maintain blinding for placebo and M2951, subjects will self-administer three tablets once daily in the morning and two tablets once daily in the evening. Subjects who choose to participate in the LTE Period will receive open-label M2951 50 mg twice daily or the eventual Phase III dose when decided, taken orally for 104 weeks.

Reference therapy: dose/mode of administration/dosing schedule

N/A

Planned trial and treatment duration per subject

Total duration of subject participation is approximately 420 days (60 weeks), which includes:

- Screening: 28 days (up to four weeks)
- DBPC Treatment: 364 days (52 weeks)
- Safety Follow-Up: 28 days (four weeks)

The optional LTE Treatment Period is approximately 104 weeks in duration and will be offered to subjects after completion of the DBPC Period.

Statistical Methods

A sample size of 103 evaluable subjects per group provides 80% power at the $\alpha = 0.025$ one-sided significance level to detect

- an absolute improvement of 20% in Week 52 SRI-4 response proportion for M2951-treated subjects relative to placebo-exposed subjects, among subjects with SLEDAI-2K total score ≥ 6 at Screening, assuming a placebo response proportion of 40%,

or

- an absolute improvement of 25% in Week 52 SRI-6 response proportion for M2951-treated subjects relative to placebo-exposed subjects, among subjects with a SLEDAI-2K total score ≥ 10 at Screening (i.e., HDA), assuming a placebo response proportion of 30%,

assuming that each co-primary endpoint is tested via a chi-squared test of the odds ratio (OR) for treatment effect at the 0.0125 one-sided level, and assuming that approximately 50% of randomized subjects are in the HDA group. If the absolute improvement in Week 52 SRI-6 response in HDA subjects is only 20%, the power is 76%. Approximately 108 subjects will be randomized per treatment group to protect against a loss of information due to drop-out (for reasons other than efficacy/safety) of 5% over 52 weeks. Given the randomization ratio 1:1:1:1, the total sample size is planned to be 432 subjects.

The study includes a Japanese cohort: 32 evaluable Japanese subjects total, increased to approximately 36 randomized Japanese subjects total to protect against loss of information. If enrollment of Japanese subjects is slow, the entire Japanese cohort may not be part of the primary analysis. Therefore, the total enrollment will range from $n = 432$ to 468, where $468 = 432 + 36$ is the number enrolled if none of the 36 Japanese subjects enroll in time to be included in the primary analysis. The number of subjects enrolled per group will range from $n = 108$ to 117.

Eligible subjects will be randomized to treatment with placebo or M2951 (doses 25 mg once daily, 75 mg once daily, or 50 mg twice daily), through a central randomization process by an Interactive Web Response System (IWRS), stratified according to race (Black versus non-Black), region (US and Western Europe, Japan, and the rest of the world [RoW]) and disease activity at Screening (SLEDAI-2K total score < 10 versus ≥ 10) prior to dosing on Day 1. Subjects with SLEDAI-2K total score ≥ 10 at Screening will be considered to have HDA.

There will be at least two planned analyses in this study - the primary and final analyses. There may be up to four planned analyses, depending on whether the optional futility interim analysis (IA) is conducted, and whether the analysis for treatment effect consistency is coincident with the primary analysis, or is conducted after the primary analysis. If the futility IA is conducted, it will be based on Week 24 SRI-4 response among all subjects in the primary analysis cohort and Week 24 SRI-6 response among HDA subjects in the primary analysis cohort. The IA will be conducted when 100% of subjects in the primary analysis cohort reach Week 24 of treatment or prematurely discontinue from treatment. If enrollment is slower than expected, consideration

will be given to conducting the interim futility analysis when the first 50% of the primary analysis cohort reach Week 24 of treatment, or prematurely discontinue from treatment.

The primary analysis cohort consists of the first 432 subjects randomized. However, if drop-out for reasons unrelated to efficacy or safety is higher than expected, effectively reducing the power of the study, the Integrated Analysis Plan (IAP) may prespecify that the primary analysis cohort will include all subjects randomized. The primary analysis will be based on Week 52 SRI-4 response among all subjects in the primary analysis cohort, and Week 52 SRI-6 response among HDA subjects in the primary analysis cohort. This analysis will be triggered when 100% of subjects in the primary analysis cohort.

- Complete Week 52 of treatment and either enter LTE or complete Safety Follow-Up, or
- Prematurely discontinue from treatment prior to Week 52 and complete Safety Follow-Up, or
- Prematurely discontinue from study without Safety Follow-Up.

The Japanese cohort may be fully, partially, or not included in this primary analysis, depending on the enrollment rate.

The Family-Wise type 1 error rate (FWER) due to the co-primary endpoints and multiple M2951 dose group comparisons versus placebo will be controlled at the two-sided $\alpha = 0.05$ level via a tree gatekeeping procedure. The four hypotheses associated with the comparisons involving the co-primary endpoints and the two highest dose groups will form the first family of hypotheses in the tree. This family will be tested via the truncated Hochberg procedure, with truncation fraction pre-specified in the IAP. The multiple-testing procedure for the remainder of the tree, including the hypotheses associated with the comparisons involving the co-primary endpoints and the lowest dose group, and the key secondary endpoints and all dose groups, will be pre-specified in the IAP.

A treatment effect consistency analysis may be scheduled if the Japanese cohort does not enroll in time to be included with the primary analysis cohort. If the Japanese cohort enrolls in time to be included, the evaluation of consistency with respect to ethnicity of Week 52 SRI-4 response can be performed at the time of the primary analysis. If the Japanese cohort enrolls slowly, then the primary analysis will occur without inclusion of the Japanese cohort, and a separate consistency analysis will be triggered when 100% of enrolled Japanese subjects:

- Complete Week 52 of treatment and either enter LTE or complete Safety Follow-Up, or
- Prematurely discontinue from treatment prior to Week 52 and complete Safety Follow-Up, or
- Prematurely discontinue from study without Safety Follow-Up.

<u>The final analysis will be triggered when 100% of subjects enrolled:</u>

- Complete Week 104 of the LTE and the Safety Follow-Up, or
- Complete Week 52 of treatment and the Safety Follow-Up (if they did not rollover into the LTE), or

- Prematurely discontinue from treatment and complete Safety Follow-Up, or
- Prematurely discontinue from study.

The final analysis will be performed by PPD staff when the final analysis trigger condition has been met, protocol violations determined, and the database is locked for the final analysis.

Analysis of Co-primary Efficacy Endpoints

The primary analysis of SRI-4 response at Week 52 among all subjects in the primary analysis cohort, and SRI-6 response at Week 52 among HDA subjects in the primary analysis cohort, will be an estimate of OR, together with associated two-sided 95% CI and p-value (testing null hypothesis H0: OR = 1.0), comparing each M2951 dose group to placebo, based on a logistic model for the odds of a given SRI response in the appropriate population, with M2951 dose group or placebo group as a factor and adjustment for covariates based on randomization strata. The primary analysis of the co-primary efficacy endpoints will be based on the modified intent-to-treat (mITT) analysis set.

Descriptive statistics for SRI-4 response, and for SRI-6 response in the HDA subgroup, will be provided for each treatment group by time point.

Analysis of Key Secondary Endpoints

Time to first severe (BILAG A) flare during the Treatment Period in all subjects will be compared between M2951 and placebo via a stratified log rank test. The adjusted hazard ratio comparing M2951 to placebo will be estimated (together with 95% CI) via a Cox regression model, with treatment group as a factor, and controlling for covariates defining randomization strata. A subject who discontinues treatment or completes treatment without experiencing severe flare will have his/her time to flare censored at the last time point at which flare could be assessed.

Kaplan-Meier estimates of probability of surviving free of severe (BILAG A) flare as a function of time on treatment will be provided for each treatment group.

The analysis of SRI-4 response at Week 52 among serologically active subjects will be an estimate of OR, together with associated 95% CI and p-value, comparing each M2951 dose group to placebo, based on a logistic model for the odds of SRI-4 response in the serologically active population, with M2951 dose group or placebo group as a factor and adjustment for covariates based on randomization strata. A test for trend in dose-response, using the same logistic model, will be reported as a supportive analysis.

Descriptive statistics for SRI-4 response in the serologically active subgroup, will be provided for each treatment group by time point.

Analysis of Other Secondary Efficacy Endpoints

Binary endpoints will be modeled via logistic regression, time to event endpoints will be modeled via Cox regression and tested via stratified log rank test, continuous endpoints

measured longitudinally (i.e., HRQoL change from baseline) will be analyzed using Mixed-effect Model for Repeated Measures (MMRM), and count endpoints (i.e., annualized flare rate) will be modeled via negative binomial regression, with treatment group as a factor, and adjusting for covariates defining randomization strata. Analysis of annualized flare rate will use the log of observation time (in years) as an offset in the model. Change in a binary endpoint between two time points will be analyzed via McNemar's test. The effect of treatment on change in a binary endpoint will be analyzed via logistic regression, with treatment group, time point, and interaction as predictors, and adjusting for covariates defining randomization strata. All tests of efficacy will be conducted at a two-sided α level of 0.05, with p-values considered nominal unless generated as part of the tree gatekeeping multiple testing strategy as described in the Integrated Analysis Plan (IAP). P-values and the 95% CIs will be presented where applicable.

Analysis of Safety

Safety data for all treatment groups (M2951 dose groups, placebo group) will be listed and summarized using descriptive statistics.

Table 1 **Schedule of Assessments; Screening and Treatment Period (All Subjects), End of Study (Subjects Not Entering LTE Period)**

Trial Period	**Screening**	**Visit Weeks During Treatment Period**																		**Follow-Up Visit 4 weeks Post-Last Dose[a]**
Week		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52/ EOT/Early Withdrawal**	**56/ Safety Follow-Up/End of Study**
Trial Day	-28 to -1	1	15	29	43	57	71	85	99	113	141	169	197	225	253	281	309	337	365	393
Visit		Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56
Visit window (±day)	+7	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5
Informed consent	X																			
LTE informed consent																			X	
Inclusion/exclusion criteria	X	X[b]																		
Demographics and medical history[c]	X																			
Chest X-ray[d]	X																			
12-lead ECG	X	X						X				X				X			X	X[e]
Physical examination	X	X[f]	X[g]	X[g]		X[g]		X[g]		X[g]	X[g]	X	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X	X[g]
Vital signs, weight, height[i]	X	X[f]	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X
SFI, SLEDAI-2K, PGA, BILAG 2004, CLASI	X	X[f]	X[j]	X		X		X		X	X	X	X	X	X	X	X	X	X	X
SLICC/ACR Damage Index		X[f]																	X	
C-SSRS	X			X				X			X		X		X		X		X	X

Trial Period	**Screening**	**Visit Weeks During Treatment Period**																		**Follow-Up Visit 4 weeks Post-Last Dose[a]**
Week		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52/ EOT/Early Withdrawal**	**56/ Safety Follow-Up/End of Study**
Trial Day	-28 to -1	1	15	29	43	57	71	85	99	113	141	169	197	225	253	281	309	337	365	393
Visit		Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56
Visit window (±day)	+7	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5
IMP administration[k]		Daily administration of IMP																		
Urinalysis and microscopy	X	X[f]	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X
Routine hematology, chemistry[m]	X	X[f]	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X
Supplementary LFTs[n]					X		X		X											
Total Ig Levels (IgG, IgA, IgM)	X	X[f]	X	X				X				X			X				X	X
CCI																				
Coagulation (INR, PTT)	X																			
HIV[q], HCV, and HBV testing	X																			
Reflex testing for HBV DNA[r]	X			X		X		X		X	X	X			X			X	X	X
Serum pregnancy and FSH testing[s]	X																			
Serum β-D-glucan[t]	X																			
TSH	X																			

Trial Period	**Screening**	**Visit Weeks During Treatment Period**																		**Follow-Up Visit 4 weeks Post-Last Dose[a]**
Week		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52/ EOT/Early Withdrawal**	**56/ Safety Follow-Up/End of Study**
Trial Day	-28 to -1	1	15	29	43	57	71	85	99	113	141	169	197	225	253	281	309	337	365	393
Visit		Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56
Visit window (±day)	+7	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5
Tuberculosis assessment[l]	X																			
Urine pregnancy test[s]		X[f]	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X
UPCR	X	X[f]	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X
SF-36v2, LupusQoL, FACIT-Fatigue, EQ-5D-5L[u]		X		X		X		X		X		X		X		X			X	X
HRU				X		X		X		X	X	X	X	X	X	X	X	X	X	X
PGIC[u]				X		X		X		X		X		X		X			X	X
Dispense IMP		X	Dispense as needed, using IWRS																	
Dispense subject diary		X	Dispense as needed.																	
Concomitant medications / procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]																				

Trial Period	**Screening**	**Visit Weeks During Treatment Period**																		**Follow-Up Visit 4 weeks Post-Last Dose[a]**
Week		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52/ EOT/Early Withdrawal**	**56/ Safety Follow-Up/End of Study**
Trial Day	-28 to -1	1	15	29	43	57	71	85	99	113	141	169	197	225	253	281	309	337	365	393
Visit		Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56
Visit window (±day)	+7	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5
Immunological Assessments																				
Anti-dsDNA, Complement (C3, C4), CRP	X	X[f]		X		X		X		X	X	X	X	X	X	X	X	X	X	X
ANA, anti-Sm	X																			
Autoantibodies		X										X							X	X
Exploratory Biomarkers																				
CCI [redacted]																				

Trial Period	Screening	Visit Weeks During Treatment Period																		Follow-Up Visit 4 weeks Post-Last Dose[a]
Week		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52/ EOT/Early Withdrawal**	**56/ Safety Follow-Up/End of Study**
Trial Day	-28 to -1	1	15	29	43	57	71	85	99	113	141	169	197	225	253	281	309	337	365	393
Visit		Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56
Visit window (±day)	+7	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+5
CCI [redacted]																				

ACR = American College of Rheumatology, ALT = alanine aminotransferase, ANA = Antinuclear Antibody(ies), Anti-dsDNA = Anti-Double-Stranded Deoxyribonucleic Acid, Anti-Sm = anti-Smith antibody, AST = aspartate aminotransferase, BILAG = British Isles Lupus Assessment Group, BP = blood pressure, CCI [redacted], CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index, CRP = C-Reactive Protein, C-SSRS = Columbia-Suicide Severity Rating Scale, DNA = deoxyribonucleic acid, ECG = Electrocardiogram, EOT = End of Treatment, EQ-5D-5L = EuroQoL 5 Dimension 5 Levels, FACIT = Functional Assessment of Chronic Illness Therapy, GGT = γ-Glutamyl-transferase, Ig = Immunoglobulin, IMP = Investigational Medicinal Product, IWRS = Interactive Web Response System, HBV = Hepatitis B Virus, HCV = Hepatitis C Virus, HIV = Human Immunodeficiency Virus, HRQoL = Health Related Quality of Life, HRU = Health Resource Utilization, INR = International Normalized Ratio, LFT = liver function test, LTE = long-term extension, LupusQoL = Lupus Quality of Life, mRNA = messenger Ribonucleic Acid, CCI [redacted] PCR = polymerase chain reaction, PGA = Physician's Global Assessment, PGIC = Patient Global Impression of Change, CCI [redacted], PTT = Partial Thromboplastin Time, SF-36v2 = Medical Outcomes Study 36-Item Short Form Health Survey, SFI = SLEDAI Flare Index, SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index-2000, SLICC = Systemic Lupus International Collaborating Clinics, TB = tuberculosis, TSH = Thyroid Stimulating Hormone, UPCR = Urine Protein To Creatinine Ratio, Wk = Week.

a Safety Follow-Up Visit will be conducted at four weeks after the last dose of IMP for subjects who have been discontinued from IMP or have completed the 52-week Treatment Period, unless subjects have entered the LTE period.

b Subject eligibility to be confirmed on Day 1 prior to randomization.

c Medical history includes documentation of SLE classification criteria, SLE medical history, medications, and surgery/procedures (see Section 7.2.1).

d The results of a chest X-ray performed within three months prior to the Screening Visit (if available) are acceptable, provided there is no reason to suspect any clinical changes, per Investigator discretion.

e Only required if change noted at Wk52/EOT, when compared to Baseline ECG.

f Predose sample/procedure to be collected/performed before the first daily dose.

g Abbreviated physical examination at these visits (see Section 7.4.4.2).

h Abbreviated physical examination may be performed at Primary Investigator discretion, as required to fully obtain information needed for the BILAG and/or SLEDAI assessments, if scheduled, as well as required to fully evaluate any subject complaints or adverse events.

i Vital signs include arterial BP, pulse rate, respiratory rate, and body temperature. Height will be measured at Screening only. Body weight will be measured with a balance beam scale, if possible. Pulse rate and BP will be measured after 10 minutes rest in the semisupine position with the subject's arm unconstrained by clothing or other material. The BP should be assessed on the same arm for each subject throughout the study.

j Only CLASI assessed at Week 2.

k On Study Visit Days, IMP should be administered during the Study Visit; otherwise, IMP should be self-administered at home at a set time each day (every 12 hours ± 2 hours). Investigational medicinal product administration at Week 52 will only occur for subjects rolling over into the LTE.

l A Quantiferon test will be performed centrally. Prior TB testing results must be entered into the eCRF.

m See Table 11 for list of clinical laboratory evaluations.

n Supplementary LFTs include AST, ALT, alkaline phosphatase, GGT, and bilirubin.

C [redacted]
C

p To be collected at Screening only in subjects who have previously received B cell depleting therapy (see Exclusion Criterion 33, in Section 5.3.2).

q HIV testing will be performed locally.

r For subjects who are negative for hepatitis B surface antigen (HBsAg) but are anti-hepatitis B surface antibody positive and/or anti-hepatitis B core antibody positive, an HBV DNA PCR reflex test is to be completed at screening. If the subject enters the study with positive HBV DNA negative OR has detectable HBV DNA < 20 IU/mL only, additional HBV DNA PCR testing must be performed (see Exclusion criteria 20, in Section 5.3.2).

s For women of childbearing potential or who are postmenopausal see inclusion criterion 7. A follicle-stimulating hormone (FSH) must be drawn at Screening if necessary to confirm postmenopausal status. The urine pregnancy test being used at all time points in this study must be a highly sensitive urine pregnancy test.

t For Japan only.

u HRQoL Questionnaires should be completed before any other procedures are performed.

CCI [redacted]

Table 2 Schedule of Assessments – Optional Long-Term Extension Period

LTE Trial Period	Visit Weeks During LTE Treatment Period														Follow-Up Visit 4 weeks Post-Last Dose[a]
Week	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**24**	**40**	**52**	**76**	**Week 104/ LTE EOT/Early Withdrawal**	**Week 108/ Safety Follow-Up/LTE End of Study**
Trial Day	1	15	29	43	57	71	85	99	113	169	281	365	545	745	774
Visit	Day 1[b]	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 24	Wk 40	Wk 52	Wk 76	Wk 104	Wk 108
Visit window (±day)	-	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	+5
Informed Consent	X														
Verify subject remains eligible for the study (no prohibited medication, etc.)	X														
Vital signs, weight[c]	X		X		X		X		X	X	X	X	X	X	X
12-lead ECG	X						X			X		X	X	X	X[d]
Physical examination	X		X[e]		X[e]		X[e]		X[e]	X[e]	X[e]	X	X[e]	X	X[e]
Routine hematology, urinalysis, chemistry	X		X		X		X			X	X	X	X	X	X
Urine microscopy	X									X		X		X	
Supplementary LFT labs		X		X		X		X	X						
Total Ig Levels (IgG, IgA, IgM)	X		X		X		X			X	X	X	X	X	X
CCI [redacted]															
Urine pregnancy test[g]	X		X		X		X		X	X	X	X	X	X	X
Urine pregnancy test kit dispensation[g]									X	X	X	X	X		
Reflex testing for HBV DNA[h]	X		X		X		X		X	X	X	X	X	X	X
UPCR	X									X		X		X	
IMP dispensation[i]	X	Dispense as needed, using IWRS and complete compliance documentation													
IMP administration[j]	Daily Administration of Evobrutinib														

LTE Trial Period	**Visit Weeks During LTE Treatment Period**														**Follow-Up Visit 4 weeks Post-Last Dose[a]**
Week	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**24**	**40**	**52**	**76**	**Week 104/ LTE EOT/Early Withdrawal**	**Week 108/ Safety Follow-Up/LTE End of Study**
Trial Day	1	15	29	43	57	71	85	99	113	169	281	365	545	745	774
Visit	Day 1[b]	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 24	Wk 40	Wk 52	Wk 76	Wk 104	Wk 108
Visit window (±day)	-	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	+5
C-SSRS	X						X			X		X	X	X	X
SFI, SLEDAI-2K, PGA, BILAG 2004, CLASI	X									X		X		X	
SLICC/ACR Damage Index	X									X		X		X	
SF-36v2, LupusQoL, FACIT-Fatigue, EQ-5D-5L[k]	X									X		X		X	
PGIC[k]	X									X		X		X	
HRU	X		X		X		X		X	X	X	X	X	X	X
Concomitant medications / procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]															
Immunological Assessments															
Anti-dsDNA Complement (C3, C4), CRP	X									X		X		X	
ANA and other Autoantibodies	X									X		X		X	

ACR = American College of Rheumatology, ANA = Antinuclear Antibody(ies), Anti-dsDNA = Anti-Double-Stranded Deoxyribonucleic Acid, BILAG 2004 = British Isles Lupus Assessment Group 2004, CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index, C-SSRS = Columbia-Suicide Severity Rating Scale, D = day, DNA = deoxyribonucleic acid, ECG = Electrocardiogram, EOT = End of Treatment, EQ-5D-5L = EuroQoL 5 Dimension 5 Levels, FACIT = Functional Assessment of Chronic Illness Therapy, HBsAg = hepatitis B surface antigen, HBV = Hepatitis B Virus, HRU = Health Resource Utilization, Ig = Immunoglobulin, IMP = Investigational Medicinal Product, LFT = liver function test, LTE = Long-Term Extension, LupusQoL = Lupus Quality of Life, PGA = Physician's Global Assessment, PGIC = Patient Global Impression of Change, CCI [redacted], SFI = SLEDAI Flare Index, SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index-2000, SLICC = Systemic Lupus International Collaborating Clinics, SoA = Schedule of Assessments, UPCR = Urine Protein To Creatinine Ratio, Wk = Week, WOCBP = women of childbearing potential.

a Safety Follow-Up Visits will be conducted at four weeks after the last dose of IMP for subjects who have been discontinued from IMP or have completed the LTE Treatment Period.

b The LTE D1 visit is the EOT/Wk 52 visit from the DBPC Period unless a subject rollsover more than four weeks after the Wk 52/EOT visit. If a subject exceeds the four weeks due to unanticipated causes (e.g., regulatory approval delay), prior approval from the Medical Monitor is required and the subject will need to complete the LTE D1 visit (see Section 7.1.3).

c Vital signs including weight, oral temperature, seated blood pressure, pulse rate, and respiratory rate.

d Only required if change noted at Wk 104/EOT, when compared to Baseline ECG.

e Abbreviated physical examination may be performed at Primary Investigator discretion, as required to fully obtain information needed for the BILAG and/or SLEDAI assessments, if scheduled, as well as required to fully evaluate any subject complaints or adverse events (see Section 7.4.4.2).

CCI [redacted]

g The urine pregnancy test being used at all time points in this study must be a highly sensitive urine pregnancy test. In-between visit urine pregnancy tests will be dispensed and performed at home per SOA (Table 3) for WOCBP. The site staff will confirm completion of the home pregnancy testing and discuss results (Section 7.1.3).

h Additional HBV DNA PCR testing must be performed for subjects who entered the study with negative HBsAg and positive for anti-hepatitis B surface antibody and/or anti-hepatitis B core antibody with an HBV DNA negative OR detectable HBV DNA < 20 IU/mL only.

i The IMP will be dispensed per IWRS and IMP compliance documented using pill counts. All remaining IMP will be collected at Week 104 for all subjects.

j IMPs will be self-administered at a set time each day (± 2 hours).

k HRQoL Questionnaires should be completed before any other procedures are performed.

CCI [redacted]

Table 3 Additional Pregnancy Testing for Long-Term Extension

LTE Trial Period	Visit Weeks During LTE Treatment Period																
Week	**20**	**28**	**32**	**36**	**44**	**48**	**56**	**60**	**64**	**68**	**72**	**80**	**84**	**88**	**92**	**96**	**100**
Trial Day	143	200	229	258	315	344	402	430	459	488	516	574	602	631	660	688	717
Visit	8a	9a	9b	9c	10a	10b	11a	11b	11c	11d	11e	12a	12b	12c	12d	12e	12f
Visit window (±day)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Highly sensitive urine pregnancy test[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse events, LTE = Long-Term Extension.

a In-between visit urine pregnancy test will be performed at home. The site staff will call the subject to confirm completion of the home pregnancy testing and discuss results. Any occurrence of pregnancy results in subject withdrawal from IMP and the trial (see Section 5.5.1 and 5.5.2).

2 Sponsor, Investigators and Trial Administrative Structure

The Sponsor of this clinical study is EMD Serono Research & Development Institute, Inc. (EMD Serono R&D), Billerica, MA, in the USA; Merck Serono Co., Ltd. (Affiliate of Merck KGaA, Darmstadt, Germany) in Japan; and Merck KGaA, Darmstadt, Germany, in rest of the world (RoW).

Study Organization in Japan:

Refer to the Study Organization in Japan in the supporting documentation for additional information.

A contract research organization (CRO), PPD , will undertake the operational aspects of this study. In Japan, PPD , will undertake the operational aspects. Details of such structures and associated procedures will be defined in a separate Integrated Project Management Plan (IPMP). The IPMP will be prepared by the PPD Clinical Project Manager in cooperation with other PPD Operational Team Leads.

2.1 Investigational Sites

The study will be conducted in multiple centers, at approximately 180 sites, across approximately 20 countries.

Approximately 40 sites are anticipated to participate in the United States.

Study sites in Japan:

Refer to the Study Sites in Japan in the supporting documentation for additional information.

2.2 Trial Coordination / Monitoring

The study will appear in the following clinical trial registry: clinicaltrials.gov.

The Sponsor will enlist the support of PPD , a CRO, to conduct the clinical part of the study including study set-up, operation of an interactive web response system (IWRS) for randomization, coordination, monitoring, medical oversight, data capture, data management, statistical analysis, and clinical study reporting. The Sponsor will also make use of the CRO's central laboratory for sample analyses, storage, and shipment to specialized bioanalytical laboratories. The Sponsor will supervise all outsourced activities.

Investigational medicinal product (IMP) will be supplied by the Clinical Trial Supply Department of the Sponsor, and packaged, labeled and distributed by a designated contract manufacturing organization.

The Coordinating Investigator PPD represents all Investigators for decisions and discussions regarding this study, consistent with the

International Council for Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP); hereafter referred to as ICH GCP. The Coordinating Investigator will provide expert medical input and advice relating to study design and execution and is responsible for the review and signoff of the clinical study report (CSR). Signature pages for the protocol lead and the Coordinating Investigator as well as a list of Sponsor responsible persons are in Appendix IV.

Subject enrollment and randomization will be managed by an IWRS.

Safety laboratory assessments will be performed centrally. Use of local laboratories is optional and to be used at the discretion of the Investigator; however, duplicate samples must also be collected and sent for central laboratory analysis. Only central laboratory data will be transferred into the clinical database. Unless otherwise specified (see Section 7.4.3), local laboratory results will not be recorded in the electronic case report forms (eCRFs). Urinalysis will be performed locally; microscopic analysis and urine protein to creatinine ratio (UPCR) will be performed centrally.

CCI [redacted]

The Global Drug Safety Department, Merck KGaA, Darmstadt, Germany, or their designated representatives will supervise drug safety and the timely reporting of adverse events (AEs), and serious adverse events (SAEs). Quality assurance of the study conduct will be performed by the Development Quality Assurance Department, Merck KGaA, Darmstadt, Germany.

The department of Global Biostatistics, Merck KGaA, Darmstadt, Germany, will supervise the statistical analyses, which will be outsourced to a CRO. Pharmacokinetic data analyses will be completed by Merck KGaA.

An independent data monitoring committee (IDMC) will be established to assess safety and tolerability of IMP during the conduct of the study and review the interim analysis (IA) if completed. The IDMC will be composed of a minimum of three members who do not have any conflict of interests with the study Sponsor, including two clinicians and a biostatistician. The full membership, mandate, and processes of the IDMC will be detailed in the IDMC charter. The IDMC will review the data from the interim futility analysis conducted by an independent third party statistician. Based on the pre-defined futility criteria, the IDMC will make recommendations to the Sponsor.

The IDMC will monitor the study until the last subject has either entered the LTE or completed the Safety Follow-Up Visit following the DBPC Treatment Period for subjects that did not rollover into the LTE, whichever occurs last. At that time, study monitoring may transition to an internal Safety Monitoring Committee (SMC). The SMC will review all available safety data on a regular basis during the open-label LTE. The SMC consists of Sponsor representatives (including, but not limited to, the Medical Responsible, the Drug Safety Product Lead, the biostatistician), the Medical Monitor from the CRO, and the Coordinating Investigator. The full membership, mandate, and processes of the SMC will be detailed in the SMC charter.

In addition, the trial will be advised and monitored by a Study Steering Committee. Details about this committee will be provided in a separate charter.

Details of structures and associated procedures will be defined in a separate Manual of Procedures, which will be prepared under the supervision of the Clinical Trial Leader.

CCI [redacted]

CCI [redacted] B cell modulators have shown efficacy in several AIIDs. Belimumab, approved in 2011 in the US and EU for the treatment of lupus, inhibits B cell survival and differentiation into plasma cells (Benlysta® 2015). CCI [redacted] Rituximab has established efficacy (approved in the USA and EU) in RA and granulomatosis with polyangiitis/microscopic polyangiitis (Rituxan® 2016) and reported efficacy in a broad range of AIID disorders, including multiple sclerosis (Naismith 2010, Tanasescu 2014) and other autoimmune disorders (Kasperkiewicz 2011,

Lunardon 2012, Tony 2011, Xin 2013). In addition, other agents targeting B cells are in late stage development for systemic lupus erythematosus (SLE) (Furie 2014, Wallace 2014).

Although randomized controlled studies with rituximab in SLE and lupus nephritis have not demonstrated significant benefit over placebo (Borba 2014, Merrill 2010, Rovin 2012), this may be related in part to study design, as significant changes in background therapy were allowed. These results contrast with numerous uncontrolled studies and observational studies that have suggested benefit; many in the rheumatology community perceive rituximab to be effective for a number of manifestations of SLE, and this off-label use is recommended in SLE treatment guidelines as an alternative for the treatment of refractory lupus nephritis (Bertsias 2008, Hahn 2012, KDIGO 2012).CCI

CCI CCI

CCI [redacted]

The present Phase II study (MS200527-0018) is designed to determine the efficacy and safety of M2951 in subjects with SLE, and to determine a dose to take forward into Phase III development. Based on the available nonclinical and clinical data to date, the conduct of the study specified in this protocol is considered justifiable.

The available nonclinical and clinical data to date clearly support the pathogenic contribution of B cells in SLE. Novel non-depleting B cell therapies may deliver a more favorable benefit-risk balance than current B cell directed therapeutic approaches. In addition to silencing B cells, M2951 prevents innate immune cell activation which contributes to its efficacy. This is underlined by in-house preclinical data demonstrating superior efficacy over B cell depletion in a mouse lupus model, as well as efficacy in a mouse arthritis model despite continued presence of collagen-specific autoantibodies.CCI [redacted]

M2951 is being considered for the treatment of autoimmune diseases, including RA, SLE, and multiple sclerosis. To date, no efficacy data are available. However, because its mechanism of action directly targets both the production of autoantibodies and cellular effectors of end-organ injury, it is reasonable to anticipate that M2951 may represent a significant advance in the treatment of SLE and other autoimmune diseases.

3.1 Benefit and Risk

No identified risks or new potential risks have emerged from clinical studies thus far. In the first in human Study EMR200527-001, M2951 was well tolerated[redacted] In the completed Phase Ib study in subjects with SLE (Study EMR200527-002) M2951 was well tolerated. There were no SAEs reported during the study and no new safety signals were identified. Evidence of clinical benefit was not expected in this 4-week safety study. [redacted]

Important potential risks to subjects are based on nonclinical safety data of M2951 and clinical data on adverse drug effects associated with compounds of a similar pharmacological class. They include infection, leukopenia, thrombocytopenia, hemorrhage, gastrointestinal intolerance, renal toxicity, hepatocellular injury, atrial fibrillation, drug-drug interactions, and embryo-fetal toxicity. Asymptomatic elevations in amylase and/or lipase have been observed in completed clinical studies of M2951. The clinical significance and risk status of these observations are being assessed. The Sponsor is also assessing the clinical significance of convulsions observed in dogs at very high levels of exposure.

Risk minimization measures inherent to early phase clinical trials are considered adequate for the proposed clinical trial in subjects with SLE. An IDMC will continually review available safety and tolerability data and will be mandated to make immediate decisions regarding the conduct of the trial; no additional risk minimization measures are proposed. During the LTE, an internal SMC may review safety data on a regular basis during the LTE in lieu of the IDMC.

[redacted]

[redacted]

CCI [redacted]

Taking the above information into account, benefit-risk considerations support conduct of the proposed clinical trial MS200527-0018 in subjects with SLE.

CCI [redacted]

CCI [redacted]

[redacted]

Refer to the Investigator's Brochure for more details of each study. This clinical trial will be conducted in compliance with the CTP, ICH GCP, and any additional applicable regulatory requirements.

4 Trial Objectives

4.1 Primary Objectives

The primary objectives are:

- To evaluate the efficacy and dose response of M2951 compared to placebo in reducing disease activity in adult subjects with active, autoantibody-positive SLE who are receiving standard of care (SoC) therapy based on SLE Responder Index (SRI)-4 response at Week 52 in all subjects, or on SRI-6 response at Week 52 in the High Disease Activity (HDA) subgroup, defined as SLE Disease Activity Index 2000 (SLEDAI-2K) $\geq$ 10.
- To evaluate the safety of M2951 in subjects with SLE on SoC therapy.

4.2 Secondary Objectives

The key secondary objectives are:

- To evaluate the efficacy and dose response of M2951 compared to placebo in delaying time to first severe flare during the Treatment Period, in subjects with SLE on SoC therapy, where a severe flare is defined as at least one British Isles Lupus Assessment Group (BILAG 2004) A in any organ system due to items that are new or worse, compared to the BILAG evaluation at the previous visit.
- To evaluate the efficacy and dose response of M2951 compared to placebo in reducing disease activity, based on the SRI-4 response at Week 52, in the serologically active subgroup, which is defined as subjects with positive anti-double-stranded deoxyribonucleic acid (anti-dsDNA) and/or low complement levels.

Other secondary objectives are:

- To evaluate the efficacy of M2951 compared to placebo on changes in disease activity over 52 weeks
- To evaluate the efficacy of M2951 compared to placebo on changes in organ-specific disease activity over 52 weeks
- To evaluate the effect of M2951 compared to placebo on the annualized flare rate
- To evaluate the impact of M2951 treatment compared to placebo on subject reported health related quality of life (HRQoL) over 52 weeks
- To evaluate the effect of M2951 on corticosteroid (CS) usage over 52 weeks.

CCI [redacted]

CCI [redacted]

4.4 Open-label Long-Term Extension (LTE) Period Objectives

The objective of the LTE Period is:

- To evaluate the long-term safety, efficacy, and HRQoL of M2951 at an initial dose of 50 mg twice daily or the eventual Phase III dose when decided for an additional two years.

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a Phase II, multicenter, international, randomized, double-blind, placebo-controlled (DBPC) parallel-arm trial, designed to determine the efficacy, dose response, and safety of M2951 in subjects with SLE, and to consider a dose to take forward into Phase III development.

Approximately 432 subjects are planned to be randomized in a ratio of 1:1:1:1 to receive one of three doses of M2951 (doses 25 mg once daily, 75 mg once daily, or 50 mg twice daily) or placebo, taken orally for 52 weeks. The study includes a Japanese cohort (approximately 36 Japanese subjects). If enrollment of Japanese subjects is slow, the entire Japanese cohort may not be part of the primary analysis. Therefore, the total enrollment will range from n = 432 to 468 (n = 108 to 117 subjects per group). All subjects that choose to enter the LTE Period will be switched to active treatment with M2951 CCI [redacted] or to the eventual Phase III dose when decided. This trial will be conducted at approximately 180 sites across 20 countries.

The study is composed of a Screening Period of four weeks, a DBPC Treatment Period of 52 weeks, an open-label LTE Period of 104 weeks, and a Safety Follow-Up Period of four weeks.

The study will be conducted on an outpatient basis. Subjects will attend clinic visits at regular intervals as indicated in the Schedule of Assessments (SOA).

Screening Period

The first visit will be a Screening Visit and will include a review of the inclusion/exclusion criteria (see Section 5.3). Subjects should undergo the Day 1 Visit as soon as possible after eligibility for the study has been confirmed. During the Screening Period, there will be no change in oral corticosteroid (OCS) dose (see Section 6.4.2). Subjects who do not meet all inclusion criteria or meet an exclusion criterion within the Screening Period and are considered screen failures may undergo rescreening once, after approval by the Medical Monitor (see Section 7.1.1).

DBPC Treatment Period

Duration of the Treatment Period will be 52 weeks starting at randomization (Day 1). The Day 1 Visit will be considered the Baseline for disease activity (e.g., BILAG 2004, SLE Disease Activity Index-2000 [SLEDAI-2K], Physician's Global Assessment [PGA], and CLASI). Subject eligibility must be reviewed on Day 1 prior to randomization, and the first dose of the IMP (M2951 or placebo) will be given while the subject is still on site for Day 1. Subjects must then return to the study site for study visits as indicated in the SOA. Subjects will receive the last dose of IMP at Week 52, which is the EOT for the study, unless they enter the LTE Period.

From Day 1 to the Week 4 Visit, corticosteroids may be increased, decreased, initiated (within the first two weeks of the treatment period), or remain unchanged. However, the daily corticosteroid dose must be ≤ 30 mg/day prednisone-equivalent by the end of Week 4. From Week 4 to the Week 8 Study Visit, OCS dose will be reduced to establish a Threshold Dose, the maximum dose allowed during the remainder of the study, other than for treatment of flares. Treatment decisions will be made by Investigator assessment for the purpose of subject management. Rescue therapy will be allowed for the treatment of flares (see Section 6.4.2.2).

Any subjects permanently withdrawn from IMP will be expected to complete the EOT/Early Withdrawal study visit within five days of IMP withdrawal, followed by the Safety Follow-Up Visit four weeks post last dose.

Optional Open-Label Long-Term Extension Period

Subjects who completed the 52-week DBPC Treatment period will be offered participation in the 104-week open-label, LTE Period of the study. The purpose of the LTE Period is to allow all the subjects with the opportunity to receive active treatment with M2951 and to collect long term safety and efficacy data. The Investigator should review the optional LTE Period with the subject prior to the DBPC Week 52 visit. Signed consent will be obtained prior to participation in the LTE Period. The DBPC Week 52/EOT Visit will be considered the LTE Day 1 Visit. The Safety Follow-Up Visit will be deferred until treatment is stopped in the LTE Period, due to either a subject's premature withdrawal/early termination from the LTE, termination of the study by the Sponsor, or completion of the LTE treatment period.

In some cases, due to Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, regulatory-specific, or other administrative delays, a subject may experience a treatment gap between the IMP last dose received in the DBPC Period (Week 52/EOT visit) and the start of the LTE IMP treatment. Upon Principal Investigator (PI) request, these subjects may still be able to enroll in the LTE with approval from Merck/EMD Serono, on a case-by-case basis. If the day of rollover to the LTE occurs after the DBPC Week 56/EOS visit, all assessments noted at the LTE Day 1 visit will need to be completed. For subjects that rollover after the Week 52/EOT visit but prior to their scheduled Week 56/EOS visit, concomitant medications and AEs will need to be reviewed and updated, and the PI will need to ensure that the subject remains eligible for the study. No other additional assessments other than dispensing of IMP will need to be completed.

Safety Follow-Up Period

The Safety Follow-Up/End of Study Visit is scheduled four weeks (+ 5 days) after the last administration of study treatment. For subjects who do not participate in the LTE Period, the Safety Follow-Up Visit is scheduled four weeks (+ 5 days) after the last administration of study treatment in the DBPC Period. For subjects who participate in the LTE Period, the Safety Follow-Up Visit is delayed until four weeks (+ 5 days) after the last administration of study treatment in the LTE Period. Subjects who are approved to rollover into LTE Period after they entered, or completed, the DBPC Safety Follow-Up Period, may have two Safety Follow-Up Visits. Additional details of the Safety Follow-Up/ End of Study Visit are provided in the SOA.

Assessment of Endpoints

During the study, efficacy endpoints will be evaluated using several activity indices, such as the BILAG 2004, SLEDAI-2K, PGA, and Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity (CLASI-A). As part of the efficacy assessment, the effects of treatment on HRQoL will be examined using Patient-Reported Outcome (PRO) measures including but not limited to: Medical Outcomes Study 36-item Short Form Health Survey (SF-36v2®), EuroQoL 5 Dimension 5 Levels (EQ-5D-5L), Lupus Quality of Life (LupusQoL), Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue), and Patient Global Impression of Change (PGIC) (see Section 7.3.5). Health Resource Utilization will also be collected as part of the efficacy assessment.

Safety will be evaluated through the nature, incidence, severity and outcome of AEs, and assessment of physical examination findings, ECGs, hematology and chemical laboratory assessments, vital signs, and absolute values of and change from Baseline in serum total immunoglobulin (Ig) levels (IgG, IgA, and IgM) and total B cell counts.

Treatment decisions will be made by Investigator assessment for the purpose of subject management. Rescue therapy will be allowed for the treatment of flares.

Statistical Methods

There will be at least two planned analyses in this study - the primary and final analyses. There may be up to four planned analyses, depending on whether the optional futility interim analysis (IA) is conducted, and whether the analysis for treatment effect consistency is coincident with the primary analysis, or is conducted after the primary analysis.

If the futility IA is conducted, it will be based on Week 24 SRI-4 response among all subjects in the primary analysis cohort and Week 24 SRI-6 response among HDA subjects in the primary analysis cohort. The IA will be conducted when 100% of subjects in the primary analysis cohort, reach Week 24 of treatment or prematurely discontinue from treatment prior to Week 24. If the response proportion difference for both co-primary endpoints is sufficiently low at Week 24, as defined in the Integrated Analysis Plan (IAP), consideration will be given to termination of the study. If enrollment is slower than expected, consideration will be given to conducting the interim futility analysis when the first 50% of the primary analysis cohort reach Week 24 of treatment, or prematurely discontinue from treatment. An IDMC will monitor safety and tolerability as well as review the data from the IA. The IA will be prepared by a team independent of the study teams (Sponsor and PPD).

The primary analysis cohort consists of the first 432 subjects randomized. However, if drop-out for reasons unrelated to efficacy or safety is higher than expected, effectively reducing the power of the study, the IAP may prespecify that the primary analysis cohort may include all subjects randomized. The primary analysis will be based on Week 52 SRI-4 response among all subjects in the primary analysis cohort, and Week 52 SRI-6 response among HDA subjects in the primary analysis cohort. This analysis is triggered when 100% of subjects in the primary analysis cohort:

- Complete Week 52 of treatment and either enter LTE or complete Safety Follow-Up, or

- Prematurely discontinue from treatment prior to Week 52 and complete Safety Follow-Up, or
- Prematurely discontinue from study without Safety Follow-Up.

The Japanese cohort may be fully, partially, or not included in this primary analysis, depending on the enrollment rate. The primary analysis will be performed by PPD staff when the primary analysis trigger condition has been met, protocol violations determined, and the database is locked for the primary analysis.

The Family-Wise type 1 error rate (FWER) due to the co-primary endpoints and multiple M2951 dose group comparisons versus placebo will be controlled at the two-sided $\alpha = 0.05$ level via a tree gatekeeping testing procedure. The four hypotheses associated with comparisons involving the co-primary endpoints and the two highest dose groups will form the first family of hypotheses in the tree. This family will be tested via the truncated Hochberg procedure, with truncation fraction pre-specified in the IAP. The multiple-testing procedure for the remainder of the tree, including the hypotheses associated with the comparisons involving the co-primary endpoints and the lowest dose group, and the key secondary endpoints and all dose groups, will be pre-specified in the IAP.

A treatment effect consistency analysis may be scheduled if the Japanese cohort does not enroll in time to be included with the primary analysis cohort. If the Japanese cohort enrolls in time to be included, the evaluation of consistency with respect to ethnicity of Week 52 SRI-4 response can be performed at the time of the primary analysis. If the Japanese cohort enrolls slowly, then the primary analysis will occur without inclusion of the Japanese cohort, and a separate consistency analysis will be triggered when 100% of enrolled Japanese subjects:

- Complete Week 52 of treatment and either enter LTE or complete Safety Follow-Up, or
- Prematurely discontinue from treatment prior to Week 52 and complete Safety Follow-Up, or
- Prematurely discontinue from study without Safety Follow-Up.

If required, the consistency analysis will be performed by PPD.

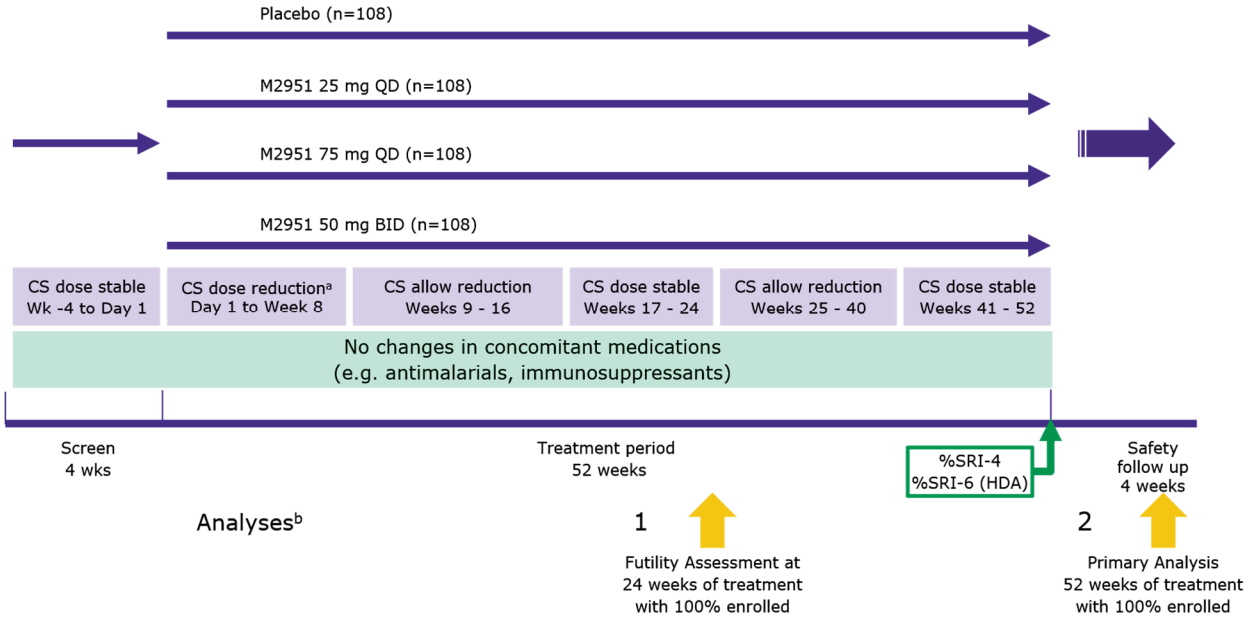
The final analysis is triggered when 100% of subjects enrolled:

- Complete Week 104 of the LTE and the Safety Follow-Up, or
- Complete Week 52 of treatment and the Safety Follow-Up (if they did not rollover into the LTE), or
- Prematurely discontinue from treatment and complete Safety Follow-Up, or
- Prematurely discontinue from study.

The final analysis will be performed by PPD staff when the final analysis trigger condition has been met, protocol violations determined, and the database is locked for the final analysis.

A schematic of the trial design is presented in Figure 2 and Figure 3 and the trial SOA is provided in Table 1, Table 2 and Table 3.

Figure 2 Study Design of MS200527-0018

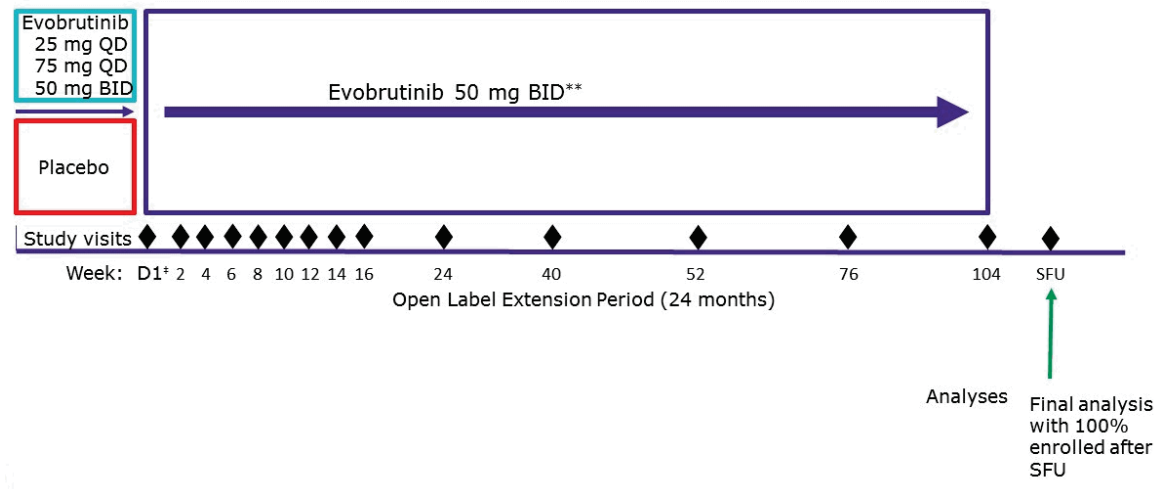


BID = Twice Daily, CS = Corticosteroid, HDA = High Disease Activity, QD = Once Daily, SRI = SLE Responder Index; Wk = week.

a CS dose may increase, decrease, be initiated, or remain unchanged from Day 1 to the Week 4 Visit, and reduce as tolerated from Week 4 through the Week 8 Visit (see Section 6.4.2).

b The Japanese cohort may be fully, partially, or not included in the primary analysis, depending on the enrollment rate.

Figure 3 Study Design for Long-Term Extension



BID = twice daily, D = day, LTE = Long-Term Extension, QD = once daily, SFU = Safety Follow-Up, SLE = Systemic Lupus Erythematosus, WOCBP = women of child bearing potential.

** = Subjects will receive an initial dose of 50 mg BID. When a Phase 3 dose is determined, all subjects may be switched to this dose at the Sponsor's discretion.

* = For subjects entering the Open Label Extension, the Week 52 visit is considered the Day 1 visit for the Open Label LTE Period.

NOTE: For WOCBP, urine pregnancy tests will be performed at home to ensure monthly pregnancy testing.

5.2 Discussion of Trial Design

5.2.1 Scientific Rationale for Study Design

The present study (MS200527-0018) is designed to determine the efficacy and safety of M2951 in subjects with active SLE without severe organ system disease (e.g., central nervous system and renal). Subjects will be on standard of care background therapy (e.g., antimalarials, immunosuppressants). The primary objective will focus on reduction in disease activity relative to placebo over 52 weeks in adult subjects with active, autoantibody-positive SLE who are receiving SoC therapy based on SRI-4 response at Week 52, or in reducing disease activity in a HDA subgroup (SLEDAI-2K total score ≥ 10) based on SRI-6 response at Week 52.

The key secondary measures will evaluate reduction in flares relative to placebo and assess SRI-4 response in the serologically active subgroup, where serologically active is defined as anti-dsDNA positive and/or low complement levels.

Both SRI-4 response in the study population as a whole and SRI-6 response in a HDA subgroup will be evaluated to ensure that a robust signal on disease activity is demonstrated.

CCI [redacted]

CCI [redacted]

Refer to the current Investigator's Brochure for more detailed results from the completed clinical studies, including final data from clinical Study EMR200527-002. Based on the available nonclinical and clinical data to date, the conduct of the study specified in this protocol is considered justifiable (see Section 3).

5.2.2 Justification for Dose

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Refer to the current Investigator's Brochure for more detailed results from the completed clinical studies.

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5.2.3 Rationale for Endpoints

The primary and key secondary endpoints are standard for SLE studies and are accepted by regulators. The co-primary endpoints are SRI-4 response in the entire study population and SRI-6 response in subjects with HDA, both at Week 52. These endpoints provide a measure of a subject's response to disease treatment. The evaluation for greater improvement in subjects with HDA reflects the goal of specifically evaluating the ability of M2951 to provide relief in the subjects with more severe disease. The key secondary endpoint, time to first severe (BILAG A) flare during the Treatment Period, characterizes another aspect of response to treatment, specifically the ability of M2951 to improve control of flares. For the other key secondary endpoint, subjects who are serologically active (i.e., positive anti-dsDNA and/or low complement) will also be evaluated for response to treatment. As shown in other SLE studies, serologically active subjects demonstrated higher treatment effect size between the active and placebo groups in the SRI-4 response rates compared to the serologically inactive subjects (Stohl 2012).

The secondary HRQoL endpoints are complementary to the disease activity endpoints. The SF-36v2 has widely been used to assess physical, psychological and social impact of chronic diseases like SLE. The disease specific LupusQoL, and the symptom specific FACIT-Fatigue are well validated tools to measure disease specific aspects of HRQoL in SLE studies. The EQ-5D-5L is the most accepted and often required instrument generating quality of life (QoL) outcomes data to be used by Health Technology Assessment bodies.

5.2.4 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

Subject enrollment will be randomized and managed by an IWRS (see Section 6.3). Only subjects meeting all inclusion criteria and no exclusion criteria may be enrolled into the study as subjects (see Section 5.4). Prior to performing any study assessments not part of the subject's routine medical care, the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent following the procedure described in Section 9.2.

Eligibility will be evaluated and confirmed by the study eligibility team. Sites will be required to submit an eligibility packet (consisting of an eligibility checklist and appropriate documentation) for potential eligible subjects. The subjects' eligibility will be assessed at a Screening Visit that

will occur up to four weeks prior to the Randomization Visit (Day 1). When a laboratory test must be repeated during the Screening Period or an unanticipated event occurs, the Screening Period can be extended to 8 weeks after discussion with the Medical Monitor. See Table 1 for a list of assessments done at Screening to determine the eligibility of the subject to participate in the study. Subjects cannot be randomized into the study until eligibility is confirmed.

Screen failures may be rescreened once (see Section 7.1.1).

5.3.1 Inclusion Criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled:

1. Signed written informed consent before any study-related procedure is undertaken that is not part of the standard subject management and able to comply with requirements of protocol. In Japan, if a subject is < 20 years of age, the written informed consent from the subject's parent or guardian will be required in addition to the subject's written consent.

2. Male or female subjects, 18 to 75 years of age.

3. Diagnosis of SLE with either the SLICC criteria for SLE (see Appendix II), or at least four of the 11 ACR classification criteria for SLE (see Appendix III), of at least six months duration prior to Screening.

4. SLEDAI-2K total score ≥ 6 (including SLEDAI-2K clinical score ≥ 4) at Screening Visit.

5. Positive test results for anti-dsDNA antibody and/or anti-nuclear antibody (human epithelial cell-2 ANA ≥ 1:80) and/or anti-Smith (anti-Sm) antibody at the time of Screening.

6. Due to newly available nonclinical data, previous requirements for male participant contraception have been removed (see Section 6.5.3).

7. A female participant is eligible to participate if she is not pregnant (see Appendix I), not breastfeeding, and at least one of the following conditions applies:

    a. Not a woman of childbearing potential (WOCBP) as defined in Appendix I

    OR

    b. A WOCBP who agrees to use 2 methods of birth control: a barrier method together with a highly effective method (i.e., methods with a failure rate of less than 1% per year) as detailed in Appendix I of this protocol for at least 28 days before start of first dose of study treatment (as appropriate), during the treatment period and for at least 90 days after the last dose of study treatment.

8. History of vaccinations, as per local guidelines:

a. Vaccination against Streptococcus pneumoniae with PPSV23 and/or PCV13 or local equivalent with repeat administration as necessary to be up to date. If vaccination during Screening, there must be at least 2 weeks between vaccination and randomization.

b. Vaccination against influenza virus (as seasonally required) or vaccination against these pathogens during Screening (as seasonally required for influenza virus). If vaccinated during Screening, there must be at least 2 weeks between vaccination and randomization. If the subject is screened after the most recent influenza season and/or the influenza vaccine is no longer available, the influenza vaccine should be given during the study once available, as per local guidelines.

9. Subjects should be on SLE standard of care (SoC) background therapy, consisting of at least one protocol permitted therapy (e.g., immunosuppressants, immunomodulators, antimalarials, corticosteroids, or nonsteroidal anti-inflammatory drugs [NSAIDs] [see Section 6.4.1]). Subjects not on SoC background therapy may be enrolled after approval by the Medical Monitor.

5.3.2 Exclusion Criteria

Subjects are not eligible for this study if they fulfill any of the following exclusion criteria:

1. Active, clinically significant, interstitial lung disease or pulmonary arterial hypertension, defined as follows:

    a. Pulmonary Hypertension (with presence of any of the following):

        i. Presence of uncontrolled World Health Organization (WHO) Pulmonary Hypertension Functional Class III or IV (Galiè 2016):

            1. WHO Class III – Pulmonary hypertension resulting in marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.

            2. WHO Class IV – Pulmonary hypertension resulting in inability to carry out any physical activity without symptoms. Signs of right heart failure are present. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

        ii. Pulmonary hypertension requiring past or current treatment with any of the following: supplemental oxygen, endothelin receptor antagonists (e.g., ambrisentan, bosentan, macitentan), phosphodiesterase type 5 inhibitors (e.g., sildenafil, tadalafil, vardenafil), riociguat, prostacyclin analogues (epoprostenol, iloprost, treprostinil, beraprost), selexipag, or any other systemic therapies targeting pulmonary hypertension. In addition, subjects that would be considered to require initiation of systemic therapy for PHTN by the Investigator or evaluating pulmonologist and/or cardiologist would also be excluded.

        iii. History of transthoracic echocardiography showing any of the following, (unless right heart catheterization subsequent to these measures did not reveal pulmonary hypertension):

            1. tricuspid regurgitation jet > 2.8 m/sec

            2. right atrial enlargement (major dimension > 53 mm)

            3. right ventricular enlargement (mid cavity dimension > 35 mm)

            4. moderate to severe left ventricular dysfunction.

b. Interstitial Lung Disease (with presence of any of the following):

iv. Interstitial lung disease requiring treatment with supplemental oxygen or cyclophosphamide within the 12 months prior to Screening.

v. Interstitial lung disease diagnosed by lung biopsy and/or high-resolution computed tomography with significant respiratory symptoms at Screening based on the Investigator's assessment.

c. Further, subjects with either diagnosis may be excluded if the Investigator or Sponsor/designee feels that the diagnosis constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct or evaluation (see Exclusion Criterion 28).

2. Proteinuria > 4 g/day (spot UPCR > 4 mg/mg), and/or estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m^2 as calculated by the 4-component Modification of Diet in Renal Disease (MDRD) equation by the central laboratory):

a. The four-component Modification of Diet in Renal Disease equation (Levey 2006): eGFR = 175 × (serum creatinine in mg/dL) $^{-1.154}$ × (age in years) $^{-0.203}$ × 0.742 (if female) × 1.212 (if race is black)

3. Evidence of recent, acutely worsened renal function (e.g., reduction in eGFR by ≥ 30 mL/min to < 60 mL/min/1.73 m^2; or a syndrome of Rapidly Progressive Glomerulonephritis, as defined by a 50% decline in glomerular filtration rate in three months; in the six months prior to Screening).

4. Subjects with any of the following will be excluded:

a. Active seizures, seizures requiring long-term treatment, or a recent seizure (in the past 2 years) with the exception of: remote seizures (e.g., in childhood or adolescence with resolution and not on treatment, or a past history of febrile seizures) OR a seizure related to a metabolic / physiologic disturbance in the past (e.g., related to low electrolytes, low glucose, or secondary to a vasovagal event). These subjects would have no greater risk of developing a seizure than a normal individual who had not had seizures, and would not need to be excluded.

b. Active central nervous system SLE deemed to be severe or progressive including any history of transverse myelitis, seizures as detailed in Exclusion Criterion 4a above, and/or associated with significant cognitive impairment leading to inability to provide informed consent and/or comply with the protocol.

If the Investigator's assessment provides for an outcome of exclusion, or a question regarding eligibility, a Neurologist may be consulted, but inclusion in the study regarding this criterion is at the discretion of the Investigator.

5. Within two weeks prior to Screening or during Screening: use of OCS > 30 mg daily prednisone-equivalent, use of injectable corticosteroids, or change in dose of corticosteroids.

6. Within two months prior to Screening or during Screening: initiation of or change in dose of antimalarial, methotrexate, 6-mercaptopurine, sulfasalazine, mycophenolate (mofetil [MMF] or sodium [MPS][*]), or azathioprine ([*]not approved in Japan).

7. Calcineurin inhibitors (cyclosporine, tacrolimus) and cyclophosphamide are prohibited during the study. Calcineurin inhibitors must be washed out one month prior to Screening. Cyclophosphamide must be washed out three months prior to Screening.

8. A stable dose of leflunomide is not exclusionary; however, subjects having discontinued leflunomide must have washed out for three months prior to Screening.

9. Within three months prior to Screening or during Screening, use of abatacept, antitumor necrosis factor alpha agents, intravenous Ig, plasmapheresis, or other disease modifying, immunosuppressive or immunomodulatory therapies not otherwise specified in protocol.

10. Within six months prior to Screening or during Screening: use of alkylating agents other than cyclophosphamide (e.g., chlorambucil).

11. Within one year prior to Screening or during Screening: use of belimumab[*] or any anti-B Lymphocyte Stimulator (BLyS) therapy.

CCI [redacted]

13. Within two weeks prior to Screening, initiation or change in dose of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, or NSAIDs, or use of NSAIDs above maximum prescribed dose per local label.

14. On anticoagulation (e.g., vitamin K antagonists) or antiplatelet therapy (e.g., clopidogrel) other than daily low-dose aspirin (≤ 350 mg/day) for cardioprotection. Low-dose aspirin therapy for other indications may be permitted after discussion with medical monitor.

15. On fish oil (unless discontinued prior to first dose).

16. Within one month prior to Screening, vaccination with live or live-attenuated virus vaccine.

17. Known hypersensitivity to any study treatment, component, or placebo.

18. Active clinically significant viral, bacterial or fungal infection, or any episode of infection requiring hospitalization or treatment with parenteral anti-infectives within four weeks prior to Screening, or completion of oral anti-infectives within two weeks before or during Screening, or a history of recurrent infections (i.e., three or more of the same type of infection in a 12 month rolling period). Vaginal candidiasis, onychomycosis and genital or oral herpes simplex virus considered by the Investigator to be sufficiently controlled would not be exclusionary.

19. Any of the following:

    a. History of or positive for human immunodeficiency virus (HIV) at Screening

    b. History of or positive for hepatitis C antibody and/or hepatitis C RNA by polymerase chain reaction (PCR) at Screening

    c. Positive for hepatitis B surface antigen (HBsAg) at Screening

    d. For subjects who are negative for HBsAg at Screening but are anti-hepatitis B surface antibody positive and/or anti-hepatitis B core antibody positive at Screening, reflex testing for hepatitis B virus DNA (HBV DNA) by PCR will be performed:

        1. Hepatitis B antibody positive subjects who have detectable HBV DNA ≥ 20 IU/mL are excluded.

        2. Hepatitis B antibody positive subjects who are HBV DNA negative OR have detectable HBV DNA < 20 IU/mL are not excluded from the study. However, these subjects will have HBV DNA measured by PCR at visits noted in the SOA.

    Note: Subjects who have previously been vaccinated for Hepatitis B will not be tested for anti-hepatitis B surface antibody, as they will be positive for anti-hepatitis B surface antibody as the protective consequence of vaccination.

20. Any of the following:

    a. History of active tuberculosis (TB)

    b. Current diagnosis of active TB

    c. Untreated latent TB infection (LTBI)

    d. Undergoing current treatment for LTBI

    e. Subjects with current household contacts with active TB.

    In the absence of a diagnosis of active TB, or clinical features consistent with a diagnosis of active TB, LTBI is determined by any of the following:

- prior TB skin test with purified protein derivative (PPD) with induration ≥ 5 mm (unless vaccinated with Bacille Calmette-Guérin)
- prior positive T-SPOT.TB (Elispot) test result
- positive Quantiferon test, either at Screening or with documented past results.

Note: All subjects, except those who have previously completed appropriate and documented LTBI treatment, are required to undergo Quantiferon testing during Screening. Individuals with indeterminate or positive Quantiferon test results felt to represent a false positive result by the Investigator, with no clinical features consistent with active TB, will be evaluated with T-SPOT.TB at the request of the Investigator. In this case, if the T-SPOT.TB is negative, the individual may be enrolled after approval by the study eligibility team.

Note: Prophylactic use of antituberculous drugs is not permitted during the study, and if used must be discontinued prior to the first dose of study medication. If an Investigator feels that a subject requires antituberculous prophylaxis while participating in the study, this may be allowed after review of the case by the Medical Monitor.

21. History of shingles within 12 months prior to Screening unless vaccinated following onset.

22. History of splenectomy at any time or any major surgery within two months prior to Screening. Major elective surgeries such as abdominal, thoracic, or joint replacement surgeries should not be planned to occur in the Study Period.

23. Clinically significant cardiovascular events (e.g., acute myocardial infarction, unstable angina or peripheral vascular disease symptoms, hospitalization for congestive heart failure, cardiac surgery, ischemic or hemorrhagic stroke, or transient ischemic attack) within six months before the Screening Visit or during Screening, or current active angina or untreated hypertension at the Screening Visit.

24. Active cardiac arrhythmia or other ECG abnormality that could constitute a clinical risk (including but not limited to): long QT syndrome, Wolff-Parkinson-White syndrome, or an untreated malignant ventricular arrhythmia (e.g., ventricular fibrillation or tachycardia) at the Screening Visit or Day 1.

25. Presence of uncontrolled or New York Heart Association (NYHA) Class 3 or 4 congestive heart failure.

    a. NYHA Class 3: Cardiac disease resulting in marked limitation of physical activity. Subjects are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

    b. NYHA Class 4: Cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome

may be present even at rest. If any physical activity is undertaken, discomfort is increased.

26. Antiphospholipid antibody syndrome associated with a thromboembolic event in the 12 months prior to or during Screening. See Exclusion Criterion 14 for discussion of anticoagulation or anti-platelet therapy.

27. Any condition, including any uncontrolled disease state other than SLE, that in the Investigator's opinion or Sponsor/designee opinion constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct or evaluation.

28. History or current systemic autoimmune diagnosis other than SLE, including demyelinating diseases (e.g., multiple sclerosis, optic neuritis), or any other condition requiring systemic corticosteroid therapy (such as asthma or inflammatory bowel disease) with the exception of concomitant Sjögren's or secondary Sjögren's syndrome.

29. History of cancer with the following exceptions:

    a. A history of non-melanoma skin cancer Stage 0 (in situ) or Stage 1, considered cured > five years is not exclusionary.

    b. A history of in situ cervical cancer, considered cured > five years, is not exclusionary.

    Any history of cancer not meeting these exceptions is exclusionary.

30. Breastfeeding/lactating or pregnant women. Lactating women are excluded regardless of whether or not they are nursing infant(s).

31. Alanine or aspartate aminotransferase, amylase or lipase > 2 × above upper limit of normal (ULN) of laboratory reference range, total bilirubin > 1.5 × ULN, thyroid stimulating hormone [TSH] < 0.01 or ≥ 7.1 mIU/L per central laboratory results) or any other clinically significant laboratory abnormality.

32. Participation in any investigational drug study within three months or five half-lives of the investigational drug, whichever is longer, prior to Screening. For this protocol, this includes JAK inhibitors, therefore JAK inhibitors must have been discontinued for at least three months prior to Screening.

33. Total B cell count < 50% of the lower limit of normal (LLN) at the Screening Visit in subjects who previously received B cell depleting therapy such as with anti-CD20 agents (e.g., rituximab, ocrelizumab*, ofatumumab, obinutuzumab*, ocaratuzumab*, veltuzumab*) (*not approved in Japan).

34. Significant cytopenia, such as neutrophil count < 1,000/mm^3, or platelet count < 75,000/mm^3.

35. Serum IgG below 6 g/L at the Screening Visit.

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37. Active infective process or any other clinically significant abnormality on chest X-ray (CXR). Chest X-ray must have been taken within three months prior to the Screening Visit, or during the Screening Period.

38. History or current alcohol, substance, or drug abuse:

    a. Excessive alcohol use is defined as alcohol and/or substance abuse or dependence (as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text revision) in the past year or a history of alcohol or substance abuse, as determined by the Investigator.

39. Subjects who have evidence of serious suicide risk including any history of suicidal behavior in the last three months and/or any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) in the month prior to Screening, OR
    Are a significant suicide risk, as determined by the Investigator, including any history of active suicidal ideation with intent to act in the last three months or any history of suicidal behavior in the subject's lifetime.

40. Legal incapacity or limited legal capacity.

41. History of bleeding disorder and/or drug-induced thrombocytopenia.

42. Any of the following diagnoses are exclusionary due to lactose present in the IMP:

    a. Galactosemia/Galactose intolerance:

        i. Classical Galactosemia, also known as galactose-1-phosphate uridyltransferase deficiency or GALT deficiency

        ii. Galactosemia type II, also known as galactokinase deficiency or GALK deficiency

        iii. Galactosemia type III, also known as galactose epimerase deficiency, UDP-Galactose-4-epimerase deficiency, or GALE deficiency

    b. Fanconi-Bickel syndrome, also known as glycogen storage disease XI, Bickel-Fanconi glycogenosis, or glucose transporter 2 (GLUT2) deficiency

c. Congenital lactase deficiency, also known as congenital alactasia or disaccharide intolerance II

d. Glucose/Galactose malabsorption, also known as monosaccharide malabsorption

e. Individuals with acquired lactose intolerance are not excluded, but should be aware that the IMP contains lactose and should be monitored for gastrointestinal symptoms related to the increased consumption of lactose in the IMP, and made aware of the risks.

43. For Japan only - Positive serum β-D-glucan test at Screening.

5.4 Criteria for Randomization/Initiation of Treatment with the Investigational Medicinal Product

Randomization can occur only after informed consent and confirmation that the Medical Monitor has reviewed the Screening Period data including SLE diagnostic criteria, inclusion/exclusion criteria, SLEDAI-2K, medical history (including date of SLE diagnosis), concomitant medications, ECG and clinical laboratory assessments.

Eligible subjects will be randomized in a 1:1:1:1 ratio to treatment with placebo or M2951 (doses 25 mg once daily, 75 mg once daily, or 50 mg twice daily), through a central randomization process by an IWRS, stratified according to race (Black versus non-Black), region (US and Western Europe, Japan, and the RoW) and disease activity (SLEDAI-2K total score < 10 versus ≥ 10 at Screening) prior to dosing on Day 1. Subjects with SLEDAI-2K total score ≥ 10 at Screening will be considered to have HDA.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from the Trial

Subjects may withdraw from the study at any time without giving a reason. Withdrawal of consent will be considered withdrawal from the study. Subjects who withdraw from the study while still on the IMP should return for an EOT/Early Withdrawal Visit upon discontinuation of the IMP and a Safety Follow-Up Visit as indicated in the SOA. Subjects who withdraw and are no longer on the IMP must complete the Safety Follow-Up/End of Study Visit assessments as indicated in the SOA provided in Table 1, and in Table 2 (for the LTE). A complete final evaluation at the time of the subject's withdrawal should be made, and AEs followed up as per Section 7.4.1.

A subject must be withdrawn if any of the following occur during the study:

- Subject withdrew consent
- Participation in any other clinical study during the duration of this study
- Occurrence of Pregnancy (for further details in case of pregnancy, see Section 7.4.2)
- Any events that endanger the safety of the subject.

- Subject lost to follow-up
- Sponsor decision to end clinical study
- Subject is considered a treatment failure
- IMP is permanently withdrawn (see Section 5.5.2)

If a subject fails to return for the Safety Follow-Up/End of Study Visit, all attempts should be made to contact the subject to ensure the reason for not returning is not an AE. Likewise, if a subject wishes to discontinue from the study (e.g., for personal reasons), attempts should be made to establish the true reason is not an AE (bearing in mind the subject is not obliged to state the reasons).

If a subject has failed to attend scheduled study assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible. At least three attempts to contact lost to follow-up subjects should be made and documented (two phone calls and one authorized organization representative letter).

If IMP is prematurely discontinued, the primary reason for discontinuation must be recorded in the appropriate section of the eCRF, and all efforts will be made to complete and report the observations as thoroughly as possible.

Subjects who are withdrawn after randomization due to safety or lack of efficacy will not be replaced. Consideration will be given to increasing enrollment to compensate for loss of information due to subjects who withdraw for reasons unrelated to safety or lack of efficacy. Subjects who are withdrawn from the study will not be allowed to re-enroll in the study.

5.5.2 Withdrawal from the Investigational Medicinal Product

Subjects who withdraw from IMP must immediately return for an EOT/Early Withdrawal Visit followed by the Safety Follow-Up/End of Study Visit as indicated in the SOA provided in Table 1, and in Table 2 (for the LTE). Subjects considered a treatment failure, as defined in the protocol, must be withdrawn from the study (see Section 5.5.1).

Escape Criteria

If during the study, in the opinion of the Investigator, the subject's SLE disease level is unacceptably high requiring therapy not permitted per the protocol, the subject may withdraw from the study treatment and initiate therapy recommended per the treating physician. In this case, the subject will be considered a treatment failure. See Section 6.4.2.2 for handling of flares.

A subject must be withdrawn from M2951 or placebo if any of the following occur:

- Withdrawal from the study (see Section 5.5.1).
- Enrollment despite violation of an exclusion criterion which, in the Investigator's and/or Sponsor's opinion, makes discontinuation of the subject necessary.

- Occurrence of an AE and if discontinuation of IMP is desired or considered necessary by the Investigator and/or the subject.
- Occurrence of pregnancy (for further details in case of pregnancy, see Section 7.4.2).
- Use of a prohibited medication, as defined in Section 6.5.2. However, any medications that are considered necessary for the subject's well-being may be given at the discretion of the Investigator. If, in the view of the Investigator, the use of a prohibited medication should not impact subject safety or bias efficacy assessments, the Investigator can request the Medical Monitor review the case. Such a request must be made as soon as the Investigator is aware of the use of prohibited medication, and the Medical Monitor, along with the Sponsor, will determine if the subject must be permanently withdrawn from IMP. See Section 6.4.2.2 for specifics regarding treatment of flares during the DBPC and LTE treatment periods of the study and withdrawal from IMP.
- Occurrence of any other clinical condition for which discontinuation is considered necessary by the Investigator and/or the Sponsor/designee.

Criteria for Withdrawal of Investigational Medical Product (Temporary and Permanent)

The IMP should be temporarily withheld or permanently withdrawn if the following laboratory abnormalities occur or re-occur, as relevant, and re-initiation following temporarily withholding of IMP should be discussed with the Medical Monitor. If a subject's pre-dose baseline value is abnormal and/or falls within any of the below criteria, consult with the Medical Monitor regarding potential withdrawal, continued participation in study, and additional monitoring if needed. Retesting should be completed within 1 week:

- For a neutrophil count < 1000/mm^3 (Grade 3 or 4) or platelet count < 50,000/mm^3 (Grade 3 or 4), temporarily hold the IMP and recheck the value. If the value is still Grade 3 or 4, permanently discontinue the IMP; if the value improves to Grade 2, Grade 1 or is within normal limits, IMP may be reinitiated after discussion with the Medical Monitor. For a recheck value that decreases to Grade 2, perform repeat testing within 1 month.
- For a lymphocyte count < 200/mm^3 (Grade 4), temporarily hold the IMP and recheck the value. If the value is still Grade 4, permanently discontinue the IMP; if the value improves to a Grade 3, discuss with the Medical Monitor; if the value improves to Grade 2, Grade 1 or is within normal limits, IMP may be reinitiated after discussion with the Medical Monitor. For a recheck value that improves to Grade 2, perform repeat testing within 1 month.
- For an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) to > 3× ULN (Grade 2 or higher), temporarily hold the IMP and recheck the value. If the value is still Grade 2 or higher, the IMP should be permanently withdrawn. The subject should be followed with additional testing as needed until a return to ULN or acceptable value as agreed upon by the Investigator and Medical Monitor. Consultations with specialists, such as a hepatologist, can be considered at the discretion of the Investigator and in conjunction with the Medical Monitor.
- For an increase in bilirubin to > 1.5 × ULN (Grade 2 or higher), temporarily hold the IMP and recheck the value. If the value is still Grade 2 or higher, the IMP should be permanently withdrawn.

- A comprehensive hepatic panel is requested for any subjects, for whom above AST or ALT withdrawal criteria are met and who permanently discontinue dosing due to elevated liver function tests. Subjects should be referred to a hepatologist who may recommend testing in addition to the following:
    - INR, PTT, fibrinogen, hsCRP
    - Hepatitis serology: anti-HAV IgG, anti-HAV IgM, HBsAg, anti-HBc, anti-HBsAg, anti-HCV, anti-HEV IgG and IgM, anti-VCA IgG and IgM, anti-EA IgG, anti-EBNA IgG, anti-CMV IgG and IgM
    - Antinuclear antibody, anti-smooth muscle antibody, and liver-kidney microsomal antibody
    - Albumin
- For an increase in amylase or lipase to > 2× ULN (Grade 3 or 4), temporarily hold the IMP and recheck the value. If the value is still Grade 3 or 4, permanently discontinue the IMP; if the value improves to Grade 2, Grade 1, or is within normal limits, IMP may be reinitiated after discussion with the Medical Monitor. For a recheck value that improves to Grade 2, perform repeat testing within 1 month.
- For an increase in serum creatinine to > 3× Baseline (Grade 3 or 4), temporarily hold the IMP and recheck the value. If the value is still a Grade 3 or 4, permanently discontinue the IMP.
- For an increase in serum creatinine > 1.5× Baseline to ≤ 3× Baseline (Grade 2), temporarily hold the IMP and recheck the value. If the value is still Grade 2, discuss with the Medical Monitor; if the value improves to Grade 1 or is within normal limits, IMP may be reinitiated after discussion with the Medical Monitor.
- For any serum IgG level < 3 g/L, temporarily hold the IMP and recheck the value. If the value is still < 3 g/L, the IMP should be permanently withdrawn.
- For any increase in HBV DNA by PCR from negative/undetectable to detectable, and/or increase in HBV DNA by PCR from < 20 IU/mL to ≥ 20 IU/mL, the IMP should be permanently withdrawn. The subject should be followed with additional testing and Hepatitis B treatment, as indicated per local guidelines, including consultation with a specialist, such as a hepatologist, at the discretion of the Investigator and in conjunction with the Medical Monitor.
- For any other laboratory abnormality of Grade 4 severity, temporarily hold the IMP and recheck the value. If the value is still a Grade 4, the IMP should be permanently withdrawn. If the retest value improves, discuss with the Medical Monitor.
- For any other laboratory increase/decrease (as relevant) from Baseline to Grade 3 (unless otherwise indicated in this section of the protocol), temporarily hold the IMP, recheck the value, and discuss results with Medical Monitor.

All laboratory abnormalities outlined must be followed to resolution. Laboratory values corresponding to Common Terminology Criteria for AEs (CTCAE) Grades 1 to 4 are presented for selected laboratory parameters in Table 5. For all other laboratory abnormalities, refer to the CTCAE, version 4.03 (CTCAE 2009).

The reason for IMP withdrawal and the nature, duration, and results of any planned follow-up observations should be recorded in the appropriate section of the eCRF.

Table 5 Common Terminology Criteria for Adverse Events Grades for Relevant Laboratory Parameters

Laboratory Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Neutrophil (/mm^3)	< LLN to 1,500	< 1,500 to 1,000	< 1,000 to 500	< 500
Platelets (/mm^3)	< LLN to 75,000	< 75,000 to 50,000	< 50,000 to 25,000	< 25,000
AST and ALT	> ULN to 3× ULN	> 3 to 5× ULN	> 5 to 20× ULN	> 20× ULN
Bilirubin	> ULN to 1.5× ULN	> 1.5 to 3× ULN	> 3 to 10× ULN	> 10× ULN
Amylase and lipase	> ULN to 1.5× ULN	> 1.5 to 2× ULN	> 2 to 5× ULN	> 5× ULN
Creatinine	> Baseline to 1.5× Baseline, or > ULN to 1.5× ULN	> 1.5 to 3× Baseline or > 1.5 to 3× ULN	> 3× Baseline, or > 3 to 6× ULN	> 6× ULN

ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase, LLN = Lower Limit of Normal, ULN = Upper Limit of Normal.

5.6 Premature Termination of the Trial

The clinical study may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavorable risk benefit judgment for any IMP. The Sponsor may discontinue the study if the IA indicates that the study is unlikely to achieve the primary endpoint at the time of the primary analysis, the study becomes unjustifiable for medical or ethical reasons, for poor enrollment, or because of discontinuation of clinical development of an IMP or withdrawal of an IMP or comparator from the market for safety reasons.

Health Authorities and Independent Ethics Committees (IECs/IRBs) will be informed about the discontinuation of the study in accordance with applicable regulations.

5.7 Definition of End of Trial

The end of the study is defined as the last contact date with the last subject who participates in this study (i.e., last subject's last visit).

A CTP may not be considered closed as long as:

- Any subject is still receiving any IMP,
- Visits specified by the protocol are still taking place,
- Procedures or interventions according to the protocol are still being undertaken in any subject,
- The post-treatment Safety Follow-Up Period, defined in the clinical study protocol as being part of the study, has not yet been completed for any subject.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

6.1 Description of the Investigational Medicinal Product

The term "Investigational Medicinal Product" refers to an active substance or a placebo being tested or used as a reference therapy in a clinical study, including products that have a marketing authorization but are formulated, packaged, or administered differently from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form.

M2951 will be administered as film-coated tablets (white to off-white, round biconvex with band and no embossing) ready for oral administration and containing 25 mg of drug substance (chemical name 1-(4-{[6-Amino-5-(4-phenoxy-phenyl)-pyrimidin-4-ylamino]-methyl}-piperidin-1-yl)-propenone) formulated with excipients. The placebo will be administered as tablets ready for oral administration matching the active both in color and in size and shape.

Reference therapy: dose/model of administration/dosing schedule

Not applicable.

Specific rules for treatment modifications

Not applicable.

6.2 Dosage and Administration

CCI [redacted]

6.3 Assignment to Treatment Groups

Following informed consent and evaluation of inclusion/exclusion criteria, eligible subjects will be randomized in a 1:1:1:1 ratio to treatment with placebo or M2951 (doses 25 mg once daily, 75 mg once daily, or 50 mg twice daily), through a central randomization process by an IWRS, stratified according to race (Black versus non-Black), region (US and Western Europe, Japan, and RoW) and disease activity (SLEDAI-2K total score < 10 versus ≥ 10 at Screening) prior to dosing on Day 1. Subjects with SLEDAI-2K total score ≥ 10 at Screening will be considered to have HDA.

For the purposes of this study, Black race will be defined as per the US Census definition. Specifically, Black race includes individuals who self-identify as Black, African American, Negro, and/or have origins in any of the Black racial groups of Africa, including individuals of sub-Saharan African origin (e.g., Kenyan, Nigerian) and individuals of Afro-Caribbean origin (e.g., Haitian, Jamaican). Individuals of North African origin (e.g., Morocco, Egypt) are classified as non-Black, along with individuals from Sudan and Cape Verde due to their complex population history. Subjects declining to identify race will be placed in the non-Black stratum.

The study is fully controlled by the IWRS, which assigns treatment individual (unique) kit numbers for each subject. The kit number is linked via the Good Manufacturing Practice qualified system to the corresponding treatment as well as to the subject.

Subject identifiers will be comprised of three sets of numbers representing the study number, the site number, and the subject number, which is allocated sequentially starting with 0001.

6.4 Non Investigational Medicinal Products to be Used

Permitted medications (including rescue medications) are any medications required per the medical history and not specifically prohibited by the protocol during the study (i.e., from Screening to the end of the 52 week Treatment Period or LTE Period) (see Section 6.5). Any such medications used should be recorded in the eCRF.

Rescue medications are medicines identified in the CTP as those that may be administered to the subject when the efficacy of the IMP is not satisfactory, in case of adverse reactions, or to manage an emergency situation.

6.4.1 Background Systemic Lupus Erythematosus Therapies

Background SLE therapies include SoC medications prescribed as part of the subject's previous SLE treatment. Not all SoC therapy will be permitted to be continued during this study. The SoC therapy that is allowed to be continued during this study for SLE is presented in Section 6.5.1 and includes the use of one single immunosuppressant or immunomodulator, and the use of antimalarials, CSs, and NSAIDs. Although it is expected subjects will be on SoC medications, not all therapies are permitted (e.g., cyclophosphamide, thalidomide, and chlorambucil* [see Section 6.5]) (*not approved in Japan).

Table 7 Permitted Background Systemic Lupus Erythematosus Therapies

Permitted SoC Therapy		
Immunosuppressants / Immunomodulators (use of one is permitted)	Azathioprine	up to 2.5 mg/kg/day
	6-Mercaptopurine	up to 1.5 mg/kg/day
	Mycophenolate	either as MMF up to 3 g/day or MPS[a] up to 2160 mg/day
	Methotrexate	up to 25 mg/week
	Sulfasalazine	up to 3 g/day
	Leflunomide	up to 20 mg/day
Antimalarials	Hydroxycholoroquine	
	Quinacrine[a]	
	Chloroquine[a]	
Corticosteroids	(see Section 6.4.2 and Section 6.5.1)	
NSAIDs	(see Section 6.5.1)	

Note: Not all SoC medications are permitted. Prohibited SoC therapies include cyclophosphamide, thalidomide, and chlorambucil (see Section 6.5)

MMF = mycophenolate mofetil, MPS = mycophenolate sodium, NSAIDs = nonsteroidal anti-inflammatory drugs.

a: not approved in Japan.

All background therapy for SLE given prior to Screening must have been kept stable or discontinued according to the specifications in the exclusion criteria for a subject to be eligible for the study. These medications (i.e., single immunosuppressant/immunomodulator and/or antimalarials, if used) must remain stable during the Screening Period as well as the 52 week Treatment Period, with the exception of CS and NSAIDs which can be adjusted as long as doses are consistent with allowed levels as indicated in Section 6.4.2. Background therapy may only be changed for documented safety issues. Initiation of any new immunosuppressant or immunomodulator therapy would be considered a treatment failure during the DBPC Treatment Period and should result in withdrawal of the subject from the IMP and study (see Section 5.5).

SoC medications are part of the subject's previous SLE treatment and thus will not be provided by the Sponsor, including CS and NSAIDs. For Peru, Baseline treatments will be provided by the Sponsor as required per local regulation.

Additional treatments commonly given to subjects with SLE are permitted during the study (see Section 6.5.4.1).

Any medications (other than those excluded per exclusion criteria in Section 5.3.2 or prohibited as per Section 6.5.2) that are considered necessary for the subjects' welfare and will not interfere with the study medication may be given at the Investigator's discretion.

6.4.2 Corticosteroids

DBPC Period

Subjects may enter the Screening Period on CS up to 30 mg/day prednisone-equivalent (see Table 8), and must be no higher than 30 mg/day on Day 1. Corticosteroid doses above 30 mg/day prednisone-equivalent should be avoided if possible, but may occur between Day 1 and Week 4. If a corticosteroid dose of 30 mg/day prednisone-equivalent or less cannot be achieved at the end of Week 4, the subject will be withdrawn from the study and will be considered a treatment failure. After Week 4 of the Treatment Period, doses above 30 mg/day are prohibited. Furthermore, injectable corticosteroids (e.g., intramuscular, intravenous, subcutaneous, and intra-articular) are prohibited during the study with the exception of a single dose of intramuscular steroid, no more than 80 mg of prednisolone equivalent, permitted prior to the twelfth week of the DBPC Period.

Table 8 Prednisone Equivalence Calculation (Total Daily Dose)

Oral CS Medication	Equivalent (mg) to 1 mg of Prednisone
Betamethasone	0.15 mg
Cortisone	5 mg
Dexamethasone	0.15 mg
Hydrocortisone	4 mg
Prednisolone	1 mg
Meprednisone[a]	0.8 mg
Methylprednisolone	0.8 mg
Triamcinolone	0.8 mg

CS = Corticosteroids.
a: not approved in Japan.

The corticosteroid dose achieved by the end of Week 8 is defined as the Threshold Dose. This is the maximum dose allowed at any time in the study other than for treatment of flares as outlined below (see Section 6.4.2.2). After treatment for a flare the corticosteroid dose must be reduced within seven days to less than or equal to the Threshold Dose. If this is not possible then the subject is considered a treatment failure and will be withdrawn from the study.

Investigators are **strongly encouraged to decrease the CS dose** of the subject as much as tolerated and as soon as possible until after the Week 16 study visit. Between Weeks 17 and 24, no changes to the CS dose may be made. After Week 24 assessments are completed, dose may be decreased, as tolerated, through the Week 40 study visit. Between Weeks 41 and 52, no changes to the CS dose may be made. The rules for CS dose changes during Screening and the DBPC Treatment Period are outlined in Table 9. There is no minimum CS dose required during the study.

Guidance regarding the use of oral CS during the study is provided below. Doses given are for a total daily dose of prednisone or prednisolone; CS other than prednisone/prednisolone may be used instead orally at the equivalent doses (Table 8).

LTE Period

During the LTE Period, CS doses up to 30 mg/day prednisone-equivalent (see Table 8) are permitted. Injectable corticosteroids (e.g., intramuscular, intravenous, subcutaneous, and intra-articular) remain prohibited during the LTE Period, with the exception of a single dose of intramuscular steroid, no more than 80 mg of prednisolone equivalent, permitted prior to the twelfth week of the LTE Period.

Screening Period, DBPC Period, and LTE Period

There are no restrictions on non-systemic corticosteroid dosage (see Section 6.5.1.2).

The Investigator will record all concomitant medications taken by the subject during the study, from the date of signature of informed consent, in the appropriate section of the eCRF, after recording them in the source documents.

Any additional concomitant therapy that becomes necessary during the study and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration and indication of each drug.

Table 9 Oral Corticosteroid Dose (in prednisone-equivalent) and Taper Guidance

Study Visit	Study Period	Maximum Allowable Dose[a]	Target Dose	Action for CS dosing
Screening	Screening Period	30 mg/day	≤ 30 mg/day	No change in CS dose[b]
Day 1 Week 1		30 mg/day	≤ 30 mg/day	After Day 1, may initiate, increase, decrease, or have no change to dose. Dose must be tapered to ≤ Day 1 dose by Week 4
	Week 1 through 3	30 mg/day[f]	≤ 30 mg/day	
Week 4 Visit	Week 4	Day 1 dose[c]	**≤Dose at Day 1 Visit**	Begin taper to ≤ 10 mg/day by Week 8, as tolerated
	Weeks 5 through 7	Week 4 Visit dose	≤ 10 mg/day	Continue to taper to ≤ 10 mg/day by Week 8, as tolerated
Week 8 Visit	Week 8	Week 4 Visit dose	**≤ 10 mg/day**	Begin taper to ≤ 7.5 mg/day by Week 12, as tolerated
	Weeks 9 through 11	Week 8 Visit dose	≤ 7.5 mg/day	Continue to taper to ≤ 7.5 mg/day by Week 12, as tolerated
Week 12 Visit	Week 12	Week 8 Visit dose	**≤ 7.5 mg/day**	Taper as tolerated
	Weeks 13 through 15	Week 8 Visit dose	≤ 7.5 mg/day	Taper as tolerated
Week 16 Visit	Week 16	Week 8 Visit dose	**≤ 7.5 mg/day**	Taper as tolerated
	Weeks 17 through 23	Week 8 Visit dose	≤ 7.5 mg/day	No change in CS dose[d]
Week 24 Visit	Week 24	Week 8 Visit dose	**≤ 7.5 mg/day**	No change in CS dose[d]
	Weeks 25 through 39	Week 8 Visit dose	≤ 5 mg/day	Taper to ≤ 5 mg/day by Week 40, as tolerated
Week 40 Visit	Week 40	Week 8 Visit dose	**≤ 5 mg/day**	Taper as tolerated
	Weeks 41 through 52	Week 8 Visit dose	≤ 5 mg/day	No change in CS dose[e]

CS = Corticosteroids.

a Violation of requirements during the Screening Period results in screen-failure; treatment period violation may result in treatment failure and withdrawal from study.

b Any dose change between Screening and Day 1 results in screen failure.

c Subjects with CS dose < 7.5 mg/day at Day 1 may have up to 7.5 mg/day at Week 4.

d Any dose increase during Weeks 17 to 24 results in treatment failure and withdrawal from study, dose may be tapered after Week 24 assessments have been completed.

e Any dose increase during Weeks 41 to 52 results in treatment failure and withdrawal from study.

f Although it is preferred that subjects do not receive a CS dose > 30 mg/day, subjects who receive > 30 mg/day between Day 1 and the Week 4 visit will not be withdrawn from the study if they are able to achieve a dose no higher than (≤) the Day 1 CS dose and ≤ 30 mg/day (whichever is lower) by the Week 4 visit.

Overview / Key Points on Corticosteroid Dose During Study

- CS dose must remain stable during the Screening Period.
- From Day 1 to the Week 4 Visit, CS dose may be initiated, increased, decreased, or remain unchanged.
- Corticosteroid dose adjustment goals and restrictions during the DBPC Treatment Period:
    - By the Week 4 Visit, the dose must be ≤ dose at Day 1. Subjects with CS dose < 7.5 mg/day at Day 1 may have up to 7.5 mg/day at Week 4.
    - By the Week 8 Visit, dose should be tapered to ≤ 10 mg/day, as tolerated
    - By the Week 12 Visit, dose should be tapered to ≤ 7.5 mg/day, as tolerated
    - No changes to CS dose should be made from Week 17 through completion of study assessments for Week 24.
    - Between study visits at Week 25 through Week 40, dose should be tapered to ≤ 5 mg/day, as tolerated.
    - No changes to CS dose are allowed from Week 41 through completion of study assessments for Week 52/EOT.
- During the LTE Period, CS doses may be initiated or increased up to 30 mg/day prednisone-equivalent, decreased, or remain the same. Investigators are strongly encouraged to decrease the CS dose of the subject as much as tolerated.

These rules are detailed in the next section (see Section 6.4.2.1).

6.4.2.1 Corticosteroid Use as Standard of Care

DBPC Period:

Screening Visit to Day 1 (No Change in CS Dose)

From the Screening Visit to Day 1, the corticosteroid dose should be maintained at the Screening Visit dose. If the corticosteroid dose is changed, the subject will be considered a screen failure. The total daily prednisone-equivalent dosage must not be higher than 30 mg/day during the Screening Period.

Day 1 to Week 4 Visit (CS Dose Adjustable)

Corticosteroids may remain unchanged, be initiated, be increased, or be decreased after Day 1 but must be no higher than (<) the Day 1 CS dose at the Week 4 Visit.

Week 4 Visit and Week 4 Study Period

At the Week 4 Visit, the CS dose is required to be no higher than (≤) the Day 1 CS dose and total daily prednisone-equivalent dosage must be ≤ 30 mg/day (whichever is lower). However, subjects taking < 7.5 mg/day at the Screening Visit can have a dose of up to 7.5 mg/day at Week 4.

Weeks 5 to 8 (CS Dose Reduction)

By the Week 8 Visit, the CS dose should be tapered to as low a dose as tolerated, targeting a prednisone-equivalent dosage ≤ 10 mg/day and must be ≤ the Week 4 dose. This is the new upper limit for subsequent doses, and is considered the Threshold Dose.

Weeks 9 to 16 (CS Dose Reduction/Rescue)

After Week 8, the CS dose must always be ≤ Week 8 dose (Threshold Dose).

Decreases in the CS dose from the Week 8 dose level should be performed to reach the target of prednisone-equivalent ≤ 7.5 mg/day, as tolerated.

Treatment for flare as outlined below will be allowed once during this period.

Weeks 17 to 24 (No Change in CS Dose)

From Week 17 to 24, the 8 weeks prior to the 24 week assessment of disease activity, the corticosteroid dose must be maintained at the Week 16 dose, with no changes. If a corticosteroid dose increase is required to treat a flare, the subject will be considered a treatment failure and will be withdrawn from study.

Weeks 25 to 40 (CS Dose Reduction/Rescue)

After Week 24, the CS dose must always be ≤ Week 8 dose (Threshold Dose).

Decreases in the CS dose from the Week 24 dose level should be performed to reach the target of prednisone-equivalent ≤ 5 mg/day, as tolerated.

Treatment for flare as outlined below will be allowed once during this period.

Weeks 41-52 (No Change in CS Dose)

The CS dose must be maintained at the Week 40 dose, with no changes. No increases are allowed. If a corticosteroid dose increase is required to treat a flare, the subject will be considered a treatment failure and will be withdrawn from study.

LTE Period:

Corticosteroid doses may be initiated or increased up to 30 mg/day prednisone-equivalent, decreased, or remain the same. Investigators are strongly encouraged to decrease the CS dose of the subject as much as tolerated.

6.4.2.2 Corticosteroid Use as Rescue Medication in Treatment of Flare

Corticosteroid Dose Increases and Treatment of Flares: DBPC Treatment Period

Subjects may increase the CS dose up to 30 mg/day only two times as rescue for worsening of SLE activity or for other reasons during the DBPC Treatment Period of the study. Each rescue is allowed only once during each of the following two time periods: 1) once between Week 8 to Week 16; and 2) once between Week 24 to Week 40. The CS dose can be increased up to prednisone-equivalent 30 mg/day, but must be returned to ≤ Week 8 dose (Threshold Dose) within seven days. A CS dose increase must not to be initiated within one week of a planned study visit. A single dose of intramuscular steroid, no more than 80 mg of prednisolone equivalent, is permitted prior to the twelfth week of the DBPC Period. CS medications are part of the subject's previous SLE treatment and thus will not be provided by the Sponsor. Doses for treatment of flares beyond these allowable rescue doses will result in the subject being considered a treatment failure, and withdrawal from the study (see Section 5.5.1).

Corticosteroid Dose Increases and Treatment of Flares: LTE Treatment Period

During the LTE Period, CS doses up to 30 mg/day are permitted. In addition, a single dose of intramuscular steroid, no more than 80 mg of prednisolone equivalent, is permitted prior to the twelfth week of the LTE Period. CS medications are part of the subject's previous SLE treatment and thus will not be provided by the Sponsor.

If medications which are not permitted (as per Section 6.5.2) are required to treat the flare, and/or the flare has been ongoing between 2 visits at least 12 weeks apart without improvement, the subject must be discussed with the Medical Monitor to determine if the subject should be considered a treatment failure, and must be withdrawn from the study (see Section 5.5.1).

6.5 Concomitant Medications and Therapies

All concomitant medications taken by the subject during the study, from the date of signature of informed consent are to be recorded in the appropriate section of the eCRF, noting the name, dose, duration (i.e., start and end dates), dosing regimen (e.g., once daily, twice daily, etc.), and indication of each drug. Nondrug interventions and any changes to a concomitant medication or other intervention should also be recorded in the eCRF.

6.5.1 Permitted Medicines

Any medications that are considered necessary to protect subject welfare and will not interfere with the study medication may be given at the Investigator's discretion.

Rescue medications may be administered to address ineffective treatment, anticipated adverse reactions or anticipated emergency situations.

Additional treatments commonly given to subjects with SLE are permitted during the study as described in Section 6.5.1.4.

6.5.1.1 Corticosteroids

Corticosteroid dose above 30 mg/day prednisone-equivalent is excluded (except between Day 1 and Week 4). There is no minimum CS dose required during the study. Rules for CS dose changes are detailed in Section 6.4.2.1.

6.5.1.2 Non-Systemic Corticosteroids

Non-systemic corticosteroid medications in this study are defined as otic, topical, intranasal, inhaled, and ophthalmic. There are no restrictions on non-systemic corticosteroid dosing. However, all injected corticosteroids, including local injections (e.g., intra-articular injections) are not permitted with the exception of a single dose of intramuscular steroid, no more than 80 mg of prednisolone equivalent prior to the twelfth week of the DBPC Treatment Period and once during the LTE Period (prior to the twelfth week).

6.5.1.3 Vaccinations

Subjects will be required to have had pneumococcal vaccination and seasonal flu vaccine, as per local guidance, to be eligible to participate in the study as per Section 5.3.1. In addition, it is strongly recommended that Investigators' review the subject's vaccination status, and ensure they are up to date with vaccines as per local guidelines. Live vaccinations will not be permitted as per Section 5.3.1 and Section 5.3.2.

6.5.1.4 Additional Permitted Medications

Additional background therapies commonly given to subjects with SLE are permitted during the study as follows:

- Vitamin D (≥ 400 IU/day) and calcium supplementation (≥ 800 mg/day) is encouraged per local SoC guidelines. Subjects not already taking these medications at Screening should, according to the Investigator's judgement, initiate treatment as soon as possible after Screening. These medications will not be supplied by the Sponsor.
- Subjects taking an NSAID (including cyclooxygenase 2 inhibitors) for SLE symptoms at randomization can continue to do so throughout the study. Subjects may have the dose adjusted during the study, with any changes in dosage captured in the eCRF (see Section 6.5). The NSAIDs should not be used above the maximum allowable doses and site should perform regular AE monitoring of these concomitant medications. NSAIDs may not be initiated during the DBPC Treatment Period.
- Low-dose aspirin (≤ 350 mg/day) for cardiovascular prophylaxis. Low-dose aspirin for other indications may be permitted after discussion with medical monitor.
- Paracetamol (acetaminophen) up to 3 g/day may be initiated or continued for pain control of SLE symptoms during the study. This should be titrated off as tolerated.
- Opioids are permitted for stable use for SLE if initiated by Day 1. Initiation of opioids and/or dosing of opioids as needed after Day 1 for SLE is not permitted during the DBPC Treatment Period. These may be titrated off as tolerated during the study.

- Analgesics, including opiates, may be used at stable doses or as needed for temporary relief of symptoms not due to SLE, but then are strongly recommended to be unchanged 24 hours prior to each study visit.
- It is recommended that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers if used at Screening be maintained at a stable dose during the study as subjects with proteinuria up to 4 g/day will be permitted into the study and the proteinuria will be followed, unless dose change or initiation is required for safety reasons.
- Any medications (other than those excluded by the CTP) that are considered necessary for the subjects' welfare and will not interfere with the study medication may be given at the Investigator's discretion.
- Rescue medications may be administered to address ineffective treatment, anticipated adverse reactions or anticipated emergency situations (see Section 6.4.2.2 for CS treatment of flare).
- During the LTE Period:
    - If a subject is on an immunosuppressant/immunomodulator when they rollover into the LTE Period, the dosage may be decreased or remain the same. After Week 24 of the LTE Period, the dosage regimen for an immunosuppressant/ immunomodulator may be increased up to the limits permitted in Table 7 or initiated as long as only 1 immunosuppressant is used
    - Antimalarials may be initiated, increased, decreased, or remain the same
    - NSAIDs for SLE may be initiated, increased, decreased, or remain the same
    - Opioids may be initiated, increased, or decreased
    - NSAIDs and paracetamol may also be used for symptoms not due to SLE. It is strongly recommended that analgesics (including opioids), paracetamol, and NSAIDs are unchanged 24 hours prior to study visits when SLE assessments are completed (see SoA).
- Medical marijuana* use (as permitted by local and/or national law) is not excluded; however, it will require a case-by-case review and approval by the Medical Monitor and/or Sponsor. Site must provide information to confirm:

    1. The marijuana is medically prescribed,
    2. The condition for which it is prescribed is not exclusionary,
    3. The medical marijuana use is not abuse (i.e., does not interfere with subject compliance or safety in the opinion of the Investigator), AND
    4. The dose is stable as to not interfere with the disease activity assessment.

*Not approved in Japan.

6.5.2 Prohibited Medicines

The following treatments and therapies are not permitted during this study:

- CCI [redacted]
- Use of cyclophosphamide, thalidomide, or chlorambucil* (alkylating agents), tacrolimus, cyclosporine, or other immunosuppressant or immunomodulator therapies not listed in Section 5.3.2 (*not approved in Japan).
- Use of more than one immunosuppressant therapy at any time (see Section 5.3.2 and 6.4.1).
- Biologic therapies for SLE are strictly prohibited. Biologic therapies for other indications must be discussed with the Medical Monitor on a case-by-case basis, with the exception of insulin and antibodies used for bone density (e.g., denosumab), which are permitted.
- JAK inhibitors (e.g., tofacitinib, baricitinib).
- Anticoagulants and anti-platelet therapy other than low dose of daily aspirin for cardioprotection.
- Fish oil.
- Ig therapy or plasmapheresis.
- Bone marrow transplant.
- Any solid organ transplant.
- Vaccines: Live and live-attenuated vaccines are prohibited within one month before Screening and during the Study Period.
- CCI [redacted]
- Use of prohibited medications, including the use of oral CS doses that are not allowed or use of injectable CS (including intraarticular CS) as mentioned in Section 6.5.
- New therapies for SLE should not be initiated during Screening or DBPC Treatment Period of the study. Initiation of any new immunosuppressant or immunomodulatory therapy would be considered a treatment failure and result in withdrawal of the subject from the IMP during the DBPC Treatment Period (see Section 5.5). For the LTE Period, see Section 6.4.1.
- Therapies for pulmonary hypertension, see Exclusion criterion 1.

CCI

[redacted]

6.5.3 Other Interventions

Other Trial Considerations

Women of childbearing potential must be willing to follow very specific restrictions for birth control as indicated in Section 5.3.1. While there is no requirement for contraception in male participants based on the nonclinical data, it is recommended that conception be avoided during exposure to M2951 as there is limited experience in humans.

Other Interventions/Therapies

Use of potentially excluded procedures such as acupuncture or joint replacement therapy is to be discussed with the Sponsor or designee on a case-by-case basis. Use of acupuncture is allowed to continue if it is started before the Screening Visit and may be initiated/and or modified during the LTE Period. Major elective surgeries such as abdominal, thoracic or joint replacement surgeries should not be planned to occur in the Study Period. Unplanned joint replacement surgery should be discussed at the earliest opportunity prior to the surgery with the Medical Monitor regarding continuation of the subject in the study.

6.5.4 Special Precautions

In this study, the inclusion and exclusion criteria, dosing regimens, and other precautionary measures specified within this CTP must be respected in addition to the recommendations provided in the Investigator's Brochure.

CCI

[redacted]

6.5.4.1 For M2951

The IMP should be temporarily withheld or permanently withdrawn if laboratory abnormalities occur or recur as relevant per Section 5.5.2.

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

No specific measures are proposed at this stage. Standard medical care will be provided at the study site for all AEs occurring during the study.

6.6 Packaging and Labeling of the Investigational Medicinal Product

M2951 and matching placebo is supplied by the Sponsor. A description of pharmaceutical properties and composition of the formulation of M2951 is provided in the Investigator Brochure. All IMPs will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines. Additional details of packaging and labeling of the IMP will be defined in a separate Manual of Procedures.

6.7 Preparation, Handling, and Storage of the Investigational Medicinal Product

IMP must be carefully stored at the study site in a closed room or cabinet with restricted access and separately from other drugs.

Storage conditions for M2951 will be specified in a separate Manual of Procedures. Any deviations from the recommended storage conditions should be immediately reported to the Sponsor, and the medication should not be used until authorization has been received from the Sponsor.

M2951 must not be used for any purpose other than the study. The administration of M2951 to subjects who have not been enrolled into the study is not covered by the study insurance.

Disposal of IMP should be according to local regulations and institutional guidelines.

6.8 Investigational Medicinal Product Accountability

The Investigator is responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of records. For Japan only - The head of the study site is responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of records. The head of the study site can delegate the control of and accountability for the study drug to an investigational product storage manager.

- Upon receipt of IMP, the Investigator (or designee) will check for accurate delivery and acknowledge receipt in the IWRS and by signing or initialing and dating the appropriate documentation and returning it to the location specified. The original or a copy will be archived for the Investigator Site File. For Japan only - Upon receipt of IMP, the head of the study site (or the investigational product storage manager) will check for accurate delivery and acknowledge receipt in the IWRS and by signing or initialing and dating the appropriate documentation and returning it to the location specified. The original or a copy will be archived for the Investigator Site File
- The dispensing of the study IMP will be carefully recorded on the appropriate drug accountability forms and an accurate accounting will be available for verification by the clinical research associate (CRA) at each Monitoring Visit.
- Study IMP accountability records will include the following:

- Confirmation of IMP delivery, in good condition and in the defined temperature range to the study site.
- The inventory of IMP provided for the clinical study by the Sponsor and prepared at the site.
- The use of each kit by each subject.
- The disposition (including return, if applicable) of any unused IMP.
- Dates, quantities, batch numbers, kit numbers, expiry dates, as well as individual subjects' study numbers.

The Investigator site should maintain records, which adequately document that subjects were provided the IMP specified in this CTP, and all IMPs provided by the Sponsor were fully reconciled.

The CRA will periodically collect the IMP accountability forms and will check them. Expired IMP can be destroyed at the study site according to local regulations and institutional guidelines while the study is ongoing if no shelf life prolongation is possible.

Unused IMP must not be discarded or used for any purpose other than the present study. Any study treatment that has been dispensed to a subject must not be re-dispensed to a different subject.

At the conclusion or termination of this study, study site personnel and the CRA will conduct a final product supply inventory on the investigational drug accountability forms and all used and unused IMP kits will be destroyed at the study site according to local regulations and institutional guidelines. The study site personnel will be supplied with a copy for filing of the investigational drug accountability forms. This documentation must contain a record of clinical supplies used, unused, and destroyed and shall include information on:

- All administered units
- All unused units
- All destroyed units (used and unused) during the study
- All destroyed units (used and unused) at the end of the study
- Date of destruction(s)
- Name and signature of the Investigator/pharmacist. For Japan only - Name and signature of the head of the study site or the investigational product storage manager.

It must be ensured at each study site that the study treatment is not used:

- After the expiry date
- After the retest date unless the study treatment is reanalyzed and its retest date is extended.

6.9 Assessment of Investigational Medicinal Product Compliance

The IMP will be administered at the site on study visit days as indicated in the SOA (Table 1). All other dosing will be done by the subject or subject's caregiver at home throughout the rest of the study. Compliance may be assessed via the patient diary for dosing and food intake around dosing.

Subjects will be instructed to bring all IMP, including the used packaging, to each study visit to allow for the assessment of compliance with study treatment. Prior to discharge from each scheduled visit as determined by IWRS, subjects will be given sufficient IMP for at-home dosing until the next scheduled visit during the Treatment Period.

Insufficient compliance with the protocol-specified dosing regimen is defined as receiving < 80% of the required number of scheduled doses of study medication. If a subject has insufficient compliance, the Investigator or designee is to counsel the subject and ensure steps are taken to improve compliance.

6.10 Blinding

Treatment with M2951 and placebo will be double-blinded. Subjects, Investigators, study staff and the study teams (Sponsor and PPD) will be blinded to treatment. All breaks of the study blind must be adequately documented.

Packaging and labeling will be prepared to protect the blinded nature of the study. IMP (M2951 or placebo) will not be distinguishable from each other and will be covered by suitable labels to prevent subjects and study personnel from noticing any differences in the tablets of M2951 versus placebo. Blinded treatment kit numbers will be obtained through the IWRS as described in Section 6.3.

After Day 1, results of analyses that could reveal the PD effects of M2951 in an individual subject will be blinded to the study site, the Sponsor, and the CRO. These analyses will include: total Ig (IgA, IgM, and IgG), IgG subclasses, C3, C4, anti-dsDNA, ANA, other autoantibodies (anticardiolipin, anti-Smith antibody [anti-Sm]; an antibody to ribonucleoproteins; and antinuclear antibodies associated with autoimmune diseases including Sjögren syndrome and SLE [anti-Ro, anti-La]), and cell counts by flow cytometry (total B cells and B cell subsets). If the Investigator considers it necessary to have any of the above results for acute medical management of the subject after Day 1, then this should be discussed with the Medical Monitor. It should be noted that in the clinical utility of monitoring anti-dsDNA levels may be diminished due to an anticipated drop in levels as a consequence of M2951's PD effects. Lymphocyte counts as assessed by routine complete blood counts will not be blinded, as these results are not anticipated to reveal PD effects, since B lymphocytes represent a small proportion of total lymphocytes (5% - 20%).

An IA for futility may be triggered when 100% of the planned enrollment required for the primary analysis reaches 24 weeks of treatment, or discontinues treatment prematurely prior to Week 24. The IDMC will be fully unblinded to treatment and will make a recommendation, as described in the IDMC charter. A limited set of endpoints will be analyzed for the IA, including Week 24 SRI-4 response for the whole study population and Week 24 SRI-6 response for the HDA subgroup.

If the planned enrollment required for the primary analysis is slower than expected, consideration will be given to conducting the interim futility analysis at an earlier time point, when the first 50% of subjects enrolled of the planned enrollment reach 24 weeks of treatment, or discontinue treatment prematurely prior to Week 24. The unblinding procedures specified above will be followed, regardless of the timing of the interim futility analysis.

Only when the trigger event for the primary analysis (Section 5.1) is reached, the protocol violations are determined, and the database is locked, will the drug codes be broken and made available for the primary analysis.

If the Japan cohort enrollment is slow and cannot be fully included in the primary analysis cohort, a consistency analysis (occurring after the primary analysis) will be scheduled for the purpose of analyzing the entire Japan cohort. Only when the trigger event for the consistency analysis (Section 5.1) is reached, the protocol violations are determined, and the database is locked, will the drug codes be broken for the Japanese subjects not included in the primary analysis, and made available for the treatment effect consistency analysis with respect to non-Japan and Japan regions.

6.11 Emergency Unblinding

The Investigator will have the ability to break the blind with regard to IMP for any subject at any time through the IWRS. However, the Investigator should make every effort to contact the responsible Medical Monitor or their designee to discuss the subject's emergency situation and the need to unblind prior to unblinding any subject and must contact the Sponsor or designee within 1 working day after the event occurs without revealing to the Sponsor personnel the result of the code break. The Investigator will be able to access the subject's treatment assignment 24 hours a day through the IWRS using a unique access code and user number (different from those used to assign subjects to treatment through the IWRS). Should the IWRS be unavailable for any reason, the Investigator will be able to break the blind via a telephone call to the IWRS help desk, which is available 24 hours a day. The help desk can access the database manually to perform the unblinding via telephone in the event that the IWRS is not operational. The Investigator must record the date of unblinding and the reason in the eCRF. Contact information for breaking the blind in an emergency is given on the subject emergency card provided to each subject (see Section 9.4).

Under certain circumstances, the IDMC or Drug Safety may be required to unblind the treatment assignment for an individual subject following a SAE or other serious event; (e.g., if an expedited

regulatory report is required). See Section 7.4.1.4 for further details on expedited reporting and SAEs.

6.11.1 Unblinding for Regulatory Authorities

In cases where unblinding is required for the purposes of reporting expedited safety events to country-specific regulatory agencies or IECs, the unblinding will be performed by an authorized person(s). A blinded version of any documents to be submitted to the authorities will be shared as appropriate with study staff and site personnel. Only the authorized person(s) within the CRO and regulatory affairs will have access to the unblinded version of any documents. The procedures for requesting and obtaining unblinded information and for maintaining the integrity of the data and clinical study are outlined in the pharmacovigilance plan for this study.

6.12 Treatment of Overdose

An overdose is defined as any dose greater than the highest total daily dose included in a CTP or planned for an individual subject enrolled in the study. CCI [redacted]. Any overdose must be recorded in the study medication section of the eCRF.

For monitoring purposes, any case of overdose – whether or not associated with an AE (serious or nonserious) – must be reported to the Sponsor's Global Drug Safety department or designee in an expedited manner using the appropriate reporting form (see Section 7.4).

The effects of an overdose of M2951 are unknown, and there is no known specific treatment in case of overdose. In the event of overdose, subjects should be considered for hospitalization for observation if clinically indicated, and the Investigator or treating physician should use appropriate clinical judgment for the management of any clinical or investigational findings.

6.13 Medical Care of Subjects after End of Trial

After a subject has completed the study or has withdrawn early, the subject is free to access further treatment as deemed appropriate by the Treating Investigator. The Sponsor will not provide any additional care to subjects after they leave the study because such care should not differ from what is normally SoC for subjects with SLE.

7 Trial Procedures and Assessments

Prior to performing any study assessments not part of the subject's routine medical care, the Investigator will ensure that the subject has provided written informed consent according to the procedure described in Section 9.2.

Upon subject's agreement, the subject's primary health care provider can be informed about subject's enrollment in the study.

Throughout the study, subjects will undergo the assessments detailed in Table 1 and Table 2, including collection of patient-reported HRQoL data and blood sampling.

HRQoL and subject self-assessment questionnaires must be completed first at visits where these assessments are collected.

Unscheduled visits may occur at any time during the study in case of suspected flares or AEs (assessments to be performed according to the Investigator's judgement).

7.1 Schedule of Assessments

Prior to performing any trial assessments that are not part of routine medical care for the subject, the Investigator will obtain written informed consent as described in Section 9.2.

7.1.1 Screening Visit

The subjects' eligibility will be assessed at a Screening Visit that will occur up to four weeks prior to the Randomization Visit (Day 1). See Table 1 for a list of assessments done at Screening to determine the eligibility of the subject to participate in the study.

Subjects should undergo the Day 1 Visit as soon as possible after eligibility for the study has been confirmed.

Subjects who do not meet all inclusion criteria or meet an exclusion criteria within the first Screening Period and are considered screen failures may undergo rescreening once after approval by the Medical Monitor. The second Screening Period is a new 28-day Screening Period, and the subject will receive a new identification number. Testing at rescreening is required to be redone as noted below:

Rescreening:

Subjects who are considered screen failures after a first Screening Period may undergo rescreening once, after approval by the Medical Monitor. If a subject is rescreened, all Screening tests will need to be repeated except as follows:

a. Documented CXR and TB testing if occurred within 3 months prior to the initial rescreening visit.

b. Hepatitis and Human Immunodeficiency Virus (HIV) testing if occurred within 1 month prior to the initial rescreening visit.

Retesting:

During the initial Screening Period or single rescreening period, testing may be repeated once for subjects if test results would preclude enrollment in the study and are thought to represent a laboratory error, or a reversible, clinically insignificant intermittent condition, or are inconsistent with the subject's historical values, after discussion with the Medical Monitor. When a laboratory test needs to be repeated during the Screening Period, or to accommodate other unanticipated

events, the Screening Period may be extended to 8 weeks after discussion with the Medical Monitor.

Information collected during the Screening Visit will be entered in the appropriate eCRF.

Subjects who meet the Screening criteria and are to be randomized will be given instructions as to the date and time they are due back at the site for Day 1 (randomization/first day of dosing).

7.1.2 DBPC Treatment Period

The treatment should start the day of randomization (Day 1). While on IMP, subjects will be asked to visit the study site and undergo assessments according to the SOA in Table 1. The Day 1 Visit will be considered the Baseline for disease activity [e.g., BILAG 2004 Disease Activity Index, SLEDAI-2K, PGA, and CLASI].

A subject diary should be provided to the subjects to capture information such as daily dosing, concomitant medications, and AEs. Site personnel should review the subject diaries with the subjects at each study visit. Site personnel will dispense IMP to the subjects, per the IWRS, during this Period.

- A scheduling window of up to three days before or after the scheduled visit day (±3 days) will be permitted as indicated in the SOA.
- Subjects who discontinue early must return for the EOT/Early Withdrawal Visit and Safety Follow-Up Visit.

7.1.2.1 DBPC End of Treatment/Early Withdrawal Visit

The EOT Visit is scheduled on the last day of administration of study treatment. The EOT Visit will include a full assessment for safety (e.g., physical examination, vital signs, weight, hematology and chemistry), and other assessments as described in Table 1. Subjects who complete the End of Treatment Visit will be given the opportunity to participate in the LTE Period.

Subjects who discontinue early from the study prior to completing 52 weeks of treatment are to complete the EOT Visit within five days after discontinuation, including assessments as detailed above and in Table 1. Subjects will also complete the Safety Follow-Up/End of Study Visit, as required (see Section 7.1.3).

7.1.3 LTE Period

Subjects who completed the 52-week DBPC Treatment period will be offered participation in the open-label, LTE Period of the study as described in Section 5.1. The Investigator will obtain written informed consent for the LTE.

At all applicable visits, patient-reported outcome questionnaires must be performed prior to any other assessments. Scheduled assessments will be performed according to Table 2.

All scheduled visits during the LTE Period may take place within the visit windows specified in Table 2. Subjects who discontinue early must return for the LTE End of Treatment/Early Withdrawal Visit and Safety Follow-Up Visit.

For WOCBP, additional highly sensitive urine pregnancy testing will be performed at home per SOA, Table 3. Urine pregnancy test kits will be provided to the subject at Week 16 (for testing at Week 20), Week 24 (for testing at Week 28, 32, and 36), Week 40 (for testing at Week 44 and 48), Week 52 (for testing at Week 56, 60, 64, 68, and 72), and Week 76 (for testing at Week 80, 84, 88, 92, 96, and 100). At and/or prior to the Week 16 visit, the PI and/or delegated site staff will train the relevant subjects to self-administer the urine pregnancy tests and will call the subject to confirm completion of urine pregnancy testing and discuss results per Table 3.

7.1.3.1 LTE End of Treatment Visit

The LTE End of Treatment Visit will be performed at Week 104 or within 5 days of early discontinuation of treatment with the IMP. Subjects will undergo assessments as described in Table 2. In case of premature discontinuation, the PRO assessments must be completed at the LTE End of Treatment Visit. Subjects will enter the Safety Follow-Up Period after completing the LTE End of Treatment Visit.

7.1.4 Safety Follow-Up/End of Study Visit

The Safety Follow-Up/End of Study Visit is scheduled four weeks (+ 5 days) after the last administration of study treatment. For subjects who do not participate in the LTE Period, the Safety Follow-Up Visit is scheduled four weeks (+ 5 days) after the last administration of study treatment in the DBPC Period. For subjects who participate in the LTE Period, the Safety Follow-Up Visit is delayed until four weeks (+ 5 days) after the last administration of study treatment in the LTE Period. Subjects who are approved to rollover into LTE Period after they entered, or completed, the DBPC Safety Follow-Up Period, may have two Safety Follow-Up Visits. Additional details of the Safety Follow-Up/ End of Study Visit are provided in the SOA.

Subjects who discontinue the IMP or withdraw from the trial early will attend the Safety Follow-Up Visit according to procedures described in Sections 5.5.1 or 5.5.2, respectively.

All SAEs ongoing at the Safety Follow-Up/End of Study Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as “lost to follow-up”.

7.2 Demographic and Other Baseline Characteristics

Demographic data such as date of birth, self-reported race and ethnic origin, gender, weight, height, and body mass index will be assessed at Screening. Information about previous and concomitant medications will also be recorded.

7.2.1 Medical History

In order to determine the subject's eligibility to the study, a complete medical history of each subject will be collected and documented during Screening, which will include, but may not be limited to the following:

- Past and concomitant disease.
- Physical examination including neurological assessment and serology.
- All medications (including herbal medications) taken and procedures carried out within 28 days prior to Screening. Any SLE-related medications and procedures from within one year prior to Screening should be documented. Additional medications and procedures (with particular attention to SLE-related medications and procedures), should be included as deemed relevant by the Investigator.

For the study entry, all of the subjects must fulfill all inclusion criteria described in Section 5.3.1, and none of the subjects should have any exclusion criterion from the list described in Section 5.3.2.

7.2.2 Diagnosis of Systemic Lupus Erythematosus

Date of documented diagnosis of SLE, and presence/absence of the SLICC criteria for diagnosis of SLE (see Appendix II) and/or the presence/absence of the 11 ACR criteria for classification of SLE (see Appendix III), serially or simultaneously, during any interval of observation, will be collected.

Diagnosis of SLE will be defined as having presence of (serially or simultaneously, during any interval of observation):

> Presence of at least four criteria, including at least one clinical criterion and at least one immunological criterion; or biopsy proven lupus nephritis with positive ANA and/or positive anti-dsDNA; as specified in the SLICC Classification Criteria for SLE (see Appendix II),
>
> Or,
>
> Presence of at least four of the 11 ACR classification criteria for SLE.

The diagnosis must have been made and documented at least six months prior to Screening. If a potential subject has not been formally diagnosed with SLE, but has 6 months of documented and sufficient diagnostic criteria (ACR or SLICC, as above), they may be included in the study. The Investigator must review the medical history, confirm the retrospective diagnosis of SLE, and the Medical Monitor must provide documented approval.

Additionally, subjects will be required to have SLEDAI-2K total score ≥ 6 (including clinical SLEDAI ≥ 4) at Screening. Subjects with SLEDAI-2K total score ≥ 10 at Screening will be considered to have HDA.

7.2.3 Other Baseline Assessments

The term 'Baseline' in this protocol is defined as Day 1, predose. Baseline measurements, such as vital signs, a complete physical examination, clinical laboratory parameters, 12-lead ECG, HRQoL assessments (SLEDAI Flare Index [SFI], SLEDAI-2K, PGA, C-SSRS, BILAG 2004, CLASI, SLICC/ACR damage index), and PD parameters will be assessed as indicated in the SOA (Table 1). The HRQoL assessments on Day 1 are to be completed after inclusion/exclusion criteria are reviewed, verified, and the subject is randomized.

7.3 Efficacy Assessments

Efficacy will be evaluated using the instruments and outcomes described below and at the visits specified in Table 1 and Table 2 in accordance with recommendations for outcome measures in SLE studies which suggest assessment of current disease activity, permanent damage, and HRQoL, ideally including an instrument sensitive to fatigue.

All data collection and all query handling will be done via an eCRF system. An electronic device (electronic PRO [ePRO] system) may be used to collect some of the HRQoL assessments.

7.3.1 British Isles Lupus Assessment Group 2004

The BILAG 2004 Disease Activity Index evaluates SLE activity in a number of organ systems, based on the principle of "physician's intention to treat" (refer to Manual of Procedures). The primary purpose of the BILAG in this study is to assess possible worsening in specific organ systems. Additional analyses of improvements in disease activity as assessed by the BILAG 2004 will also be done.

A separate alphabetic score is assigned to each organ system, corresponding in general to the following definitions:

- BILAG A: Severe disease activity requiring any of the following treatments (e.g., systemic high dose oral CS, intravenous pulse CS, systemic immunosuppressants, or therapeutic high dose anticoagulation in the presence of high dose CS or ≥ 20 mg prednisone). Note that in the context of a CTP with medication restrictions and blinded IMP, the term "requiring" is not taken literally, but indicates that if all else were equal this would be the degree of treatment indicated. It is also understood that some subjects respond to different levels of medication than others, so that in assessing subjects with the BILAG "intent to treat" really means that most subjects with this degree of symptom would require this level of treatment, not necessarily the subject in question.
- BILAG B: Moderate disease activity requiring treatment with systemic low dose oral glucocorticoids, intramuscular or intra-articular or soft tissue CS injection, topical CS or immunosuppressants, or symptomatic therapy such as antimalarials or NSAIDs.
- BILAG C: Mild disease
- BILAG D: System previously affected but now inactive
- BILAG E: System never involved

The BILAG 2004 is evaluated by scoring each of a list of signs and symptom as: improving (1); same (2); worse (3); new (4); not present (0); not done (ND). For some items, appropriate responses may be: Y/N or numerical values where indicated or Y/N confirm this is due to SLE activity.

All signs and symptoms scored must be due to SLE. Use of a glossary provided with the BILAG 2004 instrument and training of assessors in use of the instrument are essential to obtaining reliable and consistent results.

Use of the BILAG 2004 index for evaluating flares has been identified as a robust way of evaluating the efficacy of drugs; this judgment has been corroborated by external advisors and regulatory authorities.

BILAG assessments should be conducted by a trained evaluator.

Requirements for BILAG-based Composite Lupus Assessment (BICLA) response are: (1) BILAG 2004 improvement (all A scores at Baseline improved to B/C/D, and all B scores improved to C or D); (2) no worsening in disease activity (no new BILAG 2004 A scores and ≤ 1 new B score); (3) no worsening of total SLEDAI-2K score from Baseline; (4) no significant deterioration (< 10% worsening) in visual analogue PGA and (5) no treatment failure (defined as non-protocol treatment, i.e., new or increased immunosuppressives or antimalarials; or increased or parenteral corticosteroids; or premature discontinuation from study treatment) (Wallace 2014).

A copy of the BILAG 2004 and glossary is provided in the Manual of Procedures.

7.3.2 Physician Global Assessment

The PGA is used to quantify disease activity and is measured using an anchored Visual Analog Scale (VAS) (see Figure 5). The PGA will be determined on a continuous VAS that asks the Investigator to assess the subject's current disease activity from a score of 0 (none) to 3 (severe), with the assessment made relative not to the subject's most severe state but the most severe state of SLE per the Investigator's assessment. As per its validation method, the PGA is recommended to be completed prior to laboratory results from the individual study visit being available (Petri 1992).

This version of the PGA is not scored blindly. The assessor is instructed to look at the previous month's PGA, decide whether the overall condition of the subject is same, better or worse and move the line accordingly.

A score change, where score is moved to the right from 2.5 or below in the previous month to > 2.5 this month, denotes an arbitrary threshold for severe flare to be considered when determining if enough change has occurred to justify assessing the criterion as severe flare. A score change ≥ 1 unit to the right denotes a designation of mild/moderate flare.

Figure 5 Physician Global Assessment Visual Analog Scale with Anchors

7.3.3 Systemic Lupus Erythematosus Disease Activity Index-2000 and Systemic Lupus Erythematosus Disease Activity Index Flare Index

SLEDAI-2K

The SLEDAI-2K is a reliable, valid, simple 1-page index that measures disease activity and records features of active lupus as present or not present (Gladman 2002). It is a modification for the SLEDAI to reflect persistent, active disease in those descriptors that had previously only considered new or recurrent occurrences. The SLEDAI-2K was validated against the original SLEDAI for evaluation over the previous 10 days. It has been shown to be reliable at different levels of disease activity (Gladman 1992, Gladman 1994). The properties of the SLEDAI-2K are summarized in a recent publication of Romero-Diaz et al (Romero-Diaz 2011).

Subsequently, use of the SLEDAI-2K for evaluating the previous 30 days was validated, and evaluation of the previous 30 days is now the approach recommended for use in clinical studies (Touma 2010, Touma 2011).

The SLEDAI-2K uses a weighted checklist to assign a numerical score based on the presence or absence of 24 symptoms at the time of assessment or during the previous 30 days. Each symptom present is assigned between 1 and 8 points based on its usual clinical importance, yielding a total score that ranges from 0 points (no symptoms) to 105 points (presence of all defined symptoms). However, if scored correctly, it is rare for even the sickest subjects to score more than 20 points. The assessor is also requested to assess the subject's symptoms using the VAS for the PGA (see Section 7.3.2).

SLEDAI Flare Index

The SFI can be used with any version of the SLEDAI, and will be used with the SLEDAI-2K for the purposes of this trial.

A mild/moderate flare is defined as any of the following

- Increase in SLEDAI instrument score of 3 points or more (but total score not to more than 12).
- New or worse discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus; or nasopharyngeal ulcers; or pleuritic; or pericarditis; or arthritis; or fever due to SLE.
- Increase in prednisone, but not to > 0.5 mg/kg/day.
- Added NSAID or hydroxychloroquine (or chloroquine) for SLE activity.

- ≥ 1.0 increase in PGA score, but score not to exceed 2.5 (assuming the PGA score has been transformed to a 0-3 point scale).
- A severe flare is defined as any of the following:
  - Increase in SLEDAI instrument score leading to total score > 12.
  - New or worse central nervous system SLE; or vasculitis; or nephritis; or myositis; or platelets < 60,000/mm^3, or hemolytic anemia with hemoglobin < 70 g/L or decrease in hemoglobin > 30 g/L AND requiring: double prednisone, or prednisone increase to > 0.5 mg/kg/day, or hospitalization due to SLE.
  - Increase in prednisone to > 0.5 mg/kg/day.
  - New cyclophosphamide, azathioprine, methotrexate, or mycophenolate for SLE activity.
  - Hospitalization for SLE activity.
  - Increase in PGA score leading to total score > 2.5 (assuming the PGA score has been transformed to a 0-3 point scale).

The SLEDAI-2K and SFI assessments should be conducted by a trained evaluator.

A copy of the SLEDAI-2K form is provided in a separate Manual of Procedures.

7.3.4 Cutaneous Lupus Erythematosus Disease Area and Severity Index

Cutaneous Lupus Erythematosus Disease Area and Severity Index is a validated measurement instrument for lupus erythematosus developed for use in clinical studies that consists of separate scores for the activity of the disease (CLASI-A) and the damage done by the disease (CLASI-D).

The CLASI activity score is calculated on the basis of erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss and non-scarring alopecia. The CLASI damage score is calculated on the basis of dyspigmentation and scarring, including scarring alopecia. Dyspigmentation due to lesions is defined as lesions that remain visible for more than 12 months, which are considered to then be permanent (Albrecht 2005).

The CLASI assessment should be conducted by a trained evaluator, and a copy of the Index is provided in a separate Manual of Procedures.

7.3.5 Systemic Lupus International Collaborating Clinics / American College of Rheumatology Damage Index

The SLICC/ACR Damage Index evaluates cumulative damage in SLE (Gladman 1996). These changes may or may not be related to SLE. In order to ensure that features are not reversible components of active inflammation, most items are scored only if they have been present for at least six months. Scores range from 0 to 47 points, with higher scores indicating greater cumulative damage. However it would be exceedingly rare to see a damage index score of greater than 5 and most subjects in clinical studies have scores ranging from 0-2.

Further information on the SLICC/ACR Damage Index is provided in the Manual of Procedures.

7.3.6 Health Related Quality of Life Assessments

The impact of SLE on subjects' lives is significant, and thus HRQoL outcomes are meaningful to both subjects and clinicians. As part of the study's examination of efficacy, the effects of treatment on HRQoL will be assessed through changes in the SF-36v2, EQ-5D-5L, LupusQoL, PGIC, and FACIT-Fatigue scores (Hewlett 2005, McElhone 2007, Hurst 2004, Wolfe 1996, Yellen 1997). Each HRQoL assessment will be used in the countries for which validated translations are available. A copy of each HRQoL assessment is provided in the Manual of Procedures.

7.3.6.1 Medical Outcomes Study 36-item Short Form Health Survey

The SF-36v2 is a 36-item scale constructed to survey HRQoL on eight domains: limitations in physical activities due to health problems; limitations in social activities due to physical or emotional problems; limitations in usual role activities due to physical health problems; bodily pain; general mental health (psychological distress and well-being); limitations in usual role activities due to emotional problems; vitality (energy and fatigue); and general health perceptions (Ware 2008).

The SF-36v2 form asks for subjects to reply to questions (items) according to how they have felt over a specifically defined period of time. The items use Likert-type scales, some with 5 or 6 points and others with 2 or 3 points and yields scale scores for each of these eight health domains, and two summary measures of physical and mental health: the Physical Component Summary (PCS) and Mental Component Summary (MCS). The interval level scoring for all eight scales ranges from 0 (for worse health) to 100 (best possible health as measured by the questionnaire) with standardized summary scores for the PCS and MCS (mean = 50, SD = 10).

Higher scores represent a better quality of life. Low scores on the PCS indicate significant limitations in performing physical activities, high degree of bodily pain and poor general health, while high scores reflect little or no such limitations. Low scores on the MCS indicate frequent psychological distress, social and role disability due to emotional problems and poor general health, while higher scores reflect little or no psychological distress or limitations. At each Assessment Visit, the SF-36v2 will be completed by the subject prior to the initiation of any other study activities or treatments.

7.3.6.2 Lupus Quality of Life

The LupusQoL is a lupus-specific HRQoL questionnaire consisting of 34 items grouped in eight domains: physical health, pain, planning, intimate relationships, burden to others, emotional health, body image and fatigue (McElhone 2007). Subjects indicate their responses on a five point Likert response format, where 4 = never, 3 = occasionally, 2 = a good bit of the time, 1 = most of the time, and 0 = all of the time. Summary scores can be calculated for all eight domains. The LupusQoL showed good internal reliability, test-retest reliability, and concurrent validity with the SF-36v2 and discriminant validity for different levels of disease activity and damage in SLE subjects (McElhone 2007, McElhone 2016).

7.3.6.3 Patient Global Impression of Change

The PGIC is a self-rated scale that asks the subject to describe the change in activity limitations, symptoms, emotions, and overall quality of life (QoL) related to the subject's painful condition on the following scale: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse) and 7 (very much worse). The subject will select the number that matches the subject's degree of change since beginning the treatment with M2951 (Hurst 2004).

The PGIC can be used as an anchor based method to assess clinically important change in which the judgment of meaningful change is made by the subject (Amirfeyz 2009).

7.3.6.4 Functional Assessment of Chronic Illness Therapy-Fatigue

The FACIT-Fatigue is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function (Wolfe 1996). It uses a 5-point Likert-type scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much). As each of the 13 items of the FACIT-Fatigue scale ranges from 0–4, the range of possible scores is 0-52, with 0 being the worst possible score and 52 the best. To obtain the 0-52 score, each negatively worded item response is recoded so that 0 is a bad response and 4 is good response. All responses are added with equal weight to obtain the total score. Fatigue is among the most prevalent symptoms of SLE, and can have profound effects on subjects' HRQoL (Wolfe 1996, Yellen 1997). The FACIT-Fatigue has been validated in subjects with SLE being a valid and responsive measure of fatigue in subjects with SLE (Hewlett 2005, Kosinski 2013, Lai 2011, Strand 2015).

7.3.6.5 EuroQoL 5 Dimension 5 Levels

The EQ-5D-5L questionnaire is a generic measure of health status that provides a simple descriptive profile and a single index value (Aggarwal 2009).

The EQ-5D-5L profile defines health in terms of mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The digits for five dimensions can be combined in a five-digit number describing the respondent's health state.

EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single index value. The index values, presented in country specific value sets, facilitate the calculation of quality-adjusted life years that are used to inform economic evaluations of health care interventions.

The EuroQoL VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'. This information can be used as a quantitative measure of health as judged by the individual respondents.

Higher scores on both EQ-5D-5L scales represent a better QoL.

7.4 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting and analysis of Baseline medical conditions; AEs; physical examination findings including vital signs, ECGs, and laboratory tests (including Ig as detailed Section 7.3.6 and B cell counts).

Comprehensive assessment of any apparent toxicity experienced by each subject will be performed from the time of giving informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the subject (see Section 7.4.1.2). The Reporting Period for AEs is described in Section 7.4.1.3.

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the National Cancer Institute - Common Terminology Criteria for AEs (NCI-CTCAE), version 4.03 CTCAE 2010, a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

Only if a particular AE's severity is not specifically graded by the guidance document, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment.

The five general grades are:

- Grade 1 or Mild
- Grade 2 or Moderate
- Grade 3 or Severe
- Grade 4 or Life-threatening

- Grade 5 or Death.

According to Sponsor convention, any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as a separate event. Only, if no cause of death can be reported (e.g., sudden death, unexplained death), the death per se might then be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to IMP(s)/study treatment (including any other non-IMPs, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the IMP include, but may not be limited to, temporal relationship between the AE and the IMP, known side effects of IMP, medical history, concomitant medication, course of the underlying disease, study procedures.

Unrelated: Not reasonably related to the IMP/study treatment. AE could not medically (pharmacologically/clinically) be attributed to the IMP/study treatment under study in this CTP. A reasonable alternative explanation must be available.

Related: Reasonably related to the IMP/study treatment. AE could medically (pharmacologically/clinically) be attributed to the IMP/study treatment under study in this CTP.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g., anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening. (Note: The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe)
- Requires inpatient hospitalization or prolongs an existing hospitalization, except in the case of hospitalizations due to protocol-defined SLE flares.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.

- Is otherwise considered to be medically important. (Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered an SAE, as described in 7.4.1.4.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study treatment or study procedures (e.g., an overnight stay to facilitate intravenous therapy) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs, except for unplanned hospitalizations due to flare of SLE.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and are not to be considered AEs.

Worsening of the underlying disease is not routinely to be considered an AE or SAE, but is rather an efficacy endpoint, unless deemed to be causally related to the IMP.

However, if significant adverse signs or symptoms occur in association with complications or a prolonging of a hospitalization originally due to SLE flare, then these specific complications or hospital prolongation events should be recorded as AEs.

Exacerbation of SLE

SLE flares would not usually be reported as AEs unless they are unexpected in the context of the subject's medical history. Further, the AE report should describe the event, rather than reporting an AE of "SLE flare" unless it is unavoidable. SAEs due to SLE flare are always reported, whether or not it is consistent with the subjects' prior history. As for AE reports, the SAE report should describe the events, and avoid reporting an SAE of "SLE flare".

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each study visit, the subject will be asked about changes in his/her condition. During the Reporting Period of the study, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the Investigator, unless it is a lupus flare that is not unexpected based on the subject's medical history.

Complete, accurate and consistent data on all AEs experienced for the duration of the Reporting Period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs must be additionally documented and reported using an SAE Report Form as described in Section 7.4.1.4.

It is important that each AE report include a description of the event, its duration (onset and resolution dates [and times to be completed when relevant and possible to assess the time of AE onset relative to treatment administration]), its severity, its relationship with the study treatment, any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of the IMP) and its outcome. In addition, SAEs should be identified and the appropriate seriousness criteria documented.

Specific guidance can be found in the eCRF Completion and Monitoring Conventions provided by the Sponsor or designee.

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE Reporting Period for safety surveillance begins when the subject is screened (date of first signature of informed consent) and continues through the study's Post Treatment Follow-Up Period, defined as the Safety Follow-Up Period (EOT through Follow-Up Week 4). SAEs occurring after a subject has taken the last dose of IMP will be collected throughout the subject's participation until the end of the Safety Follow-Up Period, regardless of the Investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the Investigator determines the SAE was related to IMP, or protocol procedure.

Any SAE assessed as related to M2951 must be reported whenever it occurs, irrespective of the time elapsed since the last administration of M2951.

7.4.1.4 Procedure for Reporting Serious Adverse Events

Serious Adverse Events

In the event of any new SAE occurring during the Reporting Period, the Investigator must immediately (i.e., within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee by completing the SAE Report form in the eCRF following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, an SAE Report Form must be completed immediately thereafter.

Relevant pages from the eCRF may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may also be provided by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report). In all cases, the information provided in the SAE Report Form (clinical trial) must be consistent with the data on the event that are recorded in the corresponding sections of the eCRF.

The Investigator/reporter must respond to any request for follow-up information (e.g., additional information, outcome and final evaluation, specific records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible Monitor, although in exceptional circumstances the Global Drug Safety department may contact the Investigator directly to obtain further information or to discuss the event.

7.4.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators

The Sponsor or designee will send safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (and in particular, deaths) involving study subjects to the IEC/IRB that approved the study.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study." In particular and in line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (SUSARs). The Investigator should place copies of safety reports in the Investigator Site File. National regulations with regard to safety report notifications to Investigators will be taken into account.

For Japan only - In accordance with ICH GCP and the Japanese ministerial ordinance on GCP, the Sponsor/designee will inform the Investigator and the head of the study site of "findings that could adversely affect the safety of subjects, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study." In particular and in line with respective regulations, the Sponsor/designee will inform the Investigator and the head of the study sites of AEs that are both serious and unexpected and are considered to be related to the administered product (SUSARs). The Investigator should place copies of safety reports in the Investigator Site File. National regulations with regard to safety report notifications to Investigators will be taken into account. The head of the study site should also maintain copies of safety reports appropriately.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for notifying the applicable IEC/IRB of any safety reports provided by the Sponsor/designee in accordance with applicable timelines and will be required to file copies of all reports and related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/safety issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

7.4.1.6 Monitoring of Subjects with Adverse Events

Any AE that occurs during the course of a clinical study and is considered to be possibly related to the IMP must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that appropriate additional therapeutic measures and follow-up procedures are performed if possible. The Sponsor or designee will actively follow-up and collect information on any AE that occurs during the course of a clinical study; however while this activity will continue for any SAEs until stabilization or until the outcome is known, it will be discontinued at the time of database lock for nonserious AEs.

7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to study treatment (e.g., resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in Section 7.4.1.4.

If possible, Investigators must actively follow-up, document and report on the outcome of all these pregnancies, even if the subjects are withdrawn from the study (see Section 5.5.2). The Pregnancy Report Form will be used to report outcomes and in case of adverse outcomes, the AE Safety Report Form (Clinical Trials) will be used for events occurring to the subject and the Parent Child/Fetus AE Report Form will be used if the child/fetus sustains an AE.

Adverse outcomes must be reported in an expedited manner as described in Section 7.4.1.4, while nonadverse outcomes must be reported within 45 days from delivery. In the event of pregnancy in a subject occurring during the course of the study, the subject must be discontinued from study medication immediately. The Sponsor must be notified without delay and the subject should be followed as described above.

7.4.3 Clinical Laboratory Assessments

Blood and urine samples will be collected for the following clinical laboratory tests (Table 11), following the timing noted in the SOA (Table 1 and Table 2). All samples should be clearly identified. Sample collection, preparation, and handling/shipment procedures are described in the laboratory manual. For WOCBP, including those who are postmenopausal for less than 12 months, serum pregnancy tests will be performed at initial Screening, and high sensitivity urine pregnancy

tests will be performed at the visits specified in Table 1 and Table 3. Pregnancy tests will be done whenever 1 menstrual cycle is missed during the active treatment period, when potential pregnancy is otherwise suspected, and at the end of the study to confirm the subject has not become pregnant during the study. Pregnancy tests may be repeated per request of institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

Additional laboratory tests may be performed after abnormal findings. Local safety testing as requested by the study team should be entered into the eCRF.

Table 11 Clinical Laboratory Evaluations

Type of Evaluation	Tests		
Biochemistry	Albumin Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase γ-Glutamyl-transferase Lactate dehydrogenase Total Ig Levels (IgG, IgA, IgM)[b]	Bilirubin (total) Protein (total) Creatinine and eGFR calculation[a] Amylase Lipase Total carbon dioxide/serum biocarbonate Blood urea nitrogen Glucose	Sodium Potassium Chloride Calcium Magnesium Phosphate Uric acid
Supplementary LFT visits	Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase γ-Glutamyl-transferase	Bilirubin (total)	
Hepatic Panel	International normalized ratio Partial thromboplastin time Fibrinogen hsCRP	Hepatitis serology: anti HAV IgG, anti-HAV IgM, HBsAg, anti-HBc, anti HBsAg, anti-HCV, anti-HEV IgG and IgM, anti-VCA IgG and IgM, anti-EA IgG, anti-EBNA IgG, anti-CMV IgG and IgM	Antinuclear antibody, anti-smooth muscle antibody, antibody to liver kidney microsomes Albumin
Hematology	Hematocrit Hemoglobin Red blood cell count Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Reticulocyte count	Platelet count White blood cell count Flow cytometry for: B cell count[b]	White blood cell differentials and absolute counts: Basophils Eosinophils Lymphocytes Monocytes Neutrophils
Coagulation[b]	International normalized ratio Partial thromboplastin time		

Type of Evaluation	Tests		
Urinalysis/ microscopy[c] and urine chemistry	pH Nitrite Urobilinogen Bilirubin	Glucose Ketone bodies Protein Blood	Microscopy (white blood cells, red blood cells, casts, crystals) Protein/creatinine ratio
Additional urine testing	β-hCG (women only)[c]		
Other Screening tests[d]	HCV antibodies Serum β-hCG (women only) Serum β-glucan (Japan only)	HBV antibodies HIV[e] TSH	FSH HBsAg Quantiferon tuberculosis test
Reflex Testing for HBV DNA	HBV DNA PCR		

β-hCG = Beta-Human Chorionic Gonadotropin, DNA = deoxyribonucleic acid, EA = early antigen, EBNA = Epstein-Barr nuclear antigen, eGFR = Estimated Glomerular Filtration Rate, FSH = Follicle-Stimulating Hormone, HAV = Hepatitis A virus, HBc = Hepatitis B core antigen, HBsAg = Hepatitis B Surface Antigen, HBV = Hepatitis B Virus, HCV = Hepatitis C Virus, HEV = Hepatitis E virus, HIV = Human Immunodeficiency Virus, hsCRP = high sensitivity C-reactive protein, Ig = Immunoglobulin, MDRD = Modification of Diet In Renal Disease, NK = Natural Killer Cells, PPD = Purified Protein Derivative, TSH = Thyroid Stimulating Hormone, VCA = viral capsid antigen.

a Calculated using the four-component MDRD equation (Levey 2006).

b To be done only when specified in Table 1 and not as a standard laboratory evaluation. See Section 7.5.5.2 for details of flow cytometry assessments (safety and exploratory).

c Urine samples will be collected using a clean catch method. If a female is actively menstruating, urine sample will be delayed and collected preferably within the visit window (but no later than 10 days from the visit). Microscopy will be performed at the central laboratory.

d Performed only at Screening.

e HIV testing is to be performed locally and is mandatory for participation in the study.

7.4.3.1.1 Immunological Assessments

Absolute values of and changes from Baseline in complement proteins (C3, C4) and anti-dsDNA antibodies may be predictive of disease development and reflective of disease activity and response to therapy in SLE (Bernatsky 2006, Reveille 2004). Total B cell counts and serum Ig levels may change given the mechanism of action of M2951 and are being collected as safety evaluations (see Table 1 and Table 2). These additional immunological assessments will be collected according to the SOA:

- Anti-dsDNA (at Screening, may be measured using 2 assays, 1 of which is a multiplex assay that includes anti-Ro and anti-RNP. Only anti-dsDNA is used to determine subject eligibility and will be reported to the sites.)
- Complement (C3 C4)
- ANA
- C-reactive protein

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7.4.4 Vital Signs, Physical Examinations, and Other Assessments

7.4.4.1 Vital Signs

Vital signs, including blood pressure (BP), pulse rate, respiratory rate, weight, and oral temperature will be assessed predose at all study visits (Table 1). Height will be measured at Screening only.

A semiautomated pulse rate and BP recording device with an appropriate cuff size will be utilized. Pulse rate and BP will be measured after 10 minutes rest in the semisupine position with the subject's arm unconstrained by clothing or other material. The BP should be assessed on the same arm for each subject throughout the study.

7.4.4.2 Physical Examination

Physical examinations will be assessed as indicated in Table 1 and Table 2.

Physical examination includes assessment of the following: general appearance, skin, head and neck, mouth, lymph nodes, thyroid, abdomen, and nervous, musculoskeletal, cardiovascular, and respiratory systems. Physical examination findings during Screening before obtaining informed consent will be recorded as medical history events and new findings or worsening during the study as AEs.

Abbreviated physical examination should always include assessment of head, ears, eyes, nose, throat, lungs, heart, abdomen, and extremities and other systems as required by symptoms.

Additional assessments (e.g., creatine phosphokinase, ECG, chest radiograph) should be performed as needed to fully obtain information needed for the BILAG 2004 and/or SLEDAI-2K assessments (see Sections 7.3.1 and 7.3.3) if scheduled, as well as to fully evaluate any subject complaints or AEs.

7.4.4.3 Resting 12-lead Electrocardiogram and Chest X-ray

A 12-lead ECG will be performed as indicated in Table 1 and Table 2. The 12-lead ECG recordings will be obtained after 10 minutes of rest in a semisupine position.

The following ECG parameters will be obtained directly from the computerized 12-lead ECG recordings: rhythm, ventricular rate, PR interval, QRS duration, and QT interval. The corrected QT interval will be calculated using Fridericia's formula. The overall evaluation (normal/abnormal) will be recorded on the eCRF, and if abnormal, the specific abnormality will be recorded. Abnormal evaluations will be judged as clinically significant or not clinically significant by the Investigator.

The printout of the ECG is to be signed, dated, and filed in the Investigator's Site File along with a signed and dated copy (if the printouts are not on archive-quality paper). In addition, ECGs will also be stored digitally by the Sponsor.

Posteroanterior CXRs will be performed during Screening according to local standard practice. Subjects who had a CXR performed for clinical reasons within three months prior to the Screening Visit do not need to have the CXR repeated. The CXR should show no evidence of active infective process, or any other clinically significant abnormalities. The overall evaluation (normal/abnormal) will be recorded on the eCRF, and if abnormal, the specific abnormality will be recorded. Abnormal evaluations will be judged as clinically significant or not clinically significant by the Investigator.

The 12-lead ECG and CXR will be performed and read locally.

7.4.4.4 Review of Concomitant Medications and Procedures

Data concerning concomitant medications and procedures will be collected throughout the study. These data will be obtained at scheduled and unscheduled study visits, based on information spontaneously provided by the subject and through questioning of the subject.

Data concerning concomitant medications and procedures may also be obtained from the subject diary, but information thus collected must be reviewed and assessed medically before it is transcribed to the eCRF.

7.4.4.5 Unscheduled Visits

Unscheduled visits may occur at any time during the study in case of suspected flares or AEs (assessments to be performed according to the Investigator's judgment).

7.4.5 Columbia-Suicide Severity Rating Scale

The C-SSRS will be used for prospective suicidality assessment. The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior and attempts with actual/potential lethality.

The scale will be administered by the Treating Investigator or a qualified designee at Screening to identify eligible subjects. It will be self-administered at other time points during the study as per Table 1 and Table 2, using a validated, electronic, self-rated version of the C-SSRS (eC-SSRS) (Mundt 2010, Mundt 2013).

Subjects who answer "yes" to any suicidal behavior questions or to suicidal ideation questions 4 or 5 on the C-SSRS during the study should be referred for appropriate psychiatric care and the Medical Monitor notified.

Please note that assessing the risk of suicide is a difficult and complex task when applied to the individual subject. No single clinical scale can replace a thorough medical examination and suicide risk assessment. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

7.5 Exploratory Assessments

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8 Statistics

8.1 Sample Size

A sample size of 103 evaluable subjects per group provides 80% power at the $\alpha = 0.025$ one-sided significance level to detect

- an absolute improvement of 20% in Week 52 SRI-4 response proportion for M2951-treated subjects relative to placebo-exposed subjects, among subjects with SLEDAI-2K total score ≥ 6 at Screening, assuming a placebo response proportion of 40%,

  or

- an absolute improvement of 25% in Week 52 SRI-6 response proportion for M2951-treated subjects relative to placebo-exposed subjects, among subjects with SLEDAI-2K total score ≥ 10 at Screening (i.e., HDA), assuming a placebo response proportion of 30%,

assuming that each co-primary endpoint is tested via a chi-squared test of the odds ratio (OR) for treatment effect at the 0.0125 one-sided level, and assuming that approximately 50% of randomized subjects are in the HDA group. If the absolute improvement in Week 52 SRI-6 response proportion in HDA subjects is only 20%, the power is 76%. Approximately 108 subjects will be randomized per treatment group to protect against a loss of information due to drop-out (for reasons other than efficacy/safety) of 5% over 52 weeks. Given the randomization ratio 1:1:1:1, the total sample size required for the primary analysis is planned to be 432 subjects.

Approximately 432 subjects will enter the main study. Assuming an 80% rate of continuation to LTE, approximately 346 subjects are expected to enter the LTE Period.

The Japan cohort size was determined to provide a reliable evaluation of consistency in the Week 52 SRI-4 response proportion between the non-Japan and Japan regions. Assuming that:

(i) the Week 52 SRI-4 response proportion in the placebo group is 0.40 for both the non-Japan and Japan regions,

(ii) the Week 52 SRI-4 response proportion due to each of the 3 M2951 dose groups is 0.60 for both regions, so that the true underlying effect size is 0.20 for both regions,

(iii) a total evaluable sample size of 412 (i.e., 309:103 randomization for M2951: placebo) is involved in analysis of the two regions,

and applying "Method 2" from the PMDA Guidance, 32 evaluable subjects in the Japan cohort are required so that both observed region-specific effect sizes exceed 0.04 with probability of 80%. Taking into account a loss of information due to 5% drop-out at Week 52, for reasons unrelated to efficacy or safety, the total number of Japan subjects to be randomized is 36, or 8.3% of the total planned enrollment of 432.

If enrollment of Japanese subjects is slow, then the entire Japanese cohort will not be part of the primary analysis cohort. A maximum of n = 36 Japanese subjects will be analyzed for Week 52 SRI-4 at a time point after the primary analysis for the purpose of assessing consistency. Therefore, the total enrollment will range from n = 432 to 468 , where 468 = 432 + 36 is the number enrolled if none of the 36 Japanese subjects enroll in time to be included in the primary analysis. The number of subjects enrolled per group will range from n = 108 to 117.

8.2 Randomization

Eligible subjects will be randomized into either one of three M2951 groups CCI [redacted] or the placebo group in a ratio of 1:1:1:1, stratified according to race (Black versus non-Black), region (US and Western Europe, Japan, and RoW) and Screening disease activity (SLEDAI-2K total score < 10 versus ≥ 10 at Screening). A randomized allocation schedule for IMP assignment will be generated within the appropriate group of PPD , by an individual who is not on the study team. Randomization will occur using the IWRS as described in Section 6.3 upon completion of the Screening/Baseline procedures and determination of subject eligibility.

To ensure enrollment of an adequate number of subjects with HDA, recruitment of subjects without HDA may be capped, depending on enrollment rates observed during the study of subjects with and without HDA.

8.3 Endpoints

8.3.1 Primary Endpoints of Efficacy and Safety

The co-primary efficacy endpoints are SRI response at Week 52: SRI-4 in all subjects and SRI-6 in a HDA subgroup. The SRI-4 response, a measure of reduced SLE disease activity, is defined by meeting all of the following conditions compared to Baseline:

1. ≥ 4 point reduction in SLEDAI-2K total score.

2. No significant worsening in PGA score (< 0.3 increase assuming the PGA score is on a 0-3 scale).

3. No new BILAG A organ domain scores and ≤ 1 new BILAG B organ domain score compared to Day 1 using BILAG 2004.

4. No discontinuation of investigational product and no institution of protocol-prohibited medication/treatment

The SRI-6 response is defined similarly to SRI-4, based on a ≥ 6 point reduction in SLEDAI-2K total score. For SRI response, Baseline is defined as Day 1 predose.

In this study, safety endpoints are considered to be primary endpoints. The safety endpoints are:

- Nature, severity, and incidence of AEs, SAEs, vital signs, ECGs, absolute values and change from Baseline in serum total Ig levels (IgG, IgA, IgM) and total B cell counts, and clinical laboratory parameters.

8.3.2 Secondary Endpoints

The key secondary endpoints are:

- Time to first severe flare, where a severe flare is defined as at least one BILAG A score in any organ system due to items that are new or worse, compared to the BILAG evaluation at the previous visit, during the Treatment Period
- SRI-4 response at Week 52, in the serologically active subgroup, which is defined as subjects with positive anti-dsDNA and/or low complement levels.

Other Secondary endpoints are:

- SRI-6 response at Week 52, in the serologically active subgroup, which is defined as subjects with positive anti-dsDNA and/or low complement levels.
- SRI-4 Response at Week 52 with a Sustained Reduction of OCS Dose to 7.5 milligrams prednisone-equivalent per day or less (≤ 7.5 mg/day) and less than or equal to (≤) Day 1 dose during Week 41 Through Week 52, in all subjects.
- SRI-6 Response at Week 52 with a Sustained Reduction of OCS Dose to 7.5 milligrams prednisone-equivalent per day or less (≤ 7.5 mg/day) and less than or equal to (≤) Day 1 dose during Week 41 Through Week 52, in the HDA subgroup, defined as SLEDAI-2K ≥ 10 at Screening.
- SRI-4 Response at Week 52 with a Sustained Reduction of OCS Dose to 7.5 milligrams prednisone-equivalent per day or less (≤ 7.5 mg/day) and less than or equal to (≤) Day 1 dose during Week 41 Through Week 52, in the serologically active subgroup, which is defined as subjects with positive anti-dsDNA and/or low complement levels.
- Time to first flare, flare-free status at Week 52, and annualized flare rate, during the Treatment Period, will be analyzed separately, each assessed with flare defined as:
  - BILAG A Severe flare
  - BILAG A or 2B Moderate to Severe flare

- SFI Severe flare

- Disease activity over time, during the Treatment Period, as measured by:
  - Low disease activity status, defined by SLEDAI-2K ≤ 2, at Week 52
  - Low disease activity status, defined by clinical SLEDAI-2K (SLEDAI 2K excluding anti-dsDNA and low complement parameters) ≤ 2, at Week 52
  - Lupus low disease activity state (LLDAS), defined as meeting all of the following (Franklyn 2016):
    - SLEDAI-2K ≤ 4
    - No activity in any major organ systems (renal, central nervous system, cardiopulmonary, vasculitis, fever)
    - No new features of disease activity compared with the previous assessment
    - Prednisone-equivalent ≤ 7.5 mg/day
    - Unchanged background immunosuppressive therapy
  - Change from Baseline in SLEDAI-2K score by visit
  - Change from Baseline in CLASI-A by visit
  - BICLA response by visit
  - Change from Baseline in BILAG-2004 by visit
  - Change from Baseline in PGA by visit
- HRQoL over time, during the Treatment Period, as measured by:
  - Change from Baseline in SF-36v2 PCS and MCS scores (and their components) by visit
  - Change from Baseline in EQ-5D-5L score by visit
  - Change from Baseline in LupusQoL score by visit
  - PGIC score by visit
  - Change from Baseline FACIT-Fatigue score by visit
- Corticosteroid usage over time, during the Treatment Period, as measured by:
  - Reduction from Baseline in prednisone-equivalent CS dose by ≥ 25% to a dose of ≤ 7.5 mg/day, with no BILAG A or 2B flare in disease activity (at that visit)
  - Change from Baseline to Week 52 in prednisone-equivalent CS daily dose
  - Reduction from Baseline to Week 52 in prednisone-equivalent CS daily dose of zero to < 25%, 25% to 50%, > 50%, or an increase
  - Cumulative prednisone-equivalent CS dose from Baseline until completion of the Treatment Period
  - Clinically meaningful reduction in CS dose from Baseline, defined by:

- A reduction of daily prednisone-equivalent CS dose ≥ 25% to a dose of ≤ 7.5 mg/day by Week 40 and sustained through Week 52

  AND

- No new BILAG A organ domain scores and no more than one new BILAG B organ domain score during Weeks 40 through 52.

8.3.3 Exploratory Endpoints

Exploratory endpoints are:

CCI [redacted]

8.3.4 Endpoints for Long-Term Extension Period

LTE Safety:

- Nature, severity, and incidence of AEs, SAEs, vital signs, ECGs, absolute values and change from Baseline in serum total Ig levels (IgG, IgA, IgM) and total B cell counts, and clinical laboratory parameters.

LTE Efficacy:

- The following LTE efficacy endpoints will be analyzed at Week 24, Week 52, and Week 104:
    - Changes over time in SRI response
    - Changes over time in Low Disease Activity status (LLDAS, SLEDAI-2K≤2, clinical SLEDAI-2K≤2).
    - Changes over time in CLASI-A, CLASI-D, and SLICC/ACR Damage Index organ damage scores
    - Changes over time in disease activity as measured by the BILAG, SLEDAI-2K, and PGA
    - Change over time in prednisone-equivalent CS dose
    - Changes over time in HRQoL
    - Changes over time in autoantibodies and complement levels
- Changes in HRU by visit, including but not limited to doctor/home/emergency visits, hospitalizations, paid assistance, and missed work
- Time to first flare; flare-free status at Weeks 24, 52, and 104; and annualized flare rate, will be analyzed separately, each assessed with flare defined as:
    - BILAG A Severe flare
    - BILAG A or 2B Moderate to Severe flare
    - SLEDAI Flare Index (SFI) Severe flare.

8.4 Analysis Sets

The statistical analyses described in this protocol will be based on the analysis sets defined below:

Enrolled

The Enrolled analysis set will include all subjects who sign the ICF.

Intent-to-Treat

The Intent-to-Treat (ITT) Analysis Set will include all randomized subjects. Subjects will be analyzed according to randomized treatment.

Modified ITT

The modified Intent-to-Treat (mITT) Analysis Set will include all randomized subjects who have received at least one dose of IMP (M2951 or placebo), and have at least one Baseline and one post-Baseline disease assessment. Subjects will be analyzed according to randomized treatment.

Per-Protocol

The Per-Protocol (PP) Analysis Set will include all randomized and treated subjects who do not have any clinically important protocol deviations. Details of the criteria for exclusion from the PP analysis set will be provided in the IAP, including exclusion of subjects who take prohibited medications. Subjects will be analyzed according to randomized treatment.

Safety

The Safety Analysis Set will include all randomized subjects who receive at least one dose of IMP, and will be used for the evaluation of safety endpoints. Subjects will be analyzed according to the actual treatment they receive.

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[redacted]

Long Term Extension Analysis Set

The LTE Analysis Set consists of all subjects who receive at least one dose of M2951 during the LTE.

CCI [redacted]

8.4.1 Subgroups

Descriptive analyses of efficacy will be performed for the following subgroups:

- Race (Black, non-Black) (see Section 6.3 for definitions of Race used in this study)
- Ethnicity (Japanese, non-Japanese) (Hispanic/Latino, non-Hispanic/Latino)
- Severity of disease at Screening (severe, mild/moderate). Severe is defined as at least one BILAG A; mild/moderate is defined as at least one BILAG B and no BILAG A. Analyses of subgroups defined in terms of SLEDAI-2K total score at Screening (< 10 versus ≥ 10) will also be performed.
- Serological activity status (positive versus negative). Serologically active is defined as positive anti-dsDNA and/or low complement levels.
- Age (< 65, ≥ 65).
- Gender (male, female).
- Region (US and Western Europe, Japan, and RoW).
- Subjects on background therapy that includes mycophenolate versus subjects not taking mycophenolate.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Prior to locking the database, a detailed IAP will be developed.

Continuous variables will be summarized descriptively using the number of observations, mean, SD, median, first quartile (Q1), third quartile (Q3), minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of subjects in the treatment group and analysis set being presented, unless otherwise specified (e.g., on some occasions, percentages may be calculated based on the total number of subjects with available data at a particular time point).

Tests of treatment effect on each of the two co-primary efficacy endpoints will be conducted at a one-sided α-level of 0.0125, to maintain a study-wide one-sided α-level of 0.025. P-values and the two-sided CIs (97.5% or 95% as appropriate) will be presented where applicable. Actual p-values will be interpreted based on the multiple testing strategy, as specified in this protocol, and detailed further in the IAP. Treatment comparisons for each data type are described in later sections. Alternative or additional statistical methods may be used as appropriate as outlined in the IAP.

Data from all investigative sites will be pooled for all planned analyses. Analysis of individual site findings or country findings will be considered if necessary. For those measures that are analyzed using change from Baseline scores, observed scores may also be presented descriptively.

For SRI-4 or SRI-6 response at Week 52 (Week 24), a subject experiencing flare or CS dose increase during Weeks 41 to 52 (Weeks 17 to 24), or a subject with a missing response at Week 52 (Week 24), will be considered a non-responder. Four sensitivity analyses of the primary analysis are planned: (1) non-responder imputation for subjects discontinuing treatment for reasons due to efficacy/safety, with available observations used (in MMRM or multiple imputation) for subjects discontinuing treatment for reasons unrelated to efficacy/safety or completing treatment with missing response at Week 52, (2) unadjusted analysis, (3) completer analysis, and (4) per-protocol analysis (i.e., excluding subjects with clinically important protocol violations). Additional procedures for handling missing, unused, or spurious data, and sensitivity analyses exploring the impact of missing data will be described in the IAP.

The IAP will provide definitions of Baseline measurement as needed for change from Baseline endpoints.

Treatment compliance will be assessed in terms of the percentage of the actual doses taken relative to the number of scheduled doses and summarized by descriptive statistics.

All subjects will be included in individual subject data listings.

Any changes in the data analysis methods described in the protocol will require an amendment only if the change affects a principal feature of the protocol. Any other changes to the planned data analysis that does not require a protocol amendment will be described in the IAP and the CSR. CCI [redacted]

8.5.2 Analysis of Primary Endpoints

The primary analysis of SRI-4 response at Week 52 among all subjects in the primary analysis cohort, and SRI-6 response at Week 52 among HDA subjects in the primary analysis cohort, will be an estimate of OR, together with associated two-sided 95% CI and p-value (testing null hypothesis H0: OR = 1.0), comparing each M2951 dose group to placebo, based on a logistic model for the odds of a given SRI response in the appropriate population, with M2951 dose group or placebo group as a factor and adjustment for covariates based on randomization strata. Additional covariates may be included in the model as specified in the IAP. In the primary analysis of SRI-4 or SRI-6 response at Week 52, a subject experiencing flare or CS dose increase during Weeks 41 to 52, or a subject with a missing response at Week 52, will be considered a non-responder.

The primary analysis of the co-primary efficacy endpoints will be based on the mITT analysis set, with supportive analyses based on the ITT and PP analysis sets, if the size of these analysis sets differ substantially (> 10%) from the size of the mITT analysis set.

The Family-Wise type 1 error rate (FWER) due to the co-primary endpoints and multiple M2951 dose group comparisons versus placebo will be controlled at the two-sided $\alpha = 0.05$ level via a tree

gatekeeping procedure. The four hypotheses associated with the comparisons involving the co-primary endpoints and the two highest dose groups will form the first family of hypotheses in the tree. This family will be tested via the truncated Hochberg procedure, with truncation fraction pre-specified in the IAP. The multiple-testing procedure for the remainder of the tree, including the hypotheses associated with the comparisons involving the co-primary endpoints and the lowest dose group will be specified in the IAP.

A test for monotonic dose-response relationship, between ordered M2951 dose and SRI-4 response OR relative to placebo, will be performed as a supportive analysis. Similarly, a test for monotonic dose-response relationship, between ordered M2951 dose and SRI-6 response OR relative to placebo, will be performed as a supportive analysis in the HDA subgroup.

Descriptive statistics for SRI-4 response, and for SRI-6 response in the HDA subgroup, will be provided for each treatment group by time point.

Safety endpoints are considered to be primary endpoints in this study. Analysis of safety data is described in Section 8.5.4.

8.5.3 Analysis of Secondary Endpoints

The analysis of secondary endpoints will be based on the mITT analysis set. Descriptive statistics for secondary endpoints will be provided by treatment group and time point.

The multiple-comparison procedure for testing the key secondary efficacy endpoints will be provided in the IAP. Other secondary efficacy endpoints will be analyzed for CCI [redacted].

Key Secondary Endpoints

Time to first severe (BILAG A) flare during the Treatment Period in all subjects will be compared between M2951 and placebo via a stratified log rank test. The adjusted hazard ratio comparing M2951 to placebo will be estimated (together with 95% CI) via a Cox regression model, with treatment group as a factor, and controlling for covariates defining randomization strata. A subject who discontinues treatment or completes treatment without experiencing flare will have his/her time to flare censored at the last time point at which flare could be assessed. A test for trend in dose-response, using the same Cox model, will be reported as a supportive analysis.

Kaplan-Meier estimates of probability of surviving free of severe (BILAG A) flare as a function of time on treatment will be provided for each treatment group.

The analysis of SRI-4 response at Week 52 among serologically active subjects will be an estimate of OR, together with associated 95% CI and p-value, comparing each M2951 dose group to placebo, based on a logistic model for the odds of SRI-4 response in the serologically active population, with M2951 dose group or placebo group as a factor and adjustment for covariates based on randomization strata. A test for trend in dose-response, using the same logistic model, will be reported as a supportive analysis.

Descriptive statistics for SRI-4 response in the serologically active subgroup, will be provided for each treatment group by time point.

Other Secondary Endpoints

In the analysis of other secondary efficacy endpoints described in Section 8.3.2, binary endpoints will be modeled via logistic regression, time to event endpoints will be modeled via Cox regression and tested via stratified log rank test, continuous endpoints measured longitudinally will be analyzed using Mixed-effect Model for Repeated Measures (MMRM), and count endpoints (i.e., annualized flare rate) will be modeled via negative binomial regression, with treatment group as a factor, and adjusting for covariates defining randomization strata. Analysis of annualized flare rate will use the log of observation time (in years) as an offset in the model. Change in a binary endpoint between two time points will be analyzed via McNemar's test. The effect of treatment on change in a binary endpoint will be analyzed via logistic regression, with treatment group, time point, and interaction as predictors, and adjusting for covariates defining randomization strata. All tests of efficacy will be conducted at a two-sided α level of 0.05, with p-values considered nominal unless generated as part of the tree gatekeeping multiple testing strategy as described in the IAP. P-values and the 95% CIs will be presented where applicable.

Change in SF-36v2 PCS and MCS scores (and their components) over time, change in LupusQoL score over time, change in FACIT-Fatigue score over time, and change in EQ-5D-5L index over time, will be compared between M2951 treatment groups and placebo based on change from Baseline using MMRM, with treatment group as a factor, and adjustment for Baseline and covariates defining randomization strata.

The PGIC score will be analyzed based on absolute score, using MMRM to account for subjects with missing data, with treatment group as a factor, and adjustment for covariates defining randomization strata.

In the analysis of each secondary efficacy endpoint, other covariates may be included in the model, as appropriate.

8.5.4 Analysis of Safety

Adverse events will be summarized by treatment group, severity, and relationship to IMP. Serious AEs, AEs leading to treatment discontinuation, and AEs leading to treatment withdrawal will be summarized by treatment group.

Adverse events will be coded according to the medical dictionary for regulatory activities (MedDRA). The severity of AEs will be graded using the NCI-CTCAE v4.03 grading scale (Hahn 2012).

The number and percentage of subjects experiencing one or more treatment-emergent AEs (TEAEs) will be summarized according to the MedDRA system organ classes and preferred terms by treatment group, relationship to IMP, and severity.

Summary statistics will be used to present observed values and changes from Baseline in continuous laboratory, vital sign, and ECG data. Shift tables will be used to present changes in categorical laboratory parameters. Figures will be generated as needed to assist safety evaluation.

Values for all safety variables will be listed by subject and time point.

8.5.5 Analysis of Exploratory Endpoints

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8.5.6 Analysis of LTE Endpoints

Efficacy and HRQoL data collected during the LTE Period will be summarized. Details will be provided in the IAP.

Safety data collected during the LTE Period will be analyzed as described in Section 8.5.4.

8.6 Interim and Additional Planned Analyses

Interim Analysis

There may be an IA for futility based on the highest dose of M2951, triggered when 100% of subjects enrolled in the primary analysis cohort reach Week 24 of treatment, or prematurely discontinue from treatment prior to Week 24. If enrollment is sufficiently slow, consideration will be given to triggering the IA at an earlier time point, when the first 50% of subjects enrolled in the primary analysis cohort reach Week 24 of treatment, or prematurely discontinue from treatment prior to Week 24. Pharmacokinetic analysis will not be included in the IA.

The difference between Week 24 SRI-4 response proportion in all subjects in the primary analysis cohort, comparing the highest dose of M2951 to placebo, will be estimated, together with a two-sided 97.5% confidence interval. Similarly, the difference between Week 24 SRI-6 response proportion in HDA subjects in the primary analysis cohort, comparing the highest dose of M2951 to placebo, will be estimated, together with a two-sided 97.5% confidence interval. If the response proportion difference for both co-primary endpoints is sufficiently low, as defined in the IAP, consideration will be given to termination of the study, in which case all subjects will be discontinued from IMP and scheduled for a four week Safety Follow-Up Visit/End of Study Visit.

Descriptive statistics for the Week 24 SRI-4 response endpoint in all subjects in the primary analysis cohort, and for the Week 24 SRI-6 response endpoint in HDA subjects in the primary analysis cohort, will be presented by treatment group. A point estimate of the OR for the effect of treatment on Week 24 SRI-4 response, comparing each M2951 dose group to the placebo group, will be provided, together with a two-sided 97.5% CI. Similarly, a point estimate of the OR for the effect of treatment on Week 24 SRI-6 response, comparing each M2951 dose group to the placebo group among HDA subjects, will be provided, together with a two-sided 97.5% CI.

A test for a monotonic relationship, between ordered M2951 dose and Week 24 SRI-4 response OR, relative to placebo, among all subjects, will be performed as a supportive analysis. Similarly, a test for a monotonic relationship, between ordered M2951 dose and Week 24 SRI-6 response OR, relative to placebo, among HDA subjects, will be performed as a supportive analysis.

Primary Analysis

The primary analysis will occur only when primary analysis trigger event (Section 5.1) has occurred, the protocol violations are determined, and the database is locked.

Consistency Analysis

A separate analysis of treatment effect consistency between the non-Japan and Japan regions, may be performed if the Japan cohort enrollment is too slow for the consistency evaluation to take place at the time of the primary analysis. This analysis will occur only when the consistency analysis trigger event (Section 5.1) has occurred, the protocol violations are determined, and the database is locked.

Final Analysis

The final analysis will occur only when the last subject completes all study parts (including the LTE and Safety Follow-Up Visits) or discontinues prematurely, the protocol violations are determined, and the database is locked.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the study at the site and will ensure that the study is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, as well as with the ICH Note for Guidance on GCP (ICH Topic E6), and any other applicable regulations. The Investigator must ensure that only subjects who have given informed consent are included in the study. For Japan only - the Investigator is also responsible for the standards stipulated in Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Act in Japan; and “Ministerial Ordinance on Good Clinical Practice for Drugs” (GCP) in Japan.

According to United States Code of Federal Regulations Part 54.2 (e), for studies conducted in any country that could result in a product submission to the United States Food and Drug Administration for marketing approval and could contribute significantly to the demonstration of

efficacy and safety of an IMP (which are considered "covered clinical trials" by the FDA), the Investigator and all subinvestigators are obliged to disclose any financial interest which they, their spouses or their dependent children may have in the Sponsor or the Sponsor's product under study. This information is required during the study and for 12 months following completion of the study. This study is being conducted under a US Investigational New Drug (IND), therefore all investigational sites must complete an FDA Form 1572.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation in the study is his/her written informed consent. The subject's written informed consent to participate in the study must be given before any study-related activities are carried out. In Japan when a subject is < 20 years of age, the written informed consent must be obtained from the subject's parent or guardian in addition to the subject's voluntary written consent. The ICF must be approved by the IEC/IRB and regulatory authorities (in some countries) before it is provided to the subject.

Adequate information must therefore be given to the subject by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations). A subject information sheet in the local language and prepared in accordance with the Note for Guidance on GCP (ICH Topic E6, 1996) will be provided by the Sponsor for the purpose of obtaining informed consent. In Japan, a subject information sheet in the local language and prepared in accordance with Japan's GCP and the Note for Guidance on GCP (ICH Topic E6, 1996) will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or his/her designate will inform the subject verbally of all pertinent aspects of the study, including potential CCI testing (see Section 9.3). The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

Depending on national regulations, a person other than the Investigator may inform the subject and sign the ICF, as above.

Where the information is provided by the Investigator, the ICF must be signed and personally dated by the subject and the Investigator. In Japan, where the information is provided by the Investigator, the ICF must be signed and personally dated by the subject and/or the subject's legal representative as applicable, and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived by the Investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information sheet and ICF should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the subject information sheet and any other written information to be provided to the subjects and submit them to the IEC/IRB for review and favorable opinion. Using the approved revised subject information sheet and other written information, The Investigator will explain the changes to the previous version to each study subject and obtain new written consent for continued participation in the study. In Japan, the Investigator will explain the changes to the

previous version to each study subject and/or the subject's legal representative as applicable and obtain new written consent for continued participation in the study. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

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9.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the study as well as in the clinical trial database.

The subject's data collected in the study will be stored under this number. Only the Investigator will be able to link the subject's study data to the subject via an identification list kept at the site. The subject's original medical data that are reviewed at the site during source data verification by the monitor, audits and Health Authority inspections will be kept strictly confidential.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

Confidentiality of information relating to the CCI sample testing will be protected to the extent permitted by law. To protect against the risk of loss of confidentiality, all DNA samples will be marked with a code number only and will not be identified by subject name. Upon receipt at the analytical laboratory, the samples are recoded with a specific code CCI that is different from the subject code number. The data generated with these samples will also be tracked with the CCI. Only authorized personnel will have access to this code and to the key linking both codes. The key will be maintained in a restricted location. The results obtained from the CCI samples in this study are for research purposes only. The results of the tests conducted with the CCI samples will not be made available to the subject, members of their family, their personal physician, or other third parties, except as specified as follows.

Unless required by law or regulatory authorities for the purpose of verifying information obtained from this study, only the Sponsor's authorized personnel and agents will have access to the confidential genetic data. The results and other information from the CCI tests study may be submitted to the regulatory authorities and governmental agencies in countries where the IMP may be considered for approval; however, the subject will be identified by subject and study number only. The subject will not be identified in any reports or publications resulting from this study.

By default, results from genotyping will only be accessible to the Sponsor's authorized personnel and agents and be handled without disclosure of subject identification. However, upon written request by the subject, the results from genotyping will be made available to the subject, if permitted by local law and regulations. If required by law or regulatory authorities for the purpose of verifying information obtained from this study, only the Sponsor's authorized personnel and

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9.4 Emergency Medical Support and Subject Card

Subjects enrolled in this clinical study will be provided with Emergency Medical Support cards during their study participation, which will be furnished by the Sponsor. The Emergency Medical Support card is based on the need to provide clinical study subjects with a way of identifying themselves as participating in a clinical study, and subsequently to give health care providers access to the information about this participation that may be needed to determine the course of the subject's medical treatment.

This service is designed to provide information to health care providers who are not part of the clinical study; and this may include the possibility of emergency unblinding if needed, in case of blinded studies.

Clinical study Investigators, who are already aware of the CTP and treatment, have other means of accessing the necessary medical information for the management of emergencies occurring in their subjects.

The first point of contact for all emergencies will be the clinical study Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, she or he will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard processes established for the Investigators.

In cases where the Investigator is not available, Merck Serono/EMD Serono provides the appropriate means to contact a CRO/Sponsor physician. This includes the provision of a 24 hour contact number at a call center, whereby the health care providers will be given access to the appropriate CRO/Sponsor physician. The CRO/Sponsor physician will assist the health care provider in medical emergencies by providing information relating to the study and IMP. The CRO/Sponsor physician is not responsible or required for potential emergency unblinding, but should be notified as per Section 6.11 if emergency unblinding is to or has occurred, and may provide information if requested regarding the study and IMP.

9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage will be provided for each country participating to the study. Insurance conditions shall meet good local standards, as applicable.

In Japan, the Sponsor is entirely responsible for AEs that are associated with this study and impair the health of the subjects, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the study site, and/or the subject. The Sponsor will provide insurance to fulfill this responsibility.

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the study at a given site, the CTP will be submitted together with its associated documents to the responsible IEC/IRB for its favorable opinion/approval. The written favorable opinion/approval of the IEC/IRB will be filed in the Investigator Site File, and a copy will be filed in the Trial Master File.

The study must not start at a site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC/IRB. The IEC/IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the study, the CTP version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the clinical study will also be submitted to the concerned IEC/IRB, before implementation in case of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC/IRB during the course of the study in accordance with national regulations and requirements.

In Japan, the person installing an IEC/IRB must retain all records, including documents that relate to the clinical study for the required period in accordance with Japan's GCP.

9.7 Health Authorities

The CTP and any applicable documentation (eg, IMP Dossier, Subject Information and ICF) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

10 Trial Management

10.1 Case Report Form Handling

Refer to the Manual of Procedures for eCRF handling guidelines.

The main purpose of the eCRF is to obtain data required by the CTP in a complete, accurate, legible and timely. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee will be responsible for entering study data in a timely manner in the eCRF provided by the CRO's Data Management Group and follow the data standards of the Sponsor. It is the Investigator's responsibility to ensure the accuracy of the data entered in the eCRFs. For subject-reported outcome data such as QoL and pain assessments, ePRO may be used.

The data will be entered in to a validated database (InForm version 5.5). The CRO's Data Management Group will be responsible for data processing, in accordance with data management procedures agreed upon between the Sponsor and CRO. Database lock will occur once quality control procedure, and quality assurance procedures (if applicable) have been completed. Portable

document format files of the eCRFs will be provided to the Investigators at the completion of the study.

10.2 Source Data and Subject Files

The Investigator (or in Japan the head of study site) must keep a subject file (medical file, original medical records) on paper or electronically for every subject included in the study. This file will contain the available demographic and medical information for the subject, and should be as complete as possible. In particular, the following data should be available in this file:

- Subject's full name,
- Date of birth,
- Sex,
- Height,
- Weight,
- Race (as self-identified, in jurisdictions where permissible),
- Medical history and concomitant diseases,
- Prior and concomitant therapies (including changes during the study),
- Trial identification,
- Date of subject's inclusion into the study (i.e., date of giving informed consent),
- Subject number in the study,
- Dates of the subject's visits to the site,
- Any medical examinations and clinical findings predefined in the CTP,
- All AEs observed in the subject,
- Date of subject's end of study, and
- Date of and reason for early withdrawal of the subject from the study or from IMP, if applicable.

It must be possible to identify each subject by using this subject file.

Additionally, any other documents containing source data must be filed. This includes original printouts of data recorded or generated by automated instruments, ECG recordings, and laboratory value listings. Such documents must bear at least the subject number and the date when the procedure was performed. Information should be printed by the instrument used to perform the assessment or measurement, if possible. Information that cannot be printed by an automated instrument will be entered manually. Medical evaluation of such records should be documented as necessary and the documentation signed and dated by the Investigator.

10.3 Investigator Site File and Archiving

Upon initiation of the study, the Investigator will be provided with an Investigator Site File containing all necessary study documents, which will be completed throughout the study and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the study, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the study. The documents to be archived include the Subject Identification List and the signed subject Informed Consent Forms. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by GCP the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

In Japan, the head of the study site must retain all records, including documents and data, which relate to the clinical study in accordance with GCP. The head of the study site must retain the records at the site (hospital, research institute, or practice) for the longest possible time permitted by Japan's GCP, and/or as per ICH GCP guidelines, whichever is longer. In any case, the head of the study site should ensure that no destruction of medical records is performed without the written approval of the Sponsor

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This study will be monitored in accordance with the ICH Note for Guidance on GCP (ICH Topic E6, 1996), and any other applicable regulations. The site Monitor will perform visits to the study site at regular intervals.

The CTP, each step of the data capture procedure, and the handling of the data, including the final CSR, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all study documents and other materials at the site, including the Investigator Site File, the completed eCRFs, all IMP and IMP accountability records, and the original medical records or files for each subject.

10.5 Changes to the Clinical Trial Protocol

Changes to the CTP will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations.

Any amendment that could have an impact on the subject's agreement to participate in the study requires the subject's informed consent prior to implementation (see Section 9.2).

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the study, a CSR will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3 Publication.

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10.6.2 Publication

The first publication will include the results of the analysis of the primary endpoint and will include data from all study sites.

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require review by the Sponsor.

The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights.

Posting of data on applicable databases is planned and will occur 12 months after the last clinic visit of the final study subject or another appropriate date to meet applicable requirements.

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12 Appendices

Appendix I: Contraceptive Guidance and Woman of Childbearing Potential

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

1. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

2. Premenarchal

3. Postmenopausal female

- Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, an FSH will be drawn at Screening.
- Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraceptive Guidance

Highly Effective Contraceptive Methods That Are User Dependent
Failure rate of <1% per year when used consistently and correctly[a].

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]
  • oral
  • intravaginal[c]
  • transdermal[c]

• Progestogen-only hormonal contraception associated with inhibition of ovulation[b]
  • oral
  • injectable[c]

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b,c] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
• Vasectomized partner (A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used).
• Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant).
Barrier Methods
• Male or female condom with or without spermicide[d] • Cap, diaphragm, or sponge with spermicide[c]
a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 90 days after the last dose of study treatment c. Not approved in Japan. d. For Japan only – the only approved barrier method is male condom with spermicide.

Appendix II: Systemic Lupus International Collaborating Clinics Criteria for Systemic Lupus Erythematosus

The SLICC classification criteria (Petri 2012) require four criteria to be present, including at least one clinical criterion be present and one immunologic criterion be present; serially or simultaneously, during any period of observation; for classification of SLE. Alternatively, if biopsy proven nephritis consistent with lupus (lupus nephritis) is present, along with positive ANA and/or positive anti-dsDNA, SLE may be classified.

Clinical Criteria Used in the SLICC Classification Criteria

1. Acute cutaneous lupus

   including

   - lupus malar rash (do not count if malar discoid)
   - bullous lupus
   - toxic epidermal necrolysis variant of SL
   - maculopapular lupus rash
   - photosensitive lupus rash *in the absence of dermatomyositis*
   - or subacute cutaneous lupus

   (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)

2. Chronic cutaneous lupus

   including

   - classical discoid rash
     - localized (above the neck)
     - generalized (above and below the neck)
   - hypertrophic (verrucous) lupus
   - lupus panniculitis (profundus)
   - mucosal lupus
   - lupus erythematosus tumidus
   - chilblains lupus
   - discoid lupus/lichen planus overlap

3. Oral ulcers:

   - palate
   - buccal
   - tongue
   - or nasal ulcers

   in the absence of other causes, such as vasculitis, Behcets, infection (herpes), inflammatory bowel disease, reactive arthritis, and acidic foods

4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs)

   in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia

5. Synovitis involving two or more joints, characterized by swelling or effusion or tenderness in two or more joints and 30 minutes of more of morning stiffness.
6. Serositis

   Typical pleurisy for more than one day

   or pericardial effusion

   or pericardial rub

   or pericarditis by ECG

   in the absence of other causes, such as infection, uremia, and Dressler's pericarditis
7. Renal

   Urine protein/creatinine (or 24 hour urine protein) representing 500 mg of protein/24 hour

   or red blood cell casts
8. Neurologic

   seizures

   psychosis

   mononeuritis multiplex

   in the absence of other known causes such as primary vasculitis

   myelitis

   Peripheral or cranial neuropathy

   in the absence of other known causes such as primary vasculitis, infection, and diabetes millitus

   Acute confusional state

   in the absence of other known causes, including toxic-metabolic, uremia, drugs
9. Hemolytic anemia
10. Leukopenia (< 4000/mm^3 at least once)

    in the absence of other causes such as Felty's, drugs, and portal hypertension

    or

    Lymphopenia (< 1000/mm^3 at least once)

    in the absence of other known causes such as corticosteroids, drugs, and infection
11. Thrombocytopenia (< 100,00/mm^3 at least once)

    in the absence of other known causes such as drugs, portal hypertension, and TTP

Immunological Criteria Used in the SLICC Classification Criteria

1. ANA above laboratory reference range
2. Anti-dsDNA above laboratory reference range, except ELISA: twice above laboratory reference range
3. Anti-Sm
4. Antiphospholipid antibody

   Any of the following:

   lupus anticoagulant

   false-positive RPR

   medium or high titer anticardiolipin (IgA, IgG or IgM)

   anti-β_2 glycoprotein I (IgA, IgG or IgM)

5. Low complement
   - low C3
   - low C4
   - low CH50
6. Direct Coombs test *in the absence of hemolytic anemia*

Criteria are cumulative and need not be present concurrently (Petri 2012).

ANA = Antinuclear Antibody(ies), Anti-dsDNA = Anti-Double-Stranded Deoxyribonucleic Acid, Anti-Sm = Anti-Smith Antibody, ECG = Electrocardiogram, ELISA = Enzyme-Linked Immunosorbent Assay, IgA = Immunoglobulin A, IgG = Immunoglobulin G, IgM = Immunoglobulin M, RPR = Rapid Plasma Reagin, SLICC = Systemic Lupus International Collaborating Clinics, SL = Systemic Lupus, TTP = Thrombotic Thrombocytopenic Purpura.

Appendix III: Revised American College of Rheumatology Criteria for Systemic Lupus Erythematosus

For the purpose of identifying subjects in clinical studies, a person shall be said to have systemic lupus erythematosus if any four or more of the 11 criteria are present, serially or simultaneously, during any interval of observation (Hochberg 1997, Tan 1982).

Criterion	Definition
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid Rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral Ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or Pericarditis	1. Pleuritis: convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion or 2. Pericarditis: documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal Disorder	1. Persistent proteinuria: > 0.5 g per day or > than 3+ if quantitation not performed or 2. Cellular casts: may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic Disorder	1. Seizures: in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance or 2. Psychosis: in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic Disorder	1. Hemolytic anemia with reticulocytosis or 2. Leukopenia: < 4,000/mm^3 on ≥ two occasions or 3. Lymphopenia: < 1,500/mm^3 on ≥ two occasions or 4. Thrombocytopenia: < 100,000/mm^3 in the absence of offending drugs

Criterion	Definition
10. Immunologic Disorder	1. Anti-DNA: antibody to native DNA in abnormal titer or 2. Anti-Sm: presence of antibody to Sm nuclear antigen or 3. Positive finding of antiphospholipid antibodies based <u>any</u> of the following: 1. an abnormal serum level of IgG or IgM anticardiolipin antibodies 2. a positive test result for SLE anticoagulant using a standard method, or 3. a false positive serologic test result for syphilis known to be positive for at least six months and confirmed by Treponema pallidum immobilization or fluorescent Treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

Appendix IV: Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title:	A Phase II, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study To Evaluate the Safety and Efficacy of M2951 in Subjects with Systemic Lupus Erythematosus (SLE)
IND Number:	CCI [redacted]
EudraCT Number:	2016-002950-19
Clinical Trial Protocol Date / Version:	22 May 2018 / Version 7.0.

Protocol Lead:

I approve the design of the clinical trial:

PPD [redacted]

Signature

PPD [redacted]

Date of Signature

Name, academic degree:	PPD [redacted]
Function / Title:	PPD [redacted] Medical Responsible
Institution:	EMD Serono Research & Development Institute
Address:	45A Middlesex Turnpike, Billerica, MA, 01821, USA
Telephone number:	PPD [redacted]
E-mail address:	PPD [redacted]

Signature Page – Coordinating Investigator

Trial Title	A Phase II, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study To Evaluate the Safety and Efficacy of M2951 in Subjects with Systemic Lupus Erythematosus (SLE)
IND Number	CCI [redacted]
EudraCT Number	2016-002950-19
Clinical Trial Protocol Date / Version	22 May 2018 / Version 7.0.

I approve the design of the clinical trial and I unders PPD onduct the trial according to the clinical trial protocol, any approved protoc , International Council for Harmonisation Good Clinical Practice (Topic E pplicable Health Authority requirements and national laws.

PPD PPD

Signature Date of Signature

Name, academic degree: PPD

Function / Title: Coordinating Investigator

Institution: PPD

Address:

Telephone number: PPD

E-mail address: PPD

Signature Page – Principal Investigator

Trial Title	A Phase II, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study To Evaluate the Safety and Efficacy of M2951 in Subjects with Systemic Lupus Erythematosus (SLE)
IND Number	CCI [redacted]
EudraCT Number	2016-002950-19
Clinical Trial Protocol Date / Version	22 May 2018 / Version 7.0.
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also affirm that I understand that Health Authorities may require the Sponsors of clinical trials to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

Sponsor Responsible Persons Not Named on the Cover Page

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	EMD Serono Research & Development Institute
Address:	45A Middlesex Turnpike, Billerica, MA, 01821, USA
Telephone number:	PPD

Name, academic degree:	PPD
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Appendix V: Protocol Amendments and List of Changes

Table of Amendments

Actual Amendment Number	Substantial (Y/N)	Date	Region or Country	Included in the current document (Y/N)	Version
Local Amendment 1	N	11 January 2017	Taiwan	Y	Not applicable
Global Amendment 1	Y	08 February 2017	Global	Y	2.0
Local Amendment 2	N	03 April 2017	Peru	Y	Not applicable
Global Amendment 3	Y	14 July 2017	Global	Y	3.0
Local Amendment 3	Y	21 July 2017	US	N	3.1
Local Amendment 4	Y	17 August 2017	Japan	N	3.2
Global Amendment 7	Y	31 August 2017	Global	Y	4.0
Local Amendment 8	Y	10 September 2017	US	Y	4.1
Local Amendment 9	Y	14 September 2017	Japan	Y	4.2
Local Amendment 10	Y	18 October 2017	Japan	Y	4.3
Local Amendment 11	N	02 November 2017	Germany, Italy, Poland, Romania	Y	4.4
Global Amendment 12	Y	20 November 2017	Global	Y	5.0
Global Amendment 13	Y	05 January 2018	Global	Y	6.0
Global Amendment 14	Y	22 May 2018	Global	Y	7.0

Amendment 14

Protocol Version 6.0 (05 January 2018) was the global amended protocol. The revised global amended protocol (Version 7.0) was issued on 22 May 2018.

Rationale

The major reason for this amendment was the addition of a LTE. In addition, minor changes throughout the document were added to clarify or correct minor errors.

The key changes for this global amended protocol are summarized below:

- A LTE was added into the study, including 2 new SoAs, and an additional study figure
- Table 7 (now Table 9) was modified for clarity on Day 1
- Stopping rules modified due to analysis of additional safety data
- Exclusion modified to permit low dose aspirin after medical review
- Administrative and Editorial changes: Minor edits for clarity and consistency that do not affect the substance of the protocol are not individually listed here, including the addition of the cross-references to the new SoA.

Comparison with Clinical Trial Protocol Version 6.0, 05 January 2018(Global Amendment No. 13)

Change	Section	Page	Previous Wording	New Wording	Rationale
Last subject out updated.	Synopsis	14	Last subject out: Q2, 2020	Last subject out: ~~Q2, 2020~~ **Q3, 2022**	The end of the study will be later due to the addition of the LTE.
Trial registry was updated.	Synopsis	14	-	**clinicaltrials.jp**	An additional registry was added as the study will soon be added to this registry.
An objective was added for the LTE.	Synopsis, 4.4 Open-label Long-Term Extension (LTE) Period Objectives	16, 39	-	Open-label Long-Term Extension (LTE) Period Objectives The objective of the LTE Period is: •To evaluate the long-term safety, efficacy, and HRQoL of M2951 at an initial dose of 50 mg twice daily or the eventual Phase III dose when decided for an additional two years.	The LTE was added into the study.
Methodology text updated to include LTE.	Synopsis	16	All subjects will take five tablets per day (three in the morning, two in the evening), in combinations of active and placebo tablets to maintain blinding of all subjects to dose.	**During the DBPC Treatment Period, a**~~A~~ll subjects will take five tablets per day (three in the morning, two in the evening), in combinations of active and placebo tablets to maintain blinding of all subjects to dose.	The LTE was added into the study.
Methodology text updated to include LTE.	Synopsis, 5.1 Overall Trial Design and Plan	16, 39	The study is composed of a Screening Period of four weeks, a DBPC Treatment Period of 52 weeks, and a Safety Follow Up Period of four weeks. An open label, long-term extension (LTE) study may be conducted under a separate protocol for those completing 52 weeks of treatment.	The study is composed of a Screening Period of four weeks, a DBPC Treatment Period of 52 weeks, **an open-label LTE Period of 104 weeks,** and a Safety Follow-Up Period of four weeks. ~~An open label, long-term extension (LTE) study may be conducted under a separate protocol for those completing 52 weeks of treatment.~~	The LTE was added into the study.
An additional secondary endpoint was added.	Synopsis, 8.3.2 Secondary Endpoints	17, 105	-	**o Lupus low disease activity state (LLDAS), defined as meeting all of the following (Franklyn 2016):** **- SLEDAI-2K ≤ 4** **- No activity in any major organ systems (renal, central nervous system, cardiopulmonary, vasculitis, fever)**	Added per Coordinating Investigator suggestion.

Change	Section	Page	Previous Wording	New Wording	Rationale
				- No new features of disease activity compared with the previous assessment **- Prednisone-equivalent ≤ 7.5 mg/day** **- Unchanged background immunosuppressive therapy**	
New endpoints were added for the LTE Period.	Synopsis, 8.3.4 Endpoints for Long-Term Extension Period	19, 107	-	**Endpoints for Long-Term Extension Period** **<u>LTE Safety:</u>** **•Nature, severity, and incidence of AEs, SAEs, vital signs, ECGs, absolute values and change from Baseline in serum total Ig levels (IgG, IgA, IgM) and total B cell counts, and clinical laboratory parameters.** **<u>LTE Efficacy:</u>** **•The following LTE efficacy endpoints will be analyzed at Week 24, Week 52, and Week 104:** **o Changes over time in SRI response** **o Changes over time in Low Disease Activity status (LLDAS, SLEDAI-2K ≤ 2, clinical SLEDAI-2K ≤ 2).** **o Changes over time in CLASI-A, CLASI-D, and SLICC/ACR Damage Index organ damage scores** **o Changes over time in disease activity as measured by the BILAG, SLEDAI-2K, and PGA** **o Change over time in prednisone-equivalent CS dose** **o Changes over time in HRQoL** **o Changes over time in autoantibodies and complement levels** **•Changes in HRU by visit, including but not limited to doctor/home/emergency visits, hospitalizations, paid assistance, and missed work** **•Time to first flare; flare-free status at Weeks 24, 52, and 104; and annualized flare rate, will be analyzed separately, each assessed with flare defined as:** **o BILAG A Severe flare** **o BILAG A or 2B Moderate to Severe flare** **o SLEDAI Flare Index (SFI) Severe flare.**	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
Repetitious text removed.	Synopsis, 5.1 Overall Trial Design and Plan	19, 40	(e.g., BILAG 2004 Disease Activity Index, SLEDAI-2K, PGA, and CLASI).	(e.g., BILAG 2004 ~~Disease Activity Index~~, SLEDAI-2K, PGA, and CLASI).	The text was repetitive and unnecessary.
Additional text related to the LTE was added.	Synopsis, 5.1 Overall Trial Design and Plan	19, 40	Subjects will receive the last dose of IMP at Week 52, which is the End of Treatment (EOT) for the study.	Subjects will receive the last dose of IMP at Week 52, which is the End of Treatment (EOT) for the study**, unless they enter the LTE Period**.	Clarification was added due to the addition of the LTE.
New text describing the LTE was added.	Synopsis	20	-	**Optional Open-Label Long-Term Extension Period** **Subjects who completed the 52-week DBPC Treatment period will be offered participation in the 104-week open-label, LTE Period of the study. The purpose of the LTE Period is to allow all the subjects with the opportunity to receive active treatment with M2951 and to collect long term safety and efficacy data. The Investigator should review the optional LTE Period with the subject prior to the DBPC Week 52 visit. Signed consent will be obtained prior to participation in the LTE Period. The DBPC Week 52/EOT Visit will be considered the LTE Day 1 Visit. The Safety Follow-Up Visit will be deferred until treatment is stopped in the LTE Period, due to either a subject's premature withdrawal/early termination from the LTE, termination of the study by the Sponsor, or completion of the LTE treatment period.** **In some cases, due to Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, regulatory-specific, or other administrative delays, a subject may experience a treatment gap between the IMP last dose received in the DBPC Period (Week 52/EOT visit) and the start of the LTE IMP treatment. Upon Principal Investigator (PI) request, these subjects may still be able to enroll in the LTE with approval from Merck/EMD Serono, on a case by case basis. If the day of rollover to the LTE occurs after the DBPC Week 56/EOS visit, all assessments**	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
				noted at the LTE Day 1 visit will need to be completed. For subjects that rollover after the Week 52/EOT visit but prior to their scheduled Week 56/EOS visit, concomitant medications and AEs will need to be reviewed and updated, and the PI will need to ensure that the subject remains eligible for the study. No other additional assessments other than dispensing of IMP will need to be completed.	
The description of the Safety Follow-Up Period was updated to include information on subjects going into the LTE.	Synopsis	20	Subjects will enter the Safety Follow Up Period directly from the DBPC Treatment Period after the Week 52/EOT Visit. The Safety Follow Up Visit is scheduled to occur 4 weeks after the last IMP dose. This includes subjects who stop the DBPC Treatment Period prematurely. The Safety Follow Up Visit is the End of Study Visit and is the last scheduled visit for subjects participating in this clinical study.	~~Subjects will enter the Safety Follow-Up Period directly from the DBPC Treatment Period after the Week 52/EOT Visit.~~ The Safety Follow-Up**/End of Study** Visit is scheduled ~~to occur 4~~ **four** weeks **(+ 5 days)** after **administration of study treatment.** ~~the last IMP dose. This includes~~ **For** subjects who **do not participate in** ~~stop~~ the ~~DBPC Treatment Period~~ **LTE Period,** ~~prematurely.~~ **t**~~T~~he Safety Follow-Up Visit **is scheduled four weeks (+ 5 days) after the last administration of study treatment in the DBPC Period. For subjects who participate in the LTE Period, the Safety Follow-Up Visit is delayed until four weeks (+ 5 days) after the last administration of study treatment in the LTE Period. Subjects who are approved to rollover into LTE Period after they entered, or completed, the DBPC Safety Follow-Up Period, may have two Safety Follow-Up Visits. Additional details of the Safety Follow-Up/ End of Study Visit are provided in the SOA**~~the End of Study Visit and is the last scheduled visit for subjects participating in this clinical study~~.	The LTE was added into the study.
Modification was made as 1 injectable CS is now permitted.	Synopsis	21	Restrictions and guidance for the use of OCS during the course of the study include prohibiting doses above 30 mg/day after Week 4 of the Treatment Period, prohibiting injectable CSs, limits on when change in dose of CS may occur, recommendations to decrease CS dose within parameters allowed by	Restrictions and guidance for the use of OCS during the course of the study include prohibiting doses above 30 mg/day after Week 4 of the Treatment Period, prohibiting injectable CSs **(outside limited exceptions)**, limits on when change in dose of CS may occur, recommendations to decrease CS dose within parameters allowed by the study, and limits on the use of CS during treatment of SLE flares.	One injectable CS is now permitted.

Change	Section	Page	Previous Wording	New Wording	Rationale
			the study, and limits on the use of CS during treatment of SLE flares.		
Dose was added for the LTE.	Synopsis	21	-	**Subjects who choose to participate in the LTE Period will receive open-label M2951 50 mg twice daily or the eventual Phase III dose when decided, taken orally for 104 weeks.**	The LTE was added into the study.
Length of LTE was added.	Synopsis	21	-	**The optional LTE Treatment Period is approximately 104 weeks in duration and will be offered to subjects after completion of the DBPC Period.**	The LTE was added into the study.
Additional analyses are described due to the addition of the LTE.	Synopsis	22-23	Two analyses are planned. A third analysis is possible depending on the enrollment rate of the Japanese subject cohort. The first analysis will be an interim futility analysis (IA). This IA will be based on Week 24 SRI-4 response among all subjects in the n = 432 cohort and Week 24 SRI-6 response among HDA subjects in the n = 432 cohort. The IA will be conducted when 100% of subjects enrolled, out of the planned enrollment of n = 432, reach Week 24 of treatment or prematurely discontinue from treatment. If enrollment is slower than expected, consideration will be given to conducting the interim futility analysis when the first 50% of the planned enrollment of n = 432 reach Week 24 of treatment, or prematurely discontinue from treatment. The second analysis is the primary analysis, based on Week 52 SRI-4 response among all subjects in the n = 432 cohort, and Week 52 SRI-6 response among HDA subjects in the n = 432 cohort, triggered when 100% of subjects enrolled, out of the planned enrollment of n = 432, complete safety follow up, or	**There will be at least two planned** ~~Two~~ analyses **in this study – the primary and final analyses** ~~are planned. A third analysis is possible~~ **There may be up to four planned analyses,** depending on ~~the enrollment rate of~~**whether** the ~~Japanese subject cohort.~~ **optional** ~~The first analysis will be an interim~~ futility **interim** analysis (IA) **is conducted, and whether the analysis for treatment effect consistency is coincident with the primary analysis, or is conducted after the primary analysis. If the futility IA is conducted, it**~~. This IA~~ will be based on Week 24 SRI-4 response among all subjects in the **primary analysis** ~~n = 432~~ cohort and Week 24 SRI-6 response among HDA subjects in the **primary analysis** ~~n = 432~~ cohort. The IA will be conducted when 100% of subjects ~~enrolled, out of the planned enrollment of n = 432,~~ **in the primary analysis cohort** reach Week 24 of treatment or prematurely discontinue from treatment. If enrollment is slower than expected, consideration will be given to conducting the interim futility analysis when the first 50% of the **primary analysis cohort** ~~planned enrollment of n = 432~~ reach Week 24 of treatment, or prematurely discontinue from treatment. ~~The second analysis~~ **The primary analysis cohort consists of the first 432 subjects randomized. However, if drop out for reasons unrelated to efficacy or safety** is **higher than expected, effectively reducing the power of the study, the IAP may prespecify that** the	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
			prematurely discontinue from study. The Japanese cohort may be fully, partially, or not included in this primary analysis, depending on the enrollment rate CCI [redacted] A third analysis may be scheduled if the Japanese cohort does not enroll in time to be included with the n = 432 subjects required for the primary analysis. If the Japanese cohort enrolls in time to be included, the evaluation of consistency with respect to ethnicity of Week 52 SRI-4 response can be performed at the time of the primary analysis. If the Japanese cohort enrolls slowly, then the primary analysis will occur without inclusion of the Japanese cohort, and a third analysis for evaluation of consistency will be triggered when 100% of enrolled Japanese subjects: •Complete Week 52 of treatment and safety follow-up, or	primary analysis **cohort will include all subjects randomized.** ~~,~~ **The primary analysis will be** based on Week 52 SRI-4 response among all subjects in the **primary analysis** ~~n = 432~~ cohort, and Week 52 SRI-6 response among HDA subjects in the **primary analysis** ~~n = 432~~ cohort**.** ~~,~~ **This analysis will be** triggered when 100% of subjects **in the primary analysis cohort**. ~~enrolled, out of the planned enrollment of n = 432,~~ **•Complete Week 52 of treatment and either enter the LTE or** complete **S**~~s~~afety **F**~~f~~ollow-**U**~~u~~p, or •**P**~~p~~rematurely discontinue from ~~study.~~ **treatment prior to Week 52 and complete Safety Follow-Up, or** **•Prematurely discontinue from study without Safety Follow-up.** The Japanese cohort may be fully, partially, or not included in this primary analysis, depending on the enrollment rate. CCI CCI ~~t~~**T**he Family-Wise type 1 error rate (FWER) due to the **co-primary endpoints and** multiple M2951 dose group comparisons versus placebo will be controlled at the ~~one~~**two**-sided α = 0.05CC CCI [redacted] **tree gatekeeping procedure. The four hypotheses associated with the comparisons involving the co-primary endpoints and the two highest dose groups will form the first family of hypotheses in the tree. This family will be tested via the truncated Hochberg procedure, with truncation fraction pre-specified in the IAP. The multiple-**testing procedure~~, in which the~~ CCI [redacted] for **the remainder of the tree, including the hypotheses associated with the comparisons involving the co-primary endpoints and the** lowest dose, CCI [redacted]	

Change	Section	Page	Previous Wording	New Wording	Rationale
			•Prematurely discontinue from treatment and complete safety follow up, or •Prematurely discontinue from study.	CCI [redacted] **group, and the key secondary endpoints and all dose groups, will be pre-specified in the IAP**. A **treatment effect consistency** ~~third~~ analysis may be scheduled if the Japanese cohort does not enroll in time to be included with the ~~n = 432 subjects required for the~~ primary analysis **cohort**. If the Japanese cohort enrolls in time to be included, the evaluation of consistency with respect to ethnicity of Week 52 SRI-4 response can be performed at the time of the primary analysis. If the Japanese cohort enrolls slowly, then the primary analysis will occur without inclusion of the Japanese cohort, and a **separate** ~~third analysis for evaluation of~~ consistency **analysis** will be triggered when 100% of enrolled Japanese subjects: •Complete Week 52 of treatment and **either enter LTE or complete** ~~and s~~**S**afety **F**~~f~~ollow-**U**~~u~~p, or •Prematurely discontinue from treatment **prior to Week 52** and complete **S**~~s~~afety **F**~~f~~ollow-~~-~~**U**~~u~~p, or •Prematurely discontinue from study **without Safety Follow-Up.** **The final analysis will be triggered when 100% of subjects enrolled:** **•Complete Week 104 of the LTE and the Safety Follow-Up, or** **•Complete Week 52 of treatment and the Safety Follow-Up (if they did not rollover into the LTE), or** **•Prematurely discontinue from treatment and complete Safety Follow-Up, or** **•Prematurely discontinue from study.** **The final analysis will be performed by** PPD **staff when the final analysis trigger condition has been met, protocol violations determined, and the database is locked for the final analysis**	

Change	Section	Page	Previous Wording	New Wording	Rationale
Updates were made to the analysis cohort.	Synopsis, 8.5.2 Analysis of Primary Endpoints	23, 110	**Analysis of Co-primary Efficacy Endpoints** The primary analysis of SRI-4 response at Week 52 among all subjects in the n = 432 cohort, and SRI-6 response at Week 52 among HDA subjects in the n = 432 cohort, will be an estimate of OR, together with associated two-sided 97.5% CI and p-value, comparing each M2951 dose group to placebo, based on a logistic model for the odds of a given SRI response in the appropriate population, with M2951 dose group or placebo group as a factor and adjustment for covariates based on randomization strata.	**Analysis of Co-primary Efficacy Endpoints** The primary analysis of SRI-4 response at Week 52 among all subjects in the **primary analysis** ~~n = 432~~ cohort, and SRI-6 response at Week 52 among HDA subjects in the ~~n = 432~~ **primary analysis** cohort, will be an estimate of OR, together with associated two sided 9~~57.5~~% CI and p-value **(testing null hypothesis H0: OR = 1.0)**, comparing each M2951 dose group to placebo, based on a logistic model for the odds of a given SRI response in the appropriate population, with M2951 dose group or placebo group as a factor and adjustment for covariates based on randomization strata.	Drop-out rates unrelated to efficacy or safety are higher than anticipated.
The analysis of the secondary endpoint was updated based on the addition of the LTE.	Synopsis	24	**Analysis of Key Secondary Endpoints** Time to first severe (BILAG A) flare during the Treatment Period will be modeled via a Cox regression model, with treatment group as a factor, and controlling for covariates defining randomization strata. A subject who discontinues treatment or completes treatment without experiencing severe flare will have his/her time to flare censored at the last time point at which flare could be assessed. SRI-4 response at Week 52 among serologically active subjects will be an estimate of OR, together with associated two-sided CI and p-value, comparing each M2951 dose group to placebo, based on a logistic model for the odds SRI-4 response in the serologically active population, with M2951 dose group or placebo group as a factor and	**Analysis of Key Secondary Endpoints** Time to first severe (BILAG A) flare during the Treatment Period ~~will be modeled~~ **in all subjects will be compared between M2951 and placebo via a stratified log rank test. The adjusted hazard ratio comparing M2951 to placebo will be estimated (together with 95% CI)** via a Cox regression model, with treatment group as a factor, and controlling for covariates defining randomization strata. A subject who discontinues treatment or completes treatment without experiencing severe flare will have his/her time to flare censored at the last time point at which flare could be assessed. **Kaplan-Meier estimates of probability of surviving free of severe (BILAG A) flare as a function of time on treatment will be provided for each treatment group.** **The analysis of** SRI-4 response at Week 52 among serologically active subjects will be an estimate of OR, together with associated ~~two-sided~~ **95%** CI and p-value, comparing each M2951 dose group to placebo, based on a logistic model for the odds **of** SRI-4 response in the serologically active population, with M2951 dose	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
			adjustment for covariates based on randomization strata. Descriptive statistics for SRI-4 response in the serologically active subgroup, will be provided for each treatment group by time point. **Analysis of Other Secondary Efficacy Endpoints** Binary endpoints will be modeled via logistic regression, time to event endpoints will be modeled via Cox regression, continuous endpoints measured longitudinally (i.e., HRQoL change from baseline) will be analyzed using Mixed effect Model for Repeated Measures (MMRM), and count endpoints (i.e., annualized flare rate) will be modeled via negative binomial regression, with treatment group as a factor, and adjusting for covariates defining randomization strata. Analysis of annualized flare rate will use observation time (in years) as an offset in the model. Change in a binary endpoint between two time points will be analyzed via McNemar's test. The effect of treatment on change in a binary endpoint will be analyzed via logistic regression, with treatment group, time point, and interaction as predictors, and adjusting for covariates defining randomization strata. All tests of efficacy will be conducted at a two-sided α level of 0.05, with p-values considered nominal unless generated as part of a hierarchical testing strategy as described in the Statistical Analysis Plan (SAP). P values and the 95%	group or placebo group as a factor and adjustment for covariates based on randomization strata. **A test for trend in dose-response, using the same logistic model, will be reported as a supportive analysis.** Descriptive statistics for SRI-4 response in the serologically active subgroup, will be provided for each treatment group by time point. **Analysis of Other Secondary Efficacy Endpoints** Binary endpoints will be modeled via logistic regression, time to event endpoints will be modeled via Cox regression **and tested via stratified log rank test**, continuous endpoints measured longitudinally (i.e., HRQoL change from baseline) will be analyzed using Mixed effect Model for Repeated Measures (MMRM), and count endpoints (i.e., annualized flare rate) will be modeled via negative binomial regression, with treatment group as a factor, and adjusting for covariates defining randomization strata. Analysis of annualized flare rate will use **the log of** observation time (in years) as an offset in the model. Change in a binary endpoint between two time points will be analyzed via McNemar's test. The effect of treatment on change in a binary endpoint will be analyzed via logistic regression, with treatment group, time point, and interaction as predictors, and adjusting for covariates defining randomization strata. All tests of efficacy will be conducted at a two-sided α level of 0.05, with p-values considered nominal unless generated as part of ~~a hierarchical~~ **the tree gatekeeping multiple** testing strategy as described in the ~~Statistical~~ **Integrated** Analysis Plan (I~~S~~AP). P values and the 95% CIs will be presented where applicable.	

Change	Section	Page	Previous Wording	New Wording	Rationale
			CIs will be presented where applicable.		
The Sponsor designees were updated to remove repetition.	2 Sponsor, Investigators, and Trial Administrative Structure	31	The Sponsor of this clinical study is EMD Serono Research & Development Institute, Inc. (EMD Serono R&D), Billerica, MA, in the USA, and Merck KGaA, Darmstadt, Germany, in rest of the world (RoW), except in Japan. In Japan, Merck Serono Co., Ltd. (Affiliate of Merck KGaA, Darmstadt, Germany) is the Sponsor of this clinical study.	The Sponsor of this clinical study is EMD Serono Research & Development Institute, Inc. (EMD Serono R&D), Billerica, MA, in the USA, ~~and Merck KGaA, Darmstadt, Germany, in rest of the world (RoW), except in Japan. In Japan,~~ Merck Serono Co., Ltd. (Affiliate of Merck KGaA, Darmstadt, Germany) ~~is the Sponsor of this clinical study~~ **in Japan; and Merck KGaA, Darmstadt, Germany, in the rest of the world (RoW)**.	To remove repetition.
PPD was updated to PPD Services.	2 Sponsor, Investigators, and Trial Administrative Structure	31	In Japan, PPD , will undertake the operational aspects. Details of such structures and associated procedures will be defined in a separate Integrated Project Management Plan (IPMP).	In Japan, PPD , will undertake the operational aspects. Details of such structures and associated procedures will be defined in a separate Integrated Project Management Plan (IPMP).	Updated to the rebranding of PPD
Slight modification in wording on interim analysis.	2.2 Trial Coordination/Monitoring	32	An independent data monitoring committee (IDMC) will be established to assess safety and tolerability of IMP during the conduct of the study and review the interim analysis (IA).	An independent data monitoring committee (IDMC) will be established to assess safety and tolerability of IMP during the conduct of the study and review the interim analysis (IA) **if completed**.	To allow flexibility in the analysis as other additional analyses will now be done due to the addition of the LTE.
A SMC was added for the LTE Period.	2.2 Trial Coordination/Monitoring	32	-	**The IDMC will monitor the study until the last subject has either entered the LTE or completed the Safety Follow-Up Visit following the DBPC Treatment Period for subjects that did not rollover into the LTE, whichever occurs last. At that time, study monitoring may transition to an internal Safety Monitoring Committee (SMC). The SMC will review all available safety data on a regular basis during the open-label LTE. The SMC consists of Sponsor representatives (including, but not limited to, the Medical Responsible, the Drug Safety Product Lead, the biostatistician), the Medical Monitor from the CRO, and the Coordinating Investigator.**	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
				The full membership, mandate, and processes of the SMC will be detailed in the SMC charter.	
Benefit Risk text was updated.	3.1 Benefit and Risk	36	A signal of asymptomatic increases in transaminases has emerged from the ongoing study MS200527-0086 among subjects randomized to evobrutinib or placebo.	A signal of asymptomatic increases in transaminases has emerged from the ongoing study MS200527-0086 ~~among~~**in multiple sclerosis and in MS200527-0018, affecting approximately 5% of** subjects randomized to evobrutinib or placebo **in both studies. Thus far, the elevations have been asymptomatic and reversible on discontinuation of IMP. There have been no Hy's Law cases.**	More recent information was available.
A SMC was added for the LTE.	3.1 Benefit and Risk	37	-	**During the LTE, an internal SMC may review safety data on a regular basis during the LTE in lieu of the IDMC.**	The LTE was added into the study.
A SMC was added for the LTE Period.	3.1 Benefit and Risk	37	CCI [redacted]		More recent information was available.

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				is continually reviewed and modified to incorporate input from the IDMCs.	
Clarification was added on the treatment for those in the LTE.	5.1 Overall Trial Design and Plan	39	Therefore, the total enrollment will range from n = 432 to 468 (n = 108 to 117 subjects per group). This trial will be conducted at approximately 180 sites across 20 countries.	Therefore, the total enrollment will range from n = 432 to 468 (n = 108 to 117 subjects per group). CCI [redacted] This trial will be conducted at approximately 180 sites across 20 countries.	The LTE was added into the study.
Text on the LTE was changed from being a potential separate protocol to being integrated into this study.	5.1 Overall Trial Design and Plan	40	**Long-Term Extension Study** Subjects who complete the 52-week DBPC period may be offered participation in an open label, long-term extension (LTE) study. Should the Sponsor decide to conduct the LTE study, it will be conducted under a separate protocol. Subjects continuing in the LTE study will receive the first dose of LTE study at Week 52 following the completion of all Week 52 procedures. They will not attend the Safety Follow Up Visit until treatment is stopped in the LTE study, due to either a subject's premature withdrawal/early termination from the LTE study, termination of the LTE study by the Sponsor, or completion of the LTE treatment period. It is expected the placebo group of this MS200527-0018 study will be switched over to M2951 active treatment, at a dose to be identified in the IA of this study. Subjects in the M2951 treatment groups will remain on their original respective doses of M2951 when enrolled in the LTE study. Subjects are recommended to have signed the informed consent for the LTE	**Optional Open-Label Long-Term Extension ~~Study~~ Period** Subjects who complete**d** the 52-week DBPC **Treatment** period **will** ~~may~~ be offered participation in **the** ~~an~~ **104-week** open-label, **LTE Period of the study. The purpose of the LTE Period is to allow all the subjects with the opportunity to receive active treatment with M2951 and to collect** long-term ~~extension (LTE) study. Should the Sponsor decide to conduct the LTE study, it~~ **safety and efficacy data. The Investigator should review the optional LTE Period with the subject prior to the DBPC Week 52 visit. Signed consent** will be **obtained prior to participation** ~~conducted under a separate protocol. Subjects continuing~~ in the LTE **Period** ~~study will receive the first dose of LTE study at~~ **The DBPC**–Week 52 ~~following the completion of all Week 52 procedures. They~~ **EOT Visit** will ~~not attend~~ **be considered the LTE Day 1 Visit. T**~~t~~he Safety Follow–Up Visit **will be deferred** until treatment is stopped in the LTE ~~study~~**Period**, due to either a subject's premature withdrawal/early termination from the LTE ~~study~~, termination of the LTE study by the Sponsor, or completion of the LTE treatment period. ~~It is expected the placebo group of this MS200527-0018 study will be switched over to M2951 active treatment, at a dose to be identified in the IA of this study. Subjects in the M2951 treatment groups will remain on their original respective doses of M2951 when enrolled in the LTE study.~~	The LTE was added into the study.

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			study at least four weeks prior to enrollment.	~~Subjects are recommended to have signed the informed consent for the LTE study at least four weeks prior to enrollment.~~ **In some cases, due to Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, regulatory-specific, or other administrative delays, a subject may experience a treatment gap between the IMP last dose received in the DBPC Period (Week 52/EOT visit) and the start of the LTE IMP treatment. Upon Principal Investigator (PI) request, these subjects may still be able to enroll in the LTE with approval from Merck/EMD Serono, on a case by case basis. If the day of rollover to the LTE occurs after the DBPC Week 56/EOS visit, all assessments noted at the LTE Day 1 visit will need to be completed. For subjects that rollover after the Week 52/EOT visit but prior to their scheduled Week 56/EOS visit, concomitant medications and AEs will need to be reviewed and updated, and the PI will need to ensure that the subject remains eligible for the study. No other additional assessments other than dispensing of IMP will need to be completed.**	
Clarification was added on the Safety Follow-Ups to account for the addition of the LTE.	5.1 Overall Trial Design and Plan	40-41	Subjects will enter the Safety Follow Up Period directly from the DBPC Treatment Period after the Week 52/EOT Visit. The Safety Follow Up Visit is scheduled to occur four weeks after the last IMP dose. This includes subjects who stop the DBPC Treatment Period prematurely. The Safety Follow Up Visit is the End of Study Visit and is the last scheduled visit for subjects participating in this clinical trial. Subjects participating in the LTE study, if conducted, will not attend the Safety Follow Up Visit, and will instead enter the LTE study.	~~Subjects will enter the Safety Follow Up Period directly from the DBPC Treatment Period after the Week 52/EOT Visit. The Safety Follow Up Visit is scheduled to occur four weeks after the last IMP dose. This includes subjects who stop the DBPC Treatment Period prematurely. The Safety Follow Up Visit is the End of Study Visit and is the last scheduled visit for subjects participating in this clinical trial. Subjects participating in the LTE study, if conducted, will not attend the Safety Follow Up Visit, and will instead enter the LTE study.~~ **The Safety Follow-Up/End of Study Visit is scheduled four weeks (+ 5 days) after the last administration of study treatment. For subjects who do not participate in the LTE Period, the Safety Follow-Up Visit is**	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
				scheduled four weeks (+ 5 days) after the last administration of study treatment in the DBPC Period. For subjects who participate in the LTE Period, the Safety Follow-Up Visit is delayed until four weeks (+ 5 days) after the last administration of study treatment in the LTE Period. Subjects who are approved to rollover into LTE Period after they entered, or completed, the DBPC Safety Follow-Up Period, may have two Safety Follow-Up Visits. Additional details of the Safety Follow-Up/ End of Study Visit are provided in the SOA.	
Additional analyses are described due to the addition of the LTE.	5.1 Overall Trial Design and Plan	41-42	Two analyses are planned. A third analysis is possible depending on the enrollment rate of the Japanese subject cohort. The first analysis will be an interim futility analysis (IA). This IA will be based on Week 24 SRI-4 response among all subjects and Week 24 SRI-6 response among HDA subjects, and conducted when 100% of subjects enrolled, out of the planned enrollment, reach Week 24 of treatment or prematurely discontinue from treatment. If the response proportion difference for both co-primary endpoints is sufficiently low at Week 24, as defined in the Statistical Analysis Plan (SAP), consideration will be given to termination of the study. If enrollment is slower than expected, consideration will be given to conducting the interim futility analysis when the first 50% of the planned enrollment reach Week 24 of treatment, or prematurely discontinue from treatment. An IDMC will monitor safety and tolerability as well as review the data from the IA. The IA will be prepared	~~Two analyses are planned. A third analysis is possible depending on the enrollment rate of the Japanese subject cohort.~~ ~~The first analysis will be an interim futility analysis (IA). This IA~~ **There will be at least two planned analyses in this study – the primary and final analyses. There may be up to four planned analyses, depending on whether the optional futility interim analysis (IA) is conducted, and whether the analysis for treatment effect consistency is coincident with the primary analysis, or is conducted after the primary analysis.** **If the futility IA is conducted, it** will be based on Week 24 SRI-4 response among all subjects **in the primary analysis cohort** and Week 24 SRI-6 response among HDA subjects **In the primary analysis cohort. The IA will be**~~, and~~ conducted when 100% of subjects ~~enrolled, out of~~ **in** the ~~planned enrollment~~ **primary analysis cohort**, reach Week 24 of treatment or prematurely discontinue from treatment **prior to Week 24**. If the response proportion difference for both co-primary endpoints is sufficiently low at Week 24, as defined in the **Integrated** ~~Statistical~~ Analysis Plan (~~SAP~~**IAP**), consideration will be given to termination of the study. If enrollment is slower than expected, consideration will be given to conducting the interim futility analysis when the first 50% of the **primary analysis cohort** ~~planned~~	The LTE was added into the study.

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			by a team independent of the study teams (Sponsor and PPD). The second analysis is the primary analysis, based on Week 52 SRI-4 response among all subjects in the n = 432 cohort, and Week 52 SRI-6 response among HDA subjects in the n = 432 cohort. This analysis is triggered when 100% of subjects enrolled: •Complete Week 52 of treatment and safety follow-up, or •Prematurely discontinue from treatment and complete safety follow up, or •Prematurely discontinue from study. The Japanese cohort may be fully, partially, or not included in this primary analysis, depending on the enrollment rate. The primary analysis will be performed by PPD staff when the primary analysis trigger condition has been met, protocol violations determined, and the database is locked for the primary analysis. CCI [redacted]	~~enrollment~~ reach Week 24 of treatment, or prematurely discontinue from treatment. An IDMC will monitor safety and tolerability as well as review the data from the IA. The IA will be prepared by a team independent of the study teams (Sponsor and PPD). The ~~second analysis~~ **primary analysis cohort consists of the first 432 subjects randomized. However, if drop-out for reasons unrelated to efficacy or safety** is **higher than expected, effectively reducing the power of the study, the IAP may prespecify that** the primary analysis **cohort may include all subjects randomized**. **The primary analysis will be** ~~,~~ based on Week 52 SRI-4 response among all subjects in the ~~n = 432~~ **primary analysis** cohort, and Week 52 SRI-6 response among HDA subjects in the ~~n = 432~~ **primary analysis** cohort. This analysis is triggered when 100% of subjects ~~enrolled~~ **in the primary analysis cohort**: •Complete Week 52 of treatment and ~~safety follow-up~~ **either enter LTE or complete Safety Follow-Up**, or •Prematurely discontinue from treatment **prior to Week 52** and complete **Safety Follow-Up** ~~safety follow-up~~, or •Prematurely discontinue from study **without Safety Follow-Up**. The Japanese cohort may be fully, partially, or not included in this primary analysis, depending on the enrollment rate. The primary analysis will be performed by PPD staff when the primary analysis trigger condition has been met, protocol violations determined, and the database is locked for the primary analysis. C [redacted] **The** Ca Family-Wise type 1 error rate (FWER) due to the **co-primary endpoints** and multiple M2951 dose group comparisons versus placebo will be controlled at the **two** CC -sided α = 0.0125 level via a **tree gatekeeping** CCI [redacted] **. The four**	

Change	Section	Page	Previous Wording	New Wording	Rationale
			CCI CCI [redacted] A third analysis may be scheduled if the Japanese cohort does not enroll in time to be included with the n = 432 subjects required for the primary analysis. If the Japanese cohort enrolls in time to be included, the evaluation of consistency with respect to ethnicity of Week 52 SRI-4 response can be performed at the time of the primary analysis. If the Japanese cohort enrolls slowly, then the primary analysis will occur without inclusion of the Japanese cohort, and a third analysis for evaluation of consistency will be triggered when 100% of enrolled Japanese subjects: •Complete Week 52 of treatment and safety follow-up, or •Prematurely discontinue from treatment and complete safety follow up, or	**hypotheses associated with comparisons involving the co-primary endpoints and** the CCI **two highest** dose groups CCI [redacted] **will form the first family of hypotheses in the tree. This family will be tested via the truncated Hochberg procedure, with truncation fraction pre-specified in the IAP. The multiple-testing procedure for the remainder of the tree, including the hypotheses associated with the comparisons involving the co-primary endpoints and the** lowest dose **group, and the key secondary endpoints and all dose groups, will be pre-specified in the IAP.** [redacted] CCI A **treatment effect consistency analysis** ~~third analysis~~ may be scheduled if the Japanese cohort does not enroll in time to be included with the ~~n = 432 subjects required for the~~ primary analysis **cohort**. If the Japanese cohort enrolls in time to be included, the evaluation of consistency with respect to ethnicity of Week 52 SRI-4 response can be performed at the time of the primary analysis. If the Japanese cohort enrolls slowly, then the primary analysis will occur without inclusion of the Japanese cohort, and a ~~third analysis for evaluation of~~ **separate** consistency **analysis** will be triggered when 100% of enrolled Japanese subjects: •Complete Week 52 of treatment and **either enter LTE or complete Safety Follow-Up**~~safety follow-up~~, or •Prematurely discontinue from treatment **prior to Week 52** and complete **Safety Follow-Up** ~~safety follow up~~, or •Prematurely discontinue from study **without Safety Follow-Up**. **The final analysis will be triggered when 100% of subjects enrolled:**	

Change	Section	Page	Previous Wording	New Wording	Rationale
			•Prematurely discontinue from study.	**•Complete Week 104 of the LTE and the Safety Follow-Up, or** **•Complete Week 52 of treatment and the Safety Follow-Up (if they did not rollover into the LTE), or** **•Prematurely discontinue from treatment and complete Safety Follow-Up, or** **•Prematurely discontinue from study.** **The final analysis will be performed by PPD staff when the final analysis trigger condition has been met, protocol violations determined, and the database is locked for the final analysis.**	
Text was removed.	5.2.1 Scientific Rationale for Study Design	44	Important potential risks to subjects are based on nonclinical safety data of M2951 and clinical data on adverse drug effects associated with compounds of a similar pharmacological class. They include infection, leukopenia, thrombocytopenia, hemorrhage, gastrointestinal intolerance, renal toxicity, hepatocellular injury, atrial fibrillation, drug-drug interactions, and embryo-fetal toxicity. These risks will be mitigated through the use of risk minimization measures inherent to early phase clinical trials and are considered adequate for the proposed clinical trial in subjects with SLE. An IDMC will continually review available safety and tolerability data and will be mandated to make immediate decisions regarding the conduct of the trial; no additional risk minimization measures are proposed. Given the predicted therapeutic benefit in the majority of the subjects at each dose, the tolerability and safety profile demonstrated, and the risk minimization measures in place	~~Important potential risks to subjects are based on nonclinical safety data of M2951 and clinical data on adverse drug effects associated with compounds of a similar pharmacological class. They include infection, leukopenia, thrombocytopenia, hemorrhage, gastrointestinal intolerance, renal toxicity, hepatocellular injury, atrial fibrillation, drug-drug interactions, and embryo-fetal toxicity. These risks will be mitigated through the use of risk minimization measures inherent to early phase clinical trials and are considered adequate for the proposed clinical trial in subjects with SLE. An IDMC will continually review available safety and tolerability data and will be mandated to make immediate decisions regarding the conduct of the trial; no additional risk minimization measures are proposed.~~ ~~Given the predicted therapeutic benefit in the majority of the subjects at each dose, the tolerability and safety profile demonstrated, and the risk minimization measures in place for this trial, benefit risk considerations support conduct of the proposed clinical Study MS200527-0018 in subjects with SLE.~~	The text is already present in Section 3.1.

Change	Section	Page	Previous Wording	New Wording	Rationale
			for this trial, benefit risk considerations support conduct of the proposed clinical Study MS200527-0018 in subjects with SLE.		
Minor update to text was added on data for doses.	5.2.2 Justification for Dose	46	CCI [redacted]	CCI [redacted]	Data is no longer preliminary.
Updated to include unanticipated events.	5.3 Selection of Trial Population	47	When a laboratory test must be repeated during the Screening period, the Screening Period can be extended to 8 weeks after discussion with the Medical Monitor.	When a laboratory test must be repeated during the Screening ~~p~~**P**eriod **or an unanticipated event occurs**, the Screening Period can be extended to 8 weeks after discussion with the Medical Monitor.	To allow flexibility for unanticipated events.
Two drugs were added to the list of exclusion 6.	5.3.2 Exclusion Criteria	52	6. Within two months prior to Screening or during Screening: initiation of or change in dose of antimalarial, methotrexate, mycophenolate (mofetil [MMF] or sodium [MPS]*), or azathioprine (*not approved in Japan).	6. Within two months prior to Screening or during Screening: initiation of or change in dose of antimalarial, methotrexate, **6-mercaptopurine, sulfasalazine,** mycophenolate (mofetil [MMF] or sodium [MPS]*), or azathioprine (*not approved in Japan).	To add clarification as these drugs were intended to be on this list previously.
Clarification was added for the use of low dose aspirin.	5.3.2 Exclusion Criteria	52	14. On anticoagulation (e.g., vitamin K antagonists) or antiplatelet therapy (e.g., clopidogrel) other than daily aspirin for cardioprotection.	14. On anticoagulation (e.g., vitamin K antagonists) or antiplatelet therapy (e.g., clopidogrel) other than daily **low dose** aspirin **(≤ 350 mg/day)** for cardioprotection. **Low-dose aspirin therapy for other indications may be permitted after discussion with medical monitor.**	To allow inclusion, after medical review, of subjects for whom low-dose aspirin is SoC for reasons other than cardioprotection.
A note was added for additional information on Hepatitis B vaccination.	5.3.2 Exclusion Criteria	53	2. Hepatitis B antibody positive subjects who are HBV DNA negative OR have detectable HBV DNA < 20 IU/mL are not excluded from the study. However, these subjects will have HBV DNA measured by PCR at Weeks 4, 8, 12, 16, 20, 24, 36, 48, 52/EoT/Early Withdrawal, and 56/Safety Follow-Up/End of Study visits.	2. Hepatitis B antibody positive subjects who are HBV DNA negative OR have detectable HBV DNA < 20 IU/mL are not excluded from the study. However, these subjects will have HBV DNA measured by PCR at ~~Weeks 4, 8, 12, 16, 20, 24, 36, 48, 52/EoT/Early Withdrawal, and 56/Safety Follow-Up/End of Study~~**at** visits **noted in the SOA.** **Note: Subjects who have previously been vaccinated for Hepatitis B will not be tested for anti-hepatitis B surface antibody, as they will be positive for anti-hepatitis B surface**	Clarification regarding testing performed for subjects previously vaccinated for Hepatitis B, versus those who have not been vaccinated.

Change	Section	Page	Previous Wording	New Wording	Rationale
				antibody as the protective consequence of vaccination.	
A note was added regarding the prophylactic use of antituberculous drugs.	5.3.2 Exclusion Criteria	54	-	**Note: Prophylactic use of antituberculous drugs is not permitted during the study, and if used must be discontinued prior to the first dose of study medication. If an Investigator feels that a subject requires antituberculous prophylaxis while participating in the study, this may be allowed after review of the case by the Medical Monitor.**	Added to clarify protocol restrictions on use of antituberculous prophylaxis in some countries as not permitted in this study.
The exclusion was modified to cross reference another exclusion and not repeat.	5.3.2 Exclusion Criteria	54	26. Antiphospholipid antibody syndrome associated with a thromboembolic event in the 12 months prior to or during Screening. Anticoagulation or anti-platelet therapy is exclusionary, with the exception of daily aspirin for cardioprotection (see criterion 14).	26. Antiphospholipid antibody syndrome associated with a thromboembolic event in the 12 months prior to or during Screening. **See Exclusion Criterion 14 for discussion of A**~~**a**~~**n**ticoagulation or anti-platelet therapy~~ is exclusionary, with the exception of daily aspirin for cardioprotection (see criterion 14).~~	Additional details for aspirin were added into Exclusion 14 and therefore removed from here.
Additional text was added to possibly increase enrollment.	5.5.1 Withdrawal from the Trial	58	Subjects who are withdrawn after randomization (e.g., due to AEs or lack of efficacy) will not be replaced. Subjects who are withdrawn from the study will not be allowed to re-enroll in the study.	Subjects who are withdrawn after randomization ~~(e.g.,~~ due to ~~AEs~~**safety** or lack of efficacy~~)~~ will not be replaced. **Consideration will be given to increasing enrollment to compensate for loss of information due to subjects who withdraw for reasons unrelated to safety or lack of efficacy.** Subjects who are withdrawn from the study will not be allowed to re-enroll in the study.	Drop-out rates unrelated to efficacy or safety are higher than anticipated.
Additional text was added about the potential use of some prohibited medications.	5.5.2 Withdrawal from the Investigational Medicinal Product	58	•Use of a prohibited medication, as defined in Section 6.5.2. However, any medications that are considered necessary for the subject's well-being may be given at the discretion of the Investigator.	•Use of a prohibited medication, as defined in Section 6.5.2. However, any medications that are considered necessary for the subject's well-being may be given at the discretion of the Investigator. **If, in the view of the Investigator, the use of a prohibited medication should not impact subject safety or bias efficacy assessments, the Investigator can request the Medical Monitor review the case. Such a request must be made as soon as the Investigator is aware of the use of prohibited medication, and the Medical Monitor, along with the Sponsor, will determine if the subject must be permanently withdrawn from IMP. See Section 6.4.2.2 for specifics regarding treatment of flares during**	To allow some flexibility for the Investigators based on Investigator feedback.

Change	Section	Page	Previous Wording	New Wording	Rationale
				the DBPC and LTE treatment periods of the study and withdrawal from IMP.	

Clarifications were added to IMP withdrawal criteria.	5.5.2 Withdrawal from the Investigational Medicinal Product	58-60	The IMP should be temporarily withheld or permanently withdrawn if the following laboratory abnormalities occur or re-occur, as relevant, and re-initiation following temporarily withholding of IMP should be discussed with the Medical Monitor. If a subject's pre-dose baseline value falls within any of the below criteria, consult with the Medical Monitor regarding potential withdrawal, continued participation in study, and additional monitoring if needed: •For a neutrophil count < 500/mm^3 or platelet count < 25,000/mm^3 or a lymphocyte count < 200/mm^3 (Grade 4) or neutrophil count 500 to 999/mm^3 (Grade 3) with fever or platelet count 25,000 to 49,999/mm^3 (Grade 3) with bleeding, the IMP should be permanently withdrawn. •For a Grade 3 decrease in neutrophil count without fever or Grade 3 decrease in platelet count without bleeding, temporarily hold the IMP and recheck the value. If the value is still Grade 3, permanently discontinue the IMP. For a decrease to Grade 2, temporarily hold the IMP and recheck the value. Reinitiate the IMP after discussion with the Medical Monitor if no further downward trend is observed. CCI [redacted]	The IMP should be temporarily withheld or permanently withdrawn if the following laboratory abnormalities occur or re-occur, as relevant, and re-initiation following temporarily withholding of IMP should be discussed with the Medical Monitor. If a subject's pre-dose baseline value **is abnormal and/or** falls within any of the below criteria, consult with the Medical Monitor regarding potential withdrawal, continued participation in study, and additional monitoring if needed**. Retesting should be completed within 1 week:** •For a neutrophil count < ~~500~~**1000**/mm^3 **(Grade 3 or 4)** or platelet count < ~~25~~**50**,000/mm^3 ~~or a lymphocyte count < 200/mm^3 (Grade 4) or neutrophil count 500 to 999/mm^3 (Grade 3) with fever or platelet count 25,000 to 49,999/mm^3 (Grade 3) with bleeding, the IMP should be permanently withdrawn.~~ ~~•For a Grade 3 decrease in neutrophil count without fever or Grade 3 decrease in platelet count without bleeding,~~ **(Grade 3 or 4)** temporarily hold the IMP and recheck the value. If the value is still Grade 3 **or 4**, permanently discontinue the IMP**; if the value improves to Grade 2, Grade 1 or is within normal limits, IMP may be reinitiated after discussion with the Medical Monitor**. For a **recheck value that decreases to Grade 2, perform repeat testing within 1 month.** ~~decrease to Grade 2, temporarily hold the IMP and recheck the value. Reinitiate the IMP after discussion with the Medical Monitor if no further downward trend is observed.~~ **•For a lymphocyte count <200/mm^3 (Grade 4), temporarily hold the IMP and recheck the value. If the value is still Grade 4, permanently discontinue the IMP; if the value improves to a Grade 3, discuss with the Medical Monitor; if the value improves to Grade 2, Grade 1 or is within normal limits, IMP may be reinitiated after discussion with the Medical Monitor. For a recheck value that improves to Grade 2, perform repeat testing within 1 month.**	Clarified confirmatory retest process, provided guidance for additional testing if subject is not scheduled for a monthly visit during the LTE period, and revised based on review of safety data from ongoing studies.

			specialists, such as a hepatologist, can be considered at the discretion of the Investigator and in conjunction with the Medical Monitor. •For an increase in bilirubin to Grade 2, temporarily hold the IMP and recheck the value. Reinitiate the IMP after discussion with the Medical Monitor if no further upward trend is observed. •A comprehensive hepatic panel is requested for any subjects, for whom above AST or ALT withdrawal criteria are met and who permanently discontinue dosing due to elevated liver function tests. Subjects should be referred to a hepatologist who may recommend testing in addition to the following: o INR, PTT, fibrinogen, hsCRP o Hepatitis serology: anti-HAV IgG, anti-HAV IgM, HBsAg, anti-HBc, anti-HBsAg, anti-HCV, anti-HEV IgG and IgM, anti-VCA IgG and IgM, anti-EA IgG, anti-EBNA IgG, anti-CMV IgG and IgM o Antinuclear antibody, anti-smooth muscle antibody, and liver-kidney microsomal antibody o Albumin •For an increase in amylase or lipase to > 2 to 5X ULN (Grade 3), temporarily hold the IMP and recheck the value within 24 hours of receipt. If the value is still Grade 3, permanently discontinue the IMP. •For an increase in amylase or lipase to Grade 2, temporarily hold the IMP and recheck the value within 24 hours of receipt. Discontinue the IMP if the value does not decrease, or reinitiate the IMP after discussion	•For an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) to > 3~~X~~× ULN (Grade 2 or higher), **temporarily hold the IMP and recheck the value. If the value is still Grade 2 or higher,** the IMP should be permanently withdrawn. The subject should be followed with additional testing as needed until a return to ULN or acceptable value as agreed upon by the Investigator and Medical Monitor. Consultations with specialists, such as a hepatologist, can be considered at the discretion of the Investigator and in conjunction with the Medical Monitor. •For an increase in bilirubin to **> 1.5×ULN (**Grade 2 **or higher)**, temporarily hold the IMP and recheck the value. ~~Reinitiate~~ **If the value is still Grade 2 or higher,** the IMP ~~after discussion with the Medical Monitor if no further upward trend is observed~~ **should be permanently withdrawn**. •A comprehensive hepatic panel is requested for any subjects, for whom above AST or ALT withdrawal criteria are met and who permanently discontinue dosing due to elevated liver function tests. Subjects should be referred to a hepatologist who may recommend testing in addition to the following: o INR, PTT, fibrinogen, hsCRP o Hepatitis serology: anti-HAV IgG, anti-HAV IgM, HBsAg, anti-HBc, anti-HBsAg, anti-HCV, anti-HEV IgG and IgM, anti-VCA IgG and IgM, anti-EA IgG, anti-EBNA IgG, anti-CMV IgG and IgM o Antinuclear antibody, anti-smooth muscle antibody, and liver-kidney microsomal antibody o Albumin •For an increase in amylase or lipase to > 2 ~~to 5~~× ULN (Grade 3 **or 4**), temporarily hold the IMP and recheck the value ~~within 24 hours of receipt~~. If the value is still Grade 3 or 4, permanently discontinue the IMP~~.~~ ~~•For an increase in amylase or lipase to Grade 2, temporarily hold the IMP and recheck the value within 24 hours of receipt. Discontinue the IMP~~ if	

			with the Medical Monitor if a downward trend is observed. •For an increase in serum creatinine to > 3X from Baseline (Grade 3 or higher), the IMP should be permanently withdrawn. •For any other increase in serum creatinine > 1.5X from Baseline, temporarily hold the IMP and recheck the value within 24 hours of receipt. Discontinue the IMP if the value does not decrease, or reinitiate the IMP after discussion with the Medical Monitor if a downward trend is observed. •For any serum IgG level < 3 g/L, confirmed by repeat testing, the IMP should be permanently withdrawn. … •For any other laboratory abnormality of Grade 4 severity, the IMP should be permanently withdrawn. •For any other laboratory increase/decrease (as relevant) from Baseline to Grade 3, consider temporarily holding the IMP, unless otherwise indicated in this section of the protocol. Recheck values within 24 hours and discuss results with Medical Monitor, unless an improving trend is observed.	the value ~~does not decrease, or reinitiate the IMP~~ **improves to Grade 2, Grade 1, or is within normal limits, IMP may be reinitiated** after discussion with the Medical Monitor**. For** ~~if~~ a **recheck value that improves to Grade 2, perform repeat testing within 1 month**~~downward trend is observed~~. •For an increase in serum creatinine to > 3~~X~~**×** ~~from~~ Baseline (Grade 3 ~~or higher~~**4**), **temporarily hold the IMP and recheck the value. If the value is still a Grade 3 or 4**, ~~the IMP should be~~ permanently **discontinue the IMP** ~~withdrawn~~. •For an~~y other~~ increase in serum creatinine > 1.5× ~~from~~ Baseline **to ≤ 3× Baseline (Grade 2)**, temporarily hold the IMP and recheck the value ~~within 24 hours of receipt~~. ~~Discontinue the IMP if~~**If the value is still Grade 2, discuss with the Medical Monitor,** if the value ~~does not decrease, or reinitiate the IMP~~ **improves to Grade 1 or is within normal limits, IMP may be reinitiated** after discussion with the Medical Monitor ~~if a downward trend is observed~~. •For any serum IgG level < 3 g/L, ~~confirmed by repeat testing~~**temporarily hold the IMP and recheck the value. If the value is still < 3 g/L**, the IMP should be permanently withdrawn. … •For any other laboratory abnormality of Grade 4 severity, **temporarily hold the IMP and recheck the value. If the value is still a Grade 4,** the IMP should be permanently withdrawn**. If the restest value improves, discuss with the Medical Monitor.** •For any other laboratory increase/decrease (as relevant) from Baseline to Grade 3~~, consider temporarily holding the IMP,~~ **(**unless otherwise indicated in this section of the protocol**), temporarily hold the IMP, recheck the value,** ~~.Recheck values within 24 hours~~ and discuss results with Medical Monitor~~, unless an improving trend is observed~~.	

Change	Section	Page	Previous Wording	New Wording	Rationale
Dosing information for the LTE was added.	6.2 Dosage and Administration	62	CCI [redacted]		The LTE was added into the study.
Clarification was added due to the addition of the LTE.	6.4.1 Background Systemic Lupus Erythematosus Therapies	64	Initiation of any new immunosuppressant or immunomodulator therapy would be considered a treatment failure and should result in withdrawal of the subject from the IMP and study (see Section 5.5).	Initiation of any new immunosuppressant or immunomodulator therapy would be considered a treatment failure **during the DBPC Treatment Period** and should result in withdrawal of the subject from the IMP and study (see Section 5.5).	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
Clarification was added that a single dose of steroid could be given.	6.4.2 Corticosteroids	65	**DBPC Period** … Furthermore, injectable corticosteroids (e.g., intramuscular, intravenous, subcutaneous, and intra-articular) are prohibited during the study.	**DBPC Period** … Furthermore, injectable corticosteroids (e.g., intramuscular, intravenous, subcutaneous, and intra-articular) are prohibited during the study~~.~~ **with the exception of a single dose of intramuscular steroid, no more than 80 mg of prednisolone equivalent, permitted prior to the twelfth week of the DBPC Period.**	Updated to permit one time intramuscular steroid dose within the first 12 weeks of the DBPC Period as administration will not bias efficacy endpoints or impact patient safety.
Additional information was added on corticosteroid use during the LTE.	6.4.2 Corticosteroids	65	The rules for CS dose changes are outlined in Table 7. There is no minimum CS dose required during the study. … - **Screening to Week 52** There are no restrictions on non-systemic corticosteroid dosage (see Section 6.5.1.2).	The rules for CS dose changes **during Screening and the DBPC Treatment Period** are outlined in ~~Table 7~~**Table 9**. There is no minimum CS dose required during the study. … **LTE Period** **During the LTE Period, CS doses up to 30 mg/day prednisone-equivalent (see Table 8) are permitted. Injectable corticosteroids (e.g., intramuscular, intravenous, subcutaneous, and intra-articular) remain prohibited during the LTE Period, with the exception of a single dose of intramuscular steroid, no more than 80 mg of prednisolone equivalent, permitted prior to the twelfth week of the LTE Period.** **Screening ~~to Week 52~~Period, DBPC Period, and LTE Period** There are no restrictions on non-systemic corticosteroid dosage (see Section 6.5.1.2).	The LTE was added into the study.
Additional information was added on corticosteroid use during the LTE.	6.4.2 Corticosteroids, Table	68	**Overview / Key Points on Corticosteroid Dose During Study** •CS dose must remain stable during the Screening Period. •From Day 1 to the Week 4 Visit, CS dose may be initiated (no later than Week 2/Day 14), increased, decreased, or remain unchanged.	**Overview / Key Points on Corticosteroid Dose During Study** •CS dose must remain stable during the Screening Period. •From Day 1 to the Week 4 Visit, CS dose may be initiated ~~(no later than Week 2/Day 14),~~ increased, decreased, or remain unchanged. •Corticosteroid dose adjustment goals and restrictions **during the DBPC Treatment Period**:	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
			•Corticosteroid dose adjustment goals and restrictions o By the Week 4 Visit, the dose must be ≤ dose at Day 1. Subjects with CS dose < 7.5 mg/day at Day 1 may have up to 7.5 mg/day at Week 4. o By the Week 8 Visit, dose should be tapered to ≤ 10 mg/day, as tolerated o By the Week 12 Visit, dose should be tapered to ≤ 7.5 mg/day, as tolerated o No changes to CS dose should be made from Week 17 through completion of study assessments for Week 24. o Between study visits at Week 25 through Week 40, dose should be tapered to ≤ 5 mg/day, as tolerated. o No changes to CS dose are allowed from Week 41 through completion of study assessments for Week 52/EOT.	o By the Week 4 Visit, the dose must be ≤ dose at Day 1. Subjects with CS dose < 7.5 mg/day at Day 1 may have up to 7.5 mg/day at Week 4. o By the Week 8 Visit, dose should be tapered to ≤ 10 mg/day, as tolerated o By the Week 12 Visit, dose should be tapered to ≤ 7.5 mg/day, as tolerated o No changes to CS dose should be made from Week 17 through completion of study assessments for Week 24. o Between study visits at Week 25 through Week 40, dose should be tapered to ≤ 5 mg/day, as tolerated. o No changes to CS dose are allowed from Week 41 through completion of study assessments for Week 52/EOT. **•During the LTE Period, CS doses may be initiated or increased up to 30 mg/day prednisone equivalent, decreased, or remain the same. Investigators are strongly encouraged to decrease the CS dose of the subject as much as tolerated.**	
Additional information was added on corticosteroid use during the LTE.	6.4.2.1 Corticosteroid Use as Standard of Care	68	**Screening Visit to Day 1 (No Change in CS Dose)** From the Screening Visit to Day 1, the corticosteroid dose should be maintained at the Screening Visit dose. If the corticosteroid dose is changed, the subject will be considered a screen failure. The total daily prednisone equivalent dosage must not be higher than 30 mg/day during the Screening Period. **Day 1 to Week 4 Visit (CS Dose Adjustable)** Corticosteroids may remain unchanged, be increased, or be	**<u>DBPC Period</u>** **Screening Visit to Day 1 (No Change in CS Dose)** From the Screening Visit to Day 1, the corticosteroid dose should be maintained at the Screening Visit dose. If the corticosteroid dose is changed, the subject will be considered a screen failure. The total daily prednisone equivalent dosage must not be higher than 30 mg/day during the Screening Period. **Day 1 to Week 4 Visit (CS Dose Adjustable)** Corticosteroids may remain unchanged, be **initiated, be** increased, or be decreased ~~during this time. The increased dose, if needed, must occur within the first two weeks~~ after ~~the~~ Day 1. ~~The total daily prednisone equivalent dosage~~ **but**	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
			decreased during this time. The increased dose, if needed, must occur within the first two weeks after the Day 1. The total daily prednisone equivalent dosage must not be higher than 30 mg/day at the Week 4 Visit.	must ~~not~~ be **no** higher than ~~30 mg/day~~**(<) the Day 1 CS dose** at the Week 4 Visit.	
Additional information was added on corticosteroid use during the LTE.	6.4.2.1 Corticosteroid Use as Standard of Care	69	-	**LTE Period** **Corticosteroid doses may be initiated or increased up to 30 mg/day prednisone equivalent, decreased, or remain the same. Investigators are strongly encouraged to decrease the CS dose of the subject as much as tolerated.**	The LTE was added into the study.
Additional information was added on corticosteroid use during the LTE.	6.4.2.2 Corticosteroid Use as Rescue Medication in Treatment of Flare	70	**Corticosteroid Dose Increases and Treatment of Flares** Subjects may increase the CS dose up to 30 mg/day only two times as rescue for worsening of SLE activity or for other reasons. Each rescue is allowed only once during each of the following two time periods: 1) once between Week 8 to Week 16; and 2) once between Week 24 to Week 40. The CS dose can be increased up to prednisone-equivalent 30 mg/day, but must be returned to ≤ Week 8 dose (Threshold Dose) within seven days. A CS dose increase must not to be initiated within one week of a planned study visit. CS medications are part of the subject's previous SLE treatment and thus will not be provided by the Sponsor. Doses for treatment of flares beyond these allowable rescue doses will result in the subject being considered a treatment failure, and withdrawal from the study (see Section 5.5.1).	**Corticosteroid Dose Increases and Treatment of Flares: DBPC Treatment Period** Subjects may increase the CS dose up to 30 mg/day only two times as rescue for worsening of SLE activity or for other reasons~~.~~ **during the DBPC Treatment Period of the study**. Each rescue is allowed only once during each of the following two time periods: 1) once between Week 8 to Week 16; and 2) once between Week 24 to Week 40. The CS dose can be increased up to prednisone-equivalent 30 mg/day, but must be returned to ≤ Week 8 dose (Threshold Dose) within seven days. A CS dose increase must not to be initiated within one week of a planned study visit. **A single dose of intramuscular steroid, no more than 80 mg of prednisolone equivalent, is permitted prior to the twelfth week of the DBPC Period**. CS medications are part of the subject's previous SLE treatment and thus will not be provided by the Sponsor. Doses for treatment of flares beyond these allowable rescue doses will result in the subject being considered a treatment failure, and withdrawal from the study (see Section 5.5.1). **Corticosteroid Dose Increases and Treatment of Flares: LTE Treatment Period** **During the LTE Period, CS doses up to 30 mg/day are permitted. In addition, a single**	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
				dose of intramuscular steroid, no more than 80 mg of prednisolone equivalent, is permitted prior to the twelfth week of the LTE Period. CS medications are part of the subject's previous SLE treatment and thus will not be provided by the Sponsor. **If medications which are not permitted (as per Section 6.5.2) are required to treat the flare, and/or the flare has been ongoing between 2 visits at least 12 weeks apart without improvement, the subject must be discussed with the Medical Monitor to determine if the subject should be considered a treatment failure, and must be withdrawn from the study (see Section 5.5.1).**	
Additional information was added on corticosteroid use during the LTE.	6.5.1.2 Non-Systemic Corticosteroids	70	Non-systemic corticosteroid medications in this study are defined as otic, topical, intranasal, inhaled, and ophthalmic. There are no restrictions on non-systemic corticosteroid dosing. However, all injected corticosteroids, including local injections (e.g., intra-articular injections) are not permitted.	Non-systemic corticosteroid medications in this study are defined as otic, topical, intranasal, inhaled, and ophthalmic. There are no restrictions on non-systemic corticosteroid dosing. However, all injected corticosteroids, including local injections (e.g., intra-articular injections) are not permitted~~.~~ **with the exception of a single dose of intramuscular steroid, no more than 80 mg of prednisolone equivalent prior to the twelfth week of the DBPC Treatment Period and once during the LTE Period (prior to the twelfth week).**	The LTE was added into the study.
Clarification was added for the use of low dose aspirin.	6.5.1.4 Additional Permitted Medications	71	•Low-dose aspirin (≤ 350 mg/day) for cardiovascular prophylaxis.	•Low-dose aspirin (≤ 350 mg/day) for cardiovascular prophylaxis. **Low-dose aspirin for other indications may be permitted after discussion with medical monitor.**	To allow inclusion, after medical review, of subjects for whom low-dose aspirin is SoC for reasons other than cardioprotection.
Additional information was added due to the addition of the LTE.	6.5.1.4 Additional Permitted Medications	71	•Opioids are permitted for stable use for SLE if initiated by Day 1. Initiation of opioids and/or dosing of opioids as needed after Day 1 for SLE is not permitted.	•Opioids are permitted for stable use for SLE if initiated by Day 1. Initiation of opioids and/or dosing of opioids as needed after Day 1 for SLE is not permitted **during the DBPC Treatment Period**.	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
Additional information was added due to the addition of the LTE.	6.5.1.4 Additional Permitted Medications	72	-	•**During the LTE Period:** o **If a subject is on an immunosuppressant/immunomodulator when they rollover into the LTE Period, the dosage may be decreased or remain the same. After Week 24 of the LTE Period, the dosage regimen for an immunosuppressant/ immunomodulator may be increased up to the limits permitted in Table 7 or initiated as long as only 1 immunosuppressant is used.** o **Antimalarials may be initiated, increased, decreased, or remain the same** o **NSAIDs for SLE may be initiated, increased, decreased, or remain the same.** o **Opioids may be initiated, increased, or decreased.** o **NSAIDs and paracetamol may also be used for symptoms not due to SLE. It is strongly recommended that analgesics (including opioids), paracetamol, and NSAIDs are unchanged 24 hours prior to study visits when SLE assessments are completed (see SoA).**	The LTE was added into the study.
Additional information was added due to the addition of the LTE.	6.5.2 Prohibited Medicines	73	•New therapies for SLE should not be initiated during the study. Initiation of any new immunosuppressant or immunomodulatory therapy would be considered a treatment failure and result in withdrawal of the subject from the IMP (see Section 5.5).	•New therapies for SLE should not be initiated during **Screening or DBPC Treatment Period of** the study. Initiation of any new immunosuppressant or immunomodulatory therapy would be considered a treatment failure and result in withdrawal of the subject from the IMP **during the DBPC Treatment Period** (see Section 5.5). **For the LTE Period, see Section 6.4.1.**	The LTE was added into the study.
Additional information was added due to the addition of the LTE.	6.5.3 Other Interventions	74	Use of potentially excluded procedures such as acupuncture or joint replacement therapy is to be discussed with the Sponsor or designee on a case-by-case basis. Use of acupuncture is allowed to continue if it is started before the	Use of potentially excluded procedures such as acupuncture or joint replacement therapy is to be discussed with the Sponsor or designee on a case-by-case basis. Use of acupuncture is allowed to continue if it is started before the Screening Visit **and may be initiated/and or modified during the LTE Period**. Major elective	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
			Screening Visit. Major elective surgeries such as abdominal, thoracic or joint replacement surgeries should not be planned to occur in the Study Period. Unplanned joint replacement surgery should be discussed at the earliest opportunity prior to the surgery with the Medical Monitor regarding continuation of the subject in the study.	surgeries such as abdominal, thoracic or joint replacement surgeries should not be planned to occur in the Study Period. Unplanned joint replacement surgery should be discussed at the earliest opportunity prior to the surgery with the Medical Monitor regarding continuation of the subject in the study.	
C3 and C4 were added to Section 6.10.	6.10 Blinding	77	These analyses will include: total Ig (IgA, IgM, and IgG), IgG subclasses, anti-dsDNA, ANA, other autoantibodies (anticardiolipin, anti Smith antibody [anti Sm]; an antibody to ribonucleoproteins; and antinuclear antibodies associated with autoimmune diseases including Sjögren syndrome and SLE [anti-Ro, anti-La]), and cell counts by flow cytometry (total B cells and B cell subsets).	These analyses will include: total Ig (IgA, IgM, and IgG), IgG subclasses, **C3, C4,** anti-dsDNA, ANA, other autoantibodies (anticardiolipin, anti Smith antibody [anti Sm]; an antibody to ribonucleoproteins; and antinuclear antibodies associated with autoimmune diseases including Sjögren syndrome and SLE [anti-Ro, anti-La]), and cell counts by flow cytometry (total B cells and B cell subsets).	Updated to align with text from Section 7.5.2.
Additional text related to the LTE was added.	6.10 Blinding	77-78	An IA for futility will be triggered when 100% of the planned enrollment required for the primary analysis reaches 24 weeks of treatment, or discontinues treatment prematurely. The IDMC will be fully unblinded to treatment and will make a recommendation, as described in the IDMC charter. A limited set of endpoints will be analyzed for the IA, including Week 24 SRI-4 response for the whole study population and Week 24 SRI-6 response for the HDA subgroup. If the planned enrollment required for the primary analysis is slower than expected, consideration will be given to conducting the interim futility analysis at an earlier time point,	An IA for futility ~~will~~**may** be triggered when 100% of the planned enrollment required for the primary analysis reaches 24 weeks of treatment, or discontinues treatment prematurely~~.~~ **prior to Week 24**. The IDMC will be fully unblinded to treatment and will make a recommendation, as described in the IDMC charter. A limited set of endpoints will be analyzed for the IA, including Week 24 SRI-4 response for the whole study population and Week 24 SRI-6 response for the HDA subgroup. If the planned enrollment required for the primary analysis is slower than expected, consideration will be given to conducting the interim futility analysis at an earlier time point, when the first 50% of subjects enrolled of the planned enrollment reach 24 weeks of treatment, or discontinue treatment prematurely~~.~~ **prior to Week 24**. The unblinding procedures specified	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
			when the first 50% of subjects enrolled of the planned enrollment reach 24 weeks of treatment, or discontinue treatment prematurely. The unblinding procedures specified above will be followed, regardless of the timing of the interim futility analysis. The primary analysis will be triggered when 100% of subjects in the n = 432 cohort have completed safety follow up, or have discontinued study prematurely. Only when the last subject in the n = 432 cohort completes safety follow-up or discontinues from the study prematurely, the protocol violations are determined, and the database is locked, will the drug codes be broken and made available for the data analysis. If the Japan cohort enrollment is slow and cannot be fully included in the n = 432 enrollment planned for the primary analysis, a third analysis (occurring after the primary analysis) will be scheduled for the purpose of analyzing the entire Japan cohort. Only when the last subject in the Japan cohort completes safety follow-up or discontinues from the study prematurely, the protocol violations are determined, and the database is locked, will the drug codes be broken for the Japanese subjects not included in the primary analysis, and made available for the third data analysis evaluating the consistency of efficacy with respect to non-Japan and Japan regions. The bioanalytical laboratory(ies) responsible for the analysis of the	above will be followed, regardless of the timing of the interim futility analysis. ~~The primary analysis will be triggered when 100% of subjects in the n = 432 cohort have completed safety follow up, or have discontinued study prematurely.~~ ~~Only when the last subject in the n = 432 cohort completes safety follow-up or discontinues from the study prematurely~~**Only when the trigger event for the primary analysis (Section 5.1) is reached,** the protocol violations are determined, and the database is locked, will the drug codes be broken and made available for the ~~data~~primary analysis. If the Japan cohort enrollment is slow and cannot be fully included in the ~~n = 432 enrollment planned for the~~ primary analysis **cohort**, a ~~third analysis~~**consistency analysis** (occurring after the primary analysis) will be scheduled for the purpose of analyzing the entire Japan cohort. Only when the ~~last subject in~~**trigger event for** the ~~Japan cohort completes safety follow-up or discontinues from the study prematurely~~**consistency analysis (Section 5.1) is reached**, the protocol violations are determined, and the database is locked, will the drug codes be broken for the Japanese subjects not included in the primary analysis, and made available for the ~~third data analysis evaluating the~~**treatment effect** consistency ~~of efficacy~~**analysis** with respect to non-Japan and Japan regions. CCI [redacted]	

Change	Section	Page	Previous Wording	New Wording	Rationale
			CCI PPD CCI .	CCI PPD CCI	
Clarification was added to the overdose text.	6.12 Treatment of Overdose	79	An overdose is defined as any dose greater than the highest total daily dose included in a CTP or planned for an individual subject enrolled in the study. Any overdose must be recorded in the study medication section of the eCRF.	An overdose is defined as any dose greater than the highest total daily dose included in a CTP or planned for an individual subject enrolled in the study. CCI Any overdose must be recorded in the study medication section of the eCRF.	Updated to be in alignment with Section 6.2 and provide flexibility for subject scheduling
Updated to include unanticipated events.	7.1.1 Screening Visit	80-81	When a laboratory test needs to be repeated during the Screening Period, the Screening Period may be extended to 8 weeks after discussion with the Medical Monitor.	When a laboratory test needs to be repeated during the Screening Period**, or to accommodate other unanticipated events,** the Screening Period may be extended to 8 weeks after discussion with the Medical Monitor.	To allow flexibility for unanticipated events.
Updated due to addition of LTE.	7.1.2 Treatment Period	81	**7.1.2 Treatment Period**	**7.1.2 DBPC Treatment Period**	The LTE was added into the study.
Updated due to addition of LTE.	7.1.2.1 End of Treatment/Early Withdrawal Visit	81	**7.1.2.1 End of Treatment/Early Withdrawal Visit** The EOT Visit is scheduled on the last day of administration of study	**7.1.2.1 DBPC End of Treatment/Early Withdrawal Visit** The EOT Visit is scheduled on the last day of administration of study treatment. The EOT Visit	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
			treatment. The EOT Visit will include a full assessment for safety (e.g., physical examination, vital signs, weight, hematology and chemistry), and other assessments as described in Table 1	will include a full assessment for safety (e.g., physical examination, vital signs, weight, hematology and chemistry), and other assessments as described in Table 1. **Subjects who complete the End of Treatment Visit will be given the opportunity to participate in the LTE Period.**	
Updated due to addition of LTE.	7.1.3 LTE Period	81	-	**7.1.3 LTE Period** **Subjects who completed the 52-week DBPC Treatment period will be offered participation in the open-label, LTE Period of the study as described in Section 5.1. The Investigator will obtain written informed consent for the LTE.** **At all applicable visits, patient-reported outcome questionnaires must be performed prior to any other assessments. Scheduled assessments will be performed according to Table 2.** **All scheduled visits during the LTE Period may take place within the visit windows specified in Table 2. Subjects who discontinue early must return for the LTE End of Treatment/Early Withdrawal Visit and Safety Follow -up Visit.** **For WOCBP, additional highly sensitive urine pregnancy testing will be performed at home per SOA, Table 3. Urine pregnancy test kits will be provided to the subject at Week 16 (for testing at Week 20), Week 24 (for testing at Week 28, 32, and 36), Week 40 (for testing at Week 44 and 48), Week 52 (for testing at Week 56, 60, 64, 68, and 72), and Week 76 (for testing at Week 80, 84, 88, 92, 96, and 100).At and/or prior to the Week 16 visit, the PI and/or delegated site staff will train the relevant subjects to self-administer the urine pregnancy tests and will confirm completion of urine pregnancy testing and discuss results per Table 3.**	The LTE was added into the study.
Updated due to addition of LTE.	7.1.3.1 LTE End of Treatment Visit	81		**7.1.3.1 LTE End of Treatment Visit** **The LTE End of Treatment Visit will be performed at Week 104 or within 5 days of**	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
				early discontinuation of treatment with the IMP. Subjects will undergo assessments as described in Table 2. In case of premature discontinuation, the PRO assessments must be completed at the LTE End of Treatment Visit. Subjects will enter the Safety Follow-Up Period after completing the LTE End of Treatment Visit.	
Updated due to addition of LTE.	7.1.4 Safety Follow-Up/End of Study Visit	81	The Safety Follow Up/End of Study Visit is scheduled four weeks (+ 5 days) after the last administration of study treatment. Additional details of the Safety Follow Up/ End of Study Visit are provided in the SOA. Subjects who discontinue the IMP or withdraw from the trial early will attend the Safety Follow Up Visit according to procedures described in Sections 5.5.1 or 5.5.2, respectively.	The Safety Follow-Up/End of Study Visit is scheduled four weeks (+ 5 days) after the last administration of study treatment. **For subjects who do not participate in the LTE Period, the Safety Follow-Up Visit is scheduled four weeks (+ 5 days) after the last administration of study treatment in the DBPC Period. For subjects who participate in the LTE Period, the Safety Follow-Up Visit is delayed until four weeks (+ 5 days) after the last administration of study treatment in the LTE Period. Subjects who are approved to rollover into LTE Period after they entered, or completed, the DBPC Safety Follow-Up Period, may have two Safety Follow-Up Visits**. Additional details of the Safety Follow-Up/ End of Study Visit are provided in the SOA.	The LTE was added into the study.
Clarification was added to AEs related to flares.	7.4.1.1 Adverse Event Definitions	91	SLE flares would not usually be reported as AEs unless they are unexpected in the context of the subject's medical history. SAEs due to SLE are always reported whether or not consistent with the subject's prior medical history.	SLE flares would not usually be reported as AEs unless they are unexpected in the context of the subject's medical history. **Further, the AE report should describe the event, rather than reporting an AE of "SLE flare" unless it is unavoidable.** SAEs due to SLE **flare** are always reported, whether or not **it is** consistent with the subject's' prior ~~medical~~ history. **As for AE reports, the SAE report should describe the events, and avoid reporting an SAE of "SLE flare".**	Clarification added.
Updated due to addition of LTE.	7.4.1.3 Definition of the Adverse Event Reporting Period	92	For subjects entering the LTE study, if conducted, safety reporting for this trial would end upon the subject's enrollment into the LTE study, with subsequent AEs being reported in the LTE study.	~~For subjects entering the LTE study, if conducted, safety reporting for this trial would end upon the subject's enrollment into the LTE study, with subsequent AEs being reported in the LTE study.~~	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
Additional text was added regarding local safety testing.	7.4.3 Clinical Laboratory Assessments	95	-	**Local safety testing as requested by the study team should be entered into the eCRF.**	Added to permit inclusion of local safety testing results requested by study team into the database.
Clarification on anti-dsDNA assay was added.	7.4.3.1.1 Immunological Assessments	96	•Anti-dsDNA	•Anti-dsDNA **(at Screening, may be measured using 2 assays, 1 of which is a multiplex assay that includes anti-Ro and anti-RNP. Only anti-dsDNA is used to determine subject eligibility and will be reported to the sites.)**	Clarification was added as anti-Ro and anti-RNP are run by nature of the assay used for anti-dsDNA.
Updated due to addition of LTE.	CCI [redacted]				
Minor error updated.	CCI [redacted]				
Updated due to addition of LTE.	8.1 Sample Size	103	-	**Approximately 432 subjects will enter the main study. Assuming an 80% rate of continuation to LTE, approximately 346 subjects are expected to enter the LTE Period**.	The LTE was added into the study.
Updated due to addition of LTE.	8.4 Analysis Sets	107	-	**Long Term Extension Analysis Set** **The LTE Analysis Set consists of all subjects who receive at least one dose of M2951 during the LTE.**	The LTE was added into the study.
Updated due to addition of LTE.	8.5.1 General Considerations	109-110	For SRI-4 or SRI-6 response at Week 52 (Week 24), a subject experiencing flare or CS dose increase during Weeks 41 to 52 (Weeks 17 to 24), or a subject with a missing response at Week 52, will be considered a non-responder. Four sensitivity analyses of the primary analysis are planned: (1) unadjusted analysis, (2) non-responder imputation for treatment discontinuers, with last observation carried forward imputation for treatment completers with missing response (NR LOCF), (3) completer	For SRI-4 or SRI-6 response at Week 52 (Week 24), a subject experiencing flare or CS dose increase during Weeks 41 to 52 (Weeks 17 to 24), or a subject with a missing response at Week 52, **(Week 24),** will be considered a non-responder. Four sensitivity analyses of the primary analysis are planned: (1) ~~unadjusted analysis, (2)~~ non-responder imputation for **subjects discontinuing** treatment ~~discontinuers~~**for reasons due to efficacy/safety**, with ~~last observation carried forward~~**available observations used (in MMRM or multiple** imputation**)** for **subjects discontinuing** treatment ~~completers~~**for reasons unrelated to efficacy/safety or completing treatment** with	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
			analysis, and (4) PP analysis (i.e., excluding subjects with clinically important protocol violations). Additional procedures for handling missing, unused, or spurious data, and sensitivity analyses exploring the impact of missing data will be described in the SAP.	missing response ~~(NR-LOCF)~~, **(at Week 52, (2) unadjusted analysis,** (3) completer analysis, and (4) ~~PP~~**per-protocol** analysis (i.e., excluding subjects with clinically important protocol violations). Additional procedures for handling missing, unused, or spurious data, and sensitivity analyses exploring the impact of missing data will be described in the ~~S~~IAP.	
Additional details on non-responders were added.	8.5.2 Analysis of Primary Endpoints	110	-	**In the primary analysis of SRI-4 or SRI-6 response at Week 52, a subject experiencing flare or CS dose increase during Weeks 41 to 52, or a subject with a missing response at Week 52, will be considered a non-responder.**	To align with updated analyses.
The analysis of the primary endpoint was updated based on the addition of the LTE.	8.5.2 Analysis of Primary Endpoints	110	CCI [redacted]	~~For a given co-primary endpoint, the p-value testing the one-sided null hypothesis H0: OR ≤ 1.0 for each M2951 dose group will be reported, where OR denotes odds ratio comparing a given M2951 dose group to placebo. The FWER, i.e., overall type I error rate for the analysis of each co-primary endpoint, will be controlled at the one-sided α = 0.0125 level by testing the three hypotheses, corresponding to the three M2951 dose groups, via a hierarchical hypothesis testing procedure, in which the M2951 dose groups are compared to placebo from highest to lowest dose, and where formal comparisons are terminated at the first hypothesis test that results in a non significant p-value. After a non significant p-value, subsequent hypothesis tests in a hierarchy will be considered~~ CCI [redacted] **The Family-Wise type 1 error rate (FWER) due to the co-primary endpoints and multiple M2951 dose group comparisons versus placebo will be controlled at the two-sided α = 0.05 level via a tree gatekeeping procedure. The four hypotheses associated with the comparisons involving the co-primary endpoints and the two highest dose groups will form the first family of hypotheses in the tree. This family will be tested via the truncated Hochberg procedure, with truncation fraction pre-specified in the**	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
				IAP. The multiple-testing procedure for the remainder of the tree, including the hypotheses associated with the comparisons involving the co-primary endpoints and the lowest dose group will be specified in the IAP.	
The analysis of the secondary endpoint was updated based on the addition of the LTE.	8.5.3 Analysis of Secondary Endpoint	111	**Key Secondary Endpoints** Time to first severe (BILAG A) flare during the Treatment Period will be modeled via a Cox regression, with treatment group as a factor, and controlling for covariates defining randomization strata. A subject who discontinues treatment or completes treatment without experiencing severe flare will have his/her time to flare censored at the last time point at which flare could be assessed. A test for trend in dose-response, using the same Cox model, will be reported as a supportive analysis. SRI-4 response at Week 52 among serologically active subjects will be an estimate of OR, together with associated two-sided CI and p-value, comparing each M2951 dose group to placebo, based on a logistic model for the odds SRI-4 response in the serologically active population, with M2951 dose group or placebo group as a factor and adjustment for covariates based on randomization strata. Descriptive statistics for SRI-4 response in the serologically active subgroup, will be provided for each treatment group by time point. **Other Secondary Efficacy Endpoints** In the analysis of other secondary efficacy endpoints described in Section 8.3.2, binary endpoints will be modeled via logistic regression,	**Key Secondary Endpoints** Time to first severe (BILAG A) flare during the Treatment Period **in all subjects** will be ~~modeled~~ **compared between M2951 and placebo via a stratified log rank test. The adjusted hazard ratio comparing M2951 to placebo will be estimated (together with 95% CI)** via a Cox regression model, with treatment group as a factor, and controlling for covariates defining randomization strata. A subject who discontinues treatment or completes treatment without experiencing severe flare will have his/her time to flare censored at the last time point at which flare could be assessed. A test for trend in dose-response, using the same Cox model, will be reported as a supportive analysis. **Kaplan-Meier estimates of probability of surviving free of severe (BILAG A) flare as a function of time on treatment will be provided for each treatment group.** **The analysis of** SRI-4 response at Week 52 among serologically active subjects will be an estimate of OR, together with associated ~~two-sided~~ **95%** CI and p-value, comparing each M2951 dose group to placebo, based on a logistic model for the odds SRI-4 response in the serologically active population, with M2951 dose group or placebo group as a factor and adjustment for covariates based on randomization strata. **A test for trend in dose-response, using the same logistic model, will be reported as a supportive analysis.** Descriptive statistics for SRI-4 response in the serologically active subgroup, will be provided for each treatment group by time point. **Other Secondary Efficacy Endpoints**	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
			time to event endpoints will be modeled via Cox regression, continuous endpoints measured longitudinally will be analyzed using Mixed effect Model for Repeated Measures (MMRM), and count endpoints (i.e., annualized flare rate) will be modeled via negative binomial regression, with treatment group as a factor, and adjusting for covariates defining randomization strata. Analysis of annualized flare rate will use observation time (in years) as an offset in the model. Change in a binary endpoint between two time points will be analyzed via McNemar's test. The effect of treatment on change in a binary endpoint will be analyzed via logistic regression, with treatment group, time point, and interaction as predictors, and adjusting for covariates defining randomization strata. All tests of efficacy will be conducted at a two-sided α level of 0.05, with p-values considered nominal unless generated as part of a hierarchical testing strategy as described in the SAP. P values and the 95% CIs will be presented where applicable.	In the analysis of other secondary efficacy endpoints described in Section 8.3.2, binary endpoints will be modeled via logistic regression, time to event endpoints will be modeled via Cox regression **and tested via stratified log rank test**, continuous endpoints measured longitudinally will be analyzed using Mixed effect Model for Repeated Measures (MMRM), and count endpoints (i.e., annualized flare rate) will be modeled via negative binomial regression, with treatment group as a factor, and adjusting for covariates defining randomization strata. Analysis of annualized flare rate will use **the log of** observation time (in years) as an offset in the model. Change in a binary endpoint between two time points will be analyzed via McNemar's test. The effect of treatment on change in a binary endpoint will be analyzed via logistic regression, with treatment group, time point, and interaction as predictors, and adjusting for covariates defining randomization strata. All tests of efficacy will be conducted at a two-sided α level of 0.05, with p-values considered nominal unless generated as part of ~~a hierarchical~~ **the tree gatekeeping multiple** testing strategy as described in the ~~SAP~~ **IAP**. P values and the 95% CIs will be presented where applicable.	
Clarification added.	CCI [redacted]	112	CCI [redacted]	CCI [redacted]	Updated for clarity.
Updated due to addition of LTE.	8.5.6 Analysis of LTE Endpoints	113	-	**8.5.6 Analysis of LTE Endpoints** **Efficacy and HRQoL data collected during the LTE Period will be summarized. Details will be provided in the IAP.** **Safety data collected during the LTE Period will be analyzed as described in Section 8.5.4.**	The LTE was added into the study.

Change	Section	Page	Previous Wording	New Wording	Rationale
Updates added to the primary analysis cohort description.	8.6 Interim and Additional Planned Analyses	114	There will be an IA for futility based on the highest dose of M2951, triggered when 100% of subjects enrolled in the n = 432 cohort reach Week 24 of treatment, or prematurely discontinue from treatment. If enrollment is sufficiently slow, consideration will be given to triggering the IA at an earlier time point, when the first 50% of subjects enrolled in the n = 432 cohort reach Week 24 of treatment, or prematurely discontinue from treatment. Pharmacokinetic analysis will not be included in the IA. The difference between Week 24 SRI-4 response proportion in all subjects in the n = 432 cohort, comparing the highest dose of M2951 to placebo, will be estimated, together with a two-sided 97.5% confidence interval. Similarly, the difference between Week 24 SRI-6 response proportion in HDA subjects in the n = 432 cohort, comparing the highest dose of M2951 to placebo, will be estimated, together with a two-sided 97.5% confidence interval. If the response proportion difference for both co-primary endpoints is sufficiently low, as defined in the SAP, consideration will be given to termination of the study, in which case all subjects will be discontinued from IMP and scheduled for a four week Safety Follow Up Visit/End of Study Visit. Descriptive statistics for the Week 24 SRI-4 response endpoint in all subjects in the n = 432 cohort, and for the Week 24 SRI-6 response endpoint in HDA subjects in the	There ~~will~~**may** be an IA for futility based on the highest dose of M2951, triggered when 100% of subjects enrolled in the ~~n = 432~~**primary analysis** cohort reach Week 24 of treatment, or prematurely discontinue from treatment **prior to Week 24**. If enrollment is sufficiently slow, consideration will be given to triggering the IA at an earlier time point, when the first 50% of subjects enrolled in the ~~n = 432~~**primary analysis** cohort reach Week 24 of treatment, or prematurely discontinue from treatment **prior to Week 24**. Pharmacokinetic analysis will not be included in the IA. The difference between Week 24 SRI-4 response proportion in all subjects in the ~~n = 432~~**primary analysis** cohort, comparing the highest dose of M2951 to placebo, will be estimated, together with a two-sided 97.5% confidence interval. Similarly, the difference between Week 24 SRI-6 response proportion in HDA subjects in the ~~n = 432~~**primary analysis** cohort, comparing the highest dose of M2951 to placebo, will be estimated, together with a two-sided 97.5% confidence interval. If the response proportion difference for both co-primary endpoints is sufficiently low, as defined in the ~~SI~~AP, consideration will be given to termination of the study, in which case all subjects will be discontinued from IMP and scheduled for a four week Safety Follow-Up Visit/End of Study Visit. Descriptive statistics for the Week 24 SRI-4 response endpoint in all subjects in the ~~n = 432~~**primary analysis** cohort, and for the Week 24 SRI-6 response endpoint in HDA subjects in the ~~n = 432~~**primary analysis** cohort, will be presented by treatment group.	Drop-out rates unrelated to efficacy or safety are higher than anticipated.

Change	Section	Page	Previous Wording	New Wording	Rationale
			n = 432 cohort, will be presented by treatment group.		
Updated due to addition of LTE.	8.6 Interim and Additional Planned Analyses	114	**Primary Analysis** The primary analysis will occur only when the last subject in the n = 432 cohort completes all study parts, the protocol violations are determined, and the database is locked. **Third Analysis** The third analysis, evaluating efficacy consistency between the non-Japan and Japan regions, may be performed if the Japan cohort enrollment is too slow for the consistency evaluation to take place at the time of the primary analysis. The third analysis will occur only when the last subject in the Japan cohort completes all study parts, the protocol violations are determined, and the database is locked.	**Primary Analysis** The primary analysis will occur only when ~~the last subject in the n = 432 cohort completes all study parts~~**primary analysis trigger event (Section 5.1) has occurred**, the protocol violations are determined, and the database is locked. ~~**Third Analysis**~~**Consistency Analysis** ~~The third~~ **A separate** analysis~~, evaluating efficacy~~ **of treatment effect** consistency between the non-Japan and Japan regions, may be performed if the Japan cohort enrollment is too slow for the consistency evaluation to take place at the time of the primary analysis. ~~The third~~**This** analysis will occur only when the ~~last subject in the Japan cohort completes all study parts~~**consistency analysis trigger event (Section 5.1) has occurred,** the protocol violations are determined, and the database is locked. **Final Analysis** **The final analysis will occur only when the last subject completes all study parts (including the LTE and Safety Follow-Up Visits) or discontinues prematurely, the protocol violations are determined, and the database is locked.**	The LTE was added into the study.
Clarification was added to the contraceptive guidance.	Appendix 1 Contraceptive Guidance and Women of Childbearing Potential	128	•Male or female condom with or without spermicide[c] •Cap, diaphragm, or sponge with spermicide[c] … c. Not approved in Japan apart from male condom.	•Male or female condom with or without spermicide[cd] •Cap, diaphragm, or sponge with spermicide[c] … c. Not approved in Japan ~~apart from~~. d. **For Japan only – the only approved barrier method is apart from** male condom **with spermicide**.	The approved methods are different for Japan versus the rest of the world.

Updated Schedule of Assessments and Updated Protocol Amendment List

Updated Schedule of Assessments

Schedule of Assessments; Screening and Treatment Period (All Subjects), End of Study (Subjects Not Entering LTE Period)

Trial Period	**Screening**	**Visit Weeks During Treatment Period**																	**Follow-Up Visit 4 weeks Post-Last Dose[a]**
Week		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52/ EOT/Early Withdrawal**	**56/ Safety Follow-~~u~~Up/End of Study**
Trial Day	-28 to -1	1	15	29	43	57	71	85	99	113	141	169	197	225	253	281	309	337	365	393
Visit		Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56
Visit window (±day)	+7	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	~~-3/~~+5
Informed consent	X																			
LTE informed consent																			**X**	
Inclusion/exclusion criteria	X	X[b]																		
Demographics and medical history[c]	X																			
Chest X-ray[d]	X																			
12-lead ECG	X	X						X				X				X			X	X[e]
Physical examination	X	X[f]	X[g]	X[g]		X[g]		X[g]		X[g]	X[g]	X	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X	X[g]
Vital signs, weight, height[i]	X	X[f]	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X
SFI, SLEDAI-2K, PGA, BILAG 2004, CLASI	X	X[f]	X[j]	X		X		X		X	X	X	X	X	X	X	X	X	X	X

Trial Period	**Screening**	**Visit Weeks During Treatment Period**																		**Follow-Up Visit 4 weeks Post-Last Dose[a]**
Week		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52/ EOT/Early Withdrawal**	**56/ Safety Follow-~~u~~Up/End of Study**
Trial Day	-28 to -1	1	15	29	43	57	71	85	99	113	141	169	197	225	253	281	309	337	365	393
Visit		Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56
Visit window (±day)	+7	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	~~-3/~~+5
SLICC/ACR Damage Index		X[f]																	X	
C-SSRS	X			X				X			X		X		X		X		X	X
IMP administration[k]		Daily administration of IMP																		
Urinalysis and microscopy	X	X[f]	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X
Routine hematology, chemistry[m]	X	X[f]	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X
Supplementary LFTs[n]					X		X		X											
Total Ig Levels (IgG, IgA, IgM)	X	X[f]	X	X				X				X			X				X	X
Total B cell count[o]	X[p]	X[f]		X[f]								X[f]							X[f]	X
Coagulation (INR, PTT)	X																			
HIV[q], HCV, and HBV testing	X																			
Reflex testing for HBV DNA[r]	X			X		X		X		X	X	X			X			X	X	X
Serum pregnancy and FSH testing[s]	X																			

Trial Period	**Screening**	**Visit Weeks During Treatment Period**																		**Follow-Up Visit 4 weeks Post-Last Dose[a]**
Week		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52/ EOT/Early Withdrawal**	**56/ Safety Follow-~~u~~Up/End of Study**
Trial Day	-28 to -1	1	15	29	43	57	71	85	99	113	141	169	197	225	253	281	309	337	365	393
Visit		Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56
Visit window (±day)	+7	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	~~-3/~~+5
Serum β-D-glucan[t]	X																			
TSH	X																			
Tuberculosis assessment[l]	X																			
Urine pregnancy test[s]		X[f]	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X
UPCR	X	X[f]	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X
SF-36v2, LupusQoL, FACIT-Fatigue, EQ-5D-5L[u]		X		X		X		X		X		X		X		X			X	X
HRU				X		X		X		X	X	X	X	X	X	X	X	X	X	X
PGIC[u]				X		X		X		X		X		X		X			X	X
Dispense IMP		X	Dispense as needed, using IWRS																	
Dispense subject diary		X	Dispense as needed.																	
Concomitant medications / procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]																				

Trial Period	**Screening**	**Visit Weeks During Treatment Period**																		**Follow-Up Visit 4 weeks Post-Last Dose[a]**
Week		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52/ EOT/Early Withdrawal**	**56/ Safety Follow-~~u~~Up/End of Study**
Trial Day	-28 to -1	1	15	29	43	57	71	85	99	113	141	169	197	225	253	281	309	337	365	393
Visit		Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56
Visit window (±day)	+7	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	~~-3~~/+5
Immunological Assessments																				
Anti-dsDNA, Complement (C3, C4), CRP	X	X[f]		X		X		X		X	X	X	X	X	X	X	X	X	X	X
ANA, anti-Sm	X																			
Autoantibodies		X										X							X	X

CCI [redacted]

Trial Period	**Screening**	**Visit Weeks During Treatment Period**																		**Follow-Up Visit 4 weeks Post-Last Dose[a]**
Week		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52/ EOT/Early Withdrawal**	**56/ Safety Follow-~~u~~Up/End of Study**
Trial Day	-28 to -1	1	15	29	43	57	71	85	99	113	141	169	197	225	253	281	309	337	365	393
Visit		Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56
Visit window (±day)	+7	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	~~-3~~/+5
CCI [redacted]																				

ACR = American College of Rheumatology, ALT = alanine aminotransferase, ANA = Antinuclear Antibody(ies), Anti-dsDNA = Anti-Double-Stranded Deoxyribonucleic Acid, Anti-Sm = anti-Smith antibody, AST = aspartate aminotransferase, BILAG = British Isles Lupus Assessment Group, BP = blood pressure, CCI [redacted], CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index, CRP = C-Reactive Protein, C-SSRS = Columbia-Suicide Severity Rating Scale, DNA = deoxyribonucleic acid, ECG = Electrocardiogram, EOT = End of Treatment, EQ-5D-5L = EuroQoL 5 Dimension 5 Levels, FACIT = Functional Assessment of Chronic Illness Therapy, GGT = γ-Glutamyl-transferase, Ig = Immunoglobulin, IMP = Investigational Medicinal Product, IWRS = Interactive Web Response System, HBV = Hepatitis B Virus, HCV = Hepatitis C Virus, HIV = Human Immunodeficiency Virus, HRQoL = Health Related Quality of Life, HRU = Health Resource Utilization, INR = International Normalized Ratio, LFT = liver function test, **LTE = long-term extension**, LupusQoL = Lupus Quality of Life, mRNA = messenger Ribonucleic Acid, CCI [redacted] PCR = polymerase chain reaction, PGA = Physician's Global Assessment, PGIC = Patient Global Impression of Change, CCI [redacted], PTT = Partial Thromboplastin Time, SF-36v2 = Medical Outcomes Study 36-Item Short Form Health Survey, SFI = SLEDAI Flare Index, SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index-2000, SLICC = Systemic Lupus International Collaborating Clinics, TB = tuberculosis, TSH = Thyroid Stimulating Hormone, UPCR = Urine Protein To Creatinine Ratio, Wk = Week.

a Safety Follow-~~u~~Up Visits will be conducted at four weeks after the last dose of IMP for subjects who have been discontinued from IMP or have completed the 52-week Treatment Period**, unless subjects have entered the LTE period**.

b Subject eligibility to be confirmed on Day 1 prior to randomization**.**

c Medical history includes documentation of SLE classification criteria, SLE medical history, medications, and surgery/procedures (see Section 7.2.1).

d The results of a chest X-ray performed within three months prior to the Screening Visit (if available) are acceptable, provided there is no reason to suspect any clinical changes, per Investigator discretion.

e Only required if change noted at Wk52/EOT, when compared to Baseline ECG.

f Predose sample/procedure to be collected/performed before the first daily dose**.**

g Abbreviated physical examination at these visits (see Section 7.4.4.2)**.**

h Abbreviated physical examination **may be** performed at Primary Investigator discretion**, as required** to fully obtain information needed for the BILAG and/or SLEDAI assessments, if scheduled, as well as **required** to fully evaluate any subject complaints or adverse events.

i Vital signs include arterial BP, pulse rate, **respiratory rate,** and body temperature. Height will be measured at Screening only. Body weight will be measured with a balance beam scale, if possible. Pulse rate and BP will be measured after 10 minutes rest in the semisupine position with the subject's arm unconstrained by clothing or other material. The BP should be assessed on the same arm for each subject throughout the study.

j Only CLASI assessed at Week 2**.**

k On Study Visit Days, IMP should be administered during the Study Visit; otherwise, IMP should be self-administered at home at a set time each day (every 12 hours ± 2 hours). **Investigational medicinal product administration at Week 52 will only occur for subjects rolling over into the LTE.**

l A Quantiferon test will be performed centrally. Prior TB testing results must be entered into the eCRF.

m See ~~Table 9~~**Table 11** for list of clinical laboratory evaluations**.**

n Supplementary LFTs include AST, ALT, alkaline phosphatase, GGT, and bilirubin.

CCI [redacted]

p To be collected at Screening only in subjects who have previously received B cell depleting therapy (see Exclusion Criterion 33**, in Section 5.3.2**).

q HIV testing will be performed locally.

r For subjects who are negative for hepatitis B surface antigen (HBsAg) but are anti-hepatitis B surface antibody positive and/or anti-hepatitis B core antibody positive, an HBV DNA PCR reflex test is to be completed at screening. If the subject **enters** ~~is able to enter~~ the study with positive HBV DNA negative OR **has** ~~have~~ detectable HBV DNA < 20 IU/mL only, additional HBV DNA PCR testing must be performed (see Exclusion criteria 20, in Section 5.3.2).

s For women of childbearing potential or who are postmenopausal see inclusion criterion 7. A follicle-stimulating hormone (FSH) must be drawn at Screening if necessary to confirm postmenopausal status. The urine pregnancy test being used at all time points in this study must be a highly sensitive urine pregnancy test.

t For Japan only.

u HRQoL Questionnaires should be completed before any other procedures are performed.

v On Day 1, samples will be collected predose (before the first daily dose) and 0.25, 0.5, 1.0, 2.0, and 4.0 hours postdose (after the first daily dose) obtained within 10% of the nominal time from dosing, with the exception of the predose sample which must be collected predose. On Week 4, Week 24, and Week 52, a sample will be collected before the first daily dose (within 30 minutes prior to administered dose), and a sample will be collected two to eight hours postdose (after the first daily dose) (See Section 7.5.1). At the Week 2, Week 6, Week 8, Week 10, Week 12, Week 14, and Week 16, a sample will be collected during the study visit, irrespective of the time IMP was last dosed. The exact date/time of dosing and sample collections should be recorded in the eCRF.

CCI [redacted]

New Table Schedule of Assessments – Optional Long-Term Extension Period

LTE Trial Period	Visit Weeks During LTE Treatment Period														Follow-Up Visit 4 weeks Post-Last Dose[a]
Week	0	2	4	6	8	10	12	14	16	24	40	52	76	Week 104/ LTE EOT/Early Withdrawal	Week 108/ Safety Follow-Up/LTE End of Study
Trial Day	1	15	29	43	57	71	85	99	113	169	281	365	545	745	774
Visit	Day 1[b]	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 24	Wk 40	Wk 52	Wk 76	Wk 104	Wk 108
Visit window (±day)	-	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	+5
Informed Consent	X														
Verify subject remains eligible for the study (no prohibited medication, etc.)	X														
Vital signs, weight[c]	X		X		X		X		X	X	X	X	X	X	X
12-lead ECG	X						X			X		X	X	X	X[d]
Physical examination	X		X[e]		X[e]		X[e]		X[e]	X[e]	X[e]	X[e]	X[e]	X	X[e]
Routine hematology, urinalysis, chemistry	X		X		X		X			X	X	X	X	X	X
Urine microscopy	X									X		X		X	
Supplementary LFT labs		X		X		X		X	X						
Total Ig Levels (IgG, IgA, IgM)	X		X		X		X			X	X	X	X	X	X
Total B cell count[f]	X		X							X		X		X	X
Urine pregnancy test[g]	X		X		X		X		X	X	X	X	X	X	X
Urine pregnancy test kit dispensation[g]									X	X	X	X	X		
Reflex testing for HBV DNA[h]	X		X		X		X		X	X	X	X	X	X	X
UPCR	X									X		X		X	

LTE Trial Period	Visit Weeks During LTE Treatment Period													Follow-Up Visit 4 weeks Post-Last Dose[a]
Week	0	2	4	6	8	10	12	14	16	24	40	52	76	Week 104/ LTE EOT/Early Withdrawal	Week 108/ Safety Follow-Up/LTE End of Study
Trial Day	1	15	29	43	57	71	85	99	113	169	281	365	545	745	774
Visit	Day 1[b]	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 24	Wk 40	Wk 52	Wk 76	Wk 104	Wk 108
Visit window (±day)	-	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	+5
IMP dispensation[i]	X	Dispense as needed, using IWRS and complete compliance documentation													
IMP administration[j]	Daily Administration of Evobrutinib														
C-SSRS	X						X			X		X	X	X	X
SFI, SLEDAI-2K, PGA, BILAG 2004, CLASI	X									X		X		X	
SLICC/ACR Damage Index	X									X		X		X	
SF-36v2, LupusQoL, FACIT-Fatigue, EQ-5D-5L[k]	X									X		X		X	
PGIC[k]	X									X		X		X	
HRU	X		X		X		X		X	X	X	X	X	X	X
Concomitant medications / procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]															
Immunological Assessments															
Anti-dsDNA Complement (C3, C4), CRP	X									X		X		X	
ANA and other Autoantibodies	X									X		X		X	

ACR = American College of Rheumatology, ANA = Antinuclear Antibody(ies), Anti-dsDNA = Anti-Double-Stranded Deoxyribonucleic Acid, BILAG 2004 = British Isles Lupus Assessment Group 2004, CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index, C-SSRS = Columbia-Suicide Severity Rating Scale, D = day, DNA = deoxyribonucleic acid, ECG = Electrocardiogram, EOT = End of Treatment, EQ-5D-5L = EuroQoL 5 Dimension 5 Levels, FACIT = Functional Assessment of Chronic Illness Therapy, HBsAg = hepatitis B surface antigen, HBV = Hepatitis B Virus, HRU = Health Resource Utilization, Ig = Immunoglobulin, IMP = Investigational Medicinal Product, LFT = liver function test, LTE = Long-Term Extension, LupusQoL = Lupus Quality of Life, PGA = Physician's Global Assessment, PGIC = Patient Global Impression of Change, CCI [redacted], SFI = SLEDAI Flare Index, SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index-2000, SLICC = Systemic Lupus International Collaborating Clinics, SoA = Schedule of Assessments, UPCR = Urine Protein To Creatinine Ratio, Wk = Week, WOCBP = women of childbearing potential.

a Safety Follow-Up Visits will be conducted at four weeks after the last dose of IMP for subjects who have been discontinued from IMP or have completed the LTE Treatment Period.

b The LTE D1 visit is the EOT/Wk 52 visit from the DBPC Period unless a subject rollsover more than four weeks after the Wk 52/EOT visit. If a subject exceeds the four weeks due to unanticipated causes (e.g., regulatory approval delay), prior approval from the Medical Monitor is required and the subject will need to complete the LTE D1 visit (see Section 7.1.3).

c Vital signs including weight, oral temperature, seated blood pressure, pulse rate, and respiratory rate.

d Only required if change noted at Wk 104/EOT, when compared to Baseline ECG.

e Abbreviated physical examination may be performed at Primary Investigator discretion, as required to fully obtain information needed for the BILAG and/or SLEDAI assessments, if scheduled, as well as required to fully evaluate any subject complaints or adverse events (see Section 7.4.4.2).

f Only total B cell counts, flow cytometry for the other cell types and subsets, including B-cell subsets, will not be performed.

g The urine pregnancy test being used at all time points in this study must be a highly sensitive urine pregnancy test. In-between visit urine pregnancy tests will be dispensed and performed at home per SOA (Table 3) for WOCBP. The site staff will confirm completion of the home pregnancy testing and discuss results (Section 7.1.3).

h Additional HBV DNA PCR testing must be performed for subjects who entered the study with negative HBsAg and positive for anti-hepatitis B surface antibody and/or anti-hepatitis B core antibody with an HBV DNA negative OR detectable HBV DNA < 20 IU/mL only.

i The IMP will be dispensed per IWRS and IMP compliance documented using pill counts. All remaining IMP will be collected at Week 104 for all subjects.

j IMPs will be self-administered at a set time each day (± 2 hours).

k HRQoL Questionnaires should be completed before any other procedures are performed.

CCI [redacted]

New Table: Additional Pregnancy Testing for Long-Term Extension

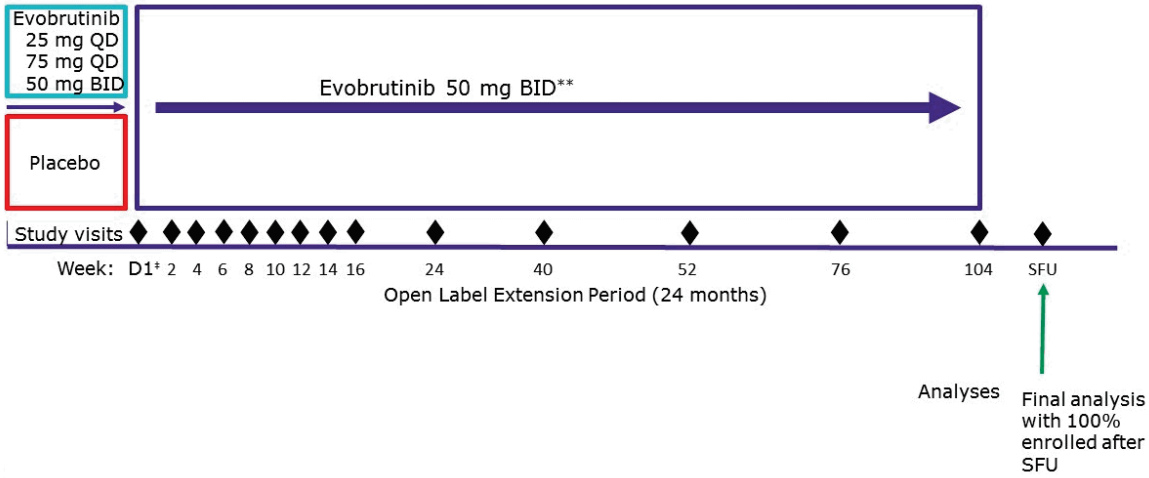
LTE Trial Period	Visit Weeks During LTE Treatment Period																
Week	20	28	32	36	44	48	56	60	64	68	72	80	84	88	92	96	100
Trial Day	143	200	229	258	315	344	402	430	459	488	516	574	602	631	660	688	717
Visit	8a	9a	9b	9c	10a	10b	11a	11b	11c	11d	11e	12a	12b	12c	12d	12e	12f
Visit window (±day)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Highly sensitive urine pregnancy test[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse events, LTE = Long-Term Extension.

a In-between visit urine pregnancy test will be performed at home. The site staff will call the subject to confirm completion of the home pregnancy testing and discuss results. Any occurrence of pregnancy results in subject withdrawal from IMP and the trial (see Section 5.5.1 and 5.5.2).

New Figure Added

Study Design for Long-Term Extension



BID = twice daily, D = day, LTE = Long-Term Extension, QD = once daily; SFU = Safety Follow-Up, SLE = Systemic Lupus Erythematosus, WOCBP = women of child bearing potential.

**** = Subjects will receive an initial dose of 50 mg BID. When a Phase 3 dose is determined, all subjects may be switched to this dose at the Sponsor's discretion.**

* = For subjects entering the Open-Label Extension, the Week 52 visit is considered the Day 1 visit for the Open-Label LTE Period.**

NOTE: For WOCBP, urine pregnancy tests will be performed at home to ensure monthly pregnancy testing.

Previous Table 7, now Table 9, Updated

Oral Corticosteroid Dose (in prednisone-equivalent) and Taper Guidance

Study Visit	Study Period	Maximum Allowable Dose[a]	Target Dose	Action for CS dosing
Screening	Screening Period	30 mg/day	≤ 30 mg/day	No change in CS dose[b]
Day 1 Week ~~0~~1		30 mg/day	≤ 30 mg/day	~~Initiate~~ **After Day 1, may initiate,** increase, decrease, or **have** no change t**o dose. Dose must be tapered to ≤ Day 1 dose by Week 4** ~~Taper to ≤Day 1 dose by Week 4~~
	Week 1 through 3	30 mg/day[f]	≤ 30 mg/day	
Week 4 Visit	Week 4	Day 1 dose[c]	**≤Dose at Day 1 Visit**	Begin taper to ≤ 10 mg/day by Week 8, as tolerated
	Weeks 5 through 7	Week 4 Visit dose	≤ 10 mg/day	Continue to taper to ≤ 10 mg/day by Week 8, as tolerated
Week 8 Visit	Week 8	Week 4 Visit dose	**≤ 10 mg/day**	Begin taper to ≤ 7.5 mg/day by Week 12, as tolerated
	Weeks 9 through 11	Week 8 Visit dose	≤ 7.5 mg/day	Continue to taper to ≤ 7.5 mg/day by Week 12, as tolerated
Week 12 Visit	Week 12	Week 8 Visit dose	**≤ 7.5 mg/day**	Taper as tolerated
	Weeks 13 through 15	Week 8 Visit dose	≤ 7.5 mg/day	Taper as tolerated
Week 16 Visit	Week 16	Week 8 Visit dose	**≤ 7.5 mg/day**	Taper as tolerated
	Weeks 17 through 23	Week 8 Visit dose	≤ 7.5 mg/day	No change in CS dose[d]
Week 24 Visit	Week 24	Week 8 Visit dose	**≤ 7.5 mg/day**	No change in CS dose[d]
	Weeks 25 through 39	Week 8 Visit dose	≤ 5 mg/day	Taper to ≤ 5 mg/day by Week 40, as tolerated
Week 40 Visit	Week 40	Week 8 Visit dose	**≤ 5 mg/day**	Taper as tolerated
	Weeks 41 through 52	Week 8 Visit dose	≤ 5 mg/day	No change in CS dose[e]

CS – Corticosteroids.

a Violation of requirements during the Screening Period results in screen-failure; treatment period violation **may result** ~~results~~ in treatment failure and withdrawal from study.

b Any dose change between Screening and Day 1 results in screen failure**.**

c Subjects with CS dose < 7.5 mg/day at Day 1 may have up to 7.5 mg/day at Week 4**.**

d Any dose increase during Weeks 17 to 24 results in treatment failure and withdrawal from study, dose may be tapered after Week 24 assessments have been completed**.**

e Any dose increase during Weeks 41 to 52 results in treatment failure and withdrawal from study**.**

f Although it is preferred that subjects do not receive a CS dose > 30 mg/day, subjects who receive > 30 mg/day between Day 1 and the Week 4 visit will not be withdrawn from the study if they are able to achieve a dose no higher than (≤) the Day 1 CS dose and ≤ 30 mg/day (whichever is lower) by the Week 4 visit.