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

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]

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																			

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	

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.

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

CCI

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

CCI

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:

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]

6.6 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:

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.

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.

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.

- 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.

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.

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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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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(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:

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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Long Term Extension Analysis Set

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

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.

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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

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																			

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]

CCI [redacted]

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.

CCI [redacted]

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.

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]																				

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]

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

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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.

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.

- 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.

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.

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.

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

- 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.

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

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.

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- 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:

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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.

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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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

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]																				