Official Title of Study: A Phase 2, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of BMS-931699 vs Placebo on a Background of Limited Standard of Care in the Treatment of Subjects with Active Systemic Lupus Erythematosus

NCT Number: NCT02265744

Document Date: May 3rd, 2015

SYNOPSIS

Clinical Protocol IM128027

Protocol Title: A Phase 2, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of BMS-931699 vs Placebo on a Background of Limited Standard of Care in the Treatment of Subjects with Active Systemic Lupus Erythematosus

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): BMS-931699 (active) or lulizumab pegol, administered subcutaneously, is formulated at 12.5 mg/mL and is provided as a liquid in single-use vials. Four treatments will be administered along with placebo treatment: 12.5 mg weekly, 12.5 mg every other week (EOW), 5 mg EOW and 1.25mg EOW, on a background of limited standard of care medications. The dose levels may be modified based on the interim analysis results. The study will comprise a short-term period (Part 1 and Part 2) and a long-term extension (LTE) period. Treatment duration will be up to 24 weeks (169 days) in the short term period. Subjects completing the short term period on study medication may be eligible to enter the LTE period. At the time of writing there is no defined end date to the long-term extension period, however, the LTE provision may be further adjusted based on results from the ongoing lulizumab development program.

Study Phase: Phase 2

Research Hypothesis: BMS-931699 will have greater clinical efficacy compared to placebo on the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) score, when added to stable background standard of care in subjects with active manifestations of systemic lupus erythematosus (SLE) including, at a minimum, elevated antinuclear antibodies, arthritis, and/or cutaneous manifestations satisfying the BILAG "A" or "B" criteria.

Objectives for the short-term period:

Primary Objective:

To compare the proportion of subjects who achieve BICLA response (BICLA response rate) at Day 169.

Secondary Objectives:

For Part 1 only:

- To evaluate the safety and receptor occupancy (RO) when 6 to 10 subjects per arm reach 29 days (4 weeks).

For both Part 1 and Part 2:

To assess:

- The safety and tolerability of treatment with BMS-931699 in subjects with active SLE
- The proportion of patients who meet response criteria for the SLE Responder Index (SRI) (4), SRI(5) and SRI(6) at Day 169 following 24-week treatment with BMS-931699 or placebo administered on a stable background therapy.
- The proportion of patients with SLE Responder Index [SRI(4), SRI(5) and SRI(6)] at Day 85 following 12-week treatment with BMS-931699 or placebo administered on a stable background therapy.
- The proportion of subjects with BICLA response at Day 85 following 12-week treatment with BMS-931699 or placebo administered on a stable background therapy
- The improvement in the extent of cutaneous and mucous membrane activity, as measured by the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) at Day 85 and Day 169
- Joint tenderness and swellings by American College of Rheumatology (ACR)28 criteria at Day 85 and Day 169
- The other indices of SLE activity measured at Days 29, 57, 85, 113, 141 and 169 including:
  - The change from baseline in overall BILAG-2004 score. A major response is defined as described in Yee et al 2010 (A=12; B=8; C=1; D/E=0).
  - The change in overall Systemic Lupus Erythematosus Disease Activity Index 2K score (SLEDAI 2K)

  - The change from baseline in Physician's Global Assessment of disease activity (MDGA) score
- The systemic exposure of BMS-931699 in subjects with SLE
- The cumulative corticosteroids use and immunosuppressants use over time
- The immunogenicity of BMS-931699
- Serum biomarkers C3, C4, anti-double-stranded deoxyribonucleic acid (anti-dsDNA), anti-nuclear antibody (ANA) and other autoantibodies at Day 85 and Day 169
- The pharmacodynamics (PD) of BMS-931699, including assessments potentially associated with target engagement (including receptor occupancy [RO]).

Objectives for the long-term extension period:

Assess the long term clinical safety, tolerability and efficacy of lulizumab pegol.

Study Design:

Phase 2, parallel-arm, randomized, double-blinded, multicenter, international study, with an adaptive design. Dose arm(s) may be adapted based on results of the planned interim analyses from Part 1 and Part 2, as follows:

- Safety and RO interim analysis: safety and RO analysis will be performed when approximately 6 to 10 subjects per arm have reached Study Day 29. Based on the results of this analysis, dose arms(s) may be adjusted or may be dropped.
- Interim analysis for futility and dose adaptation on BICLA response, SRI response, ACR28 and some SLE biomarkers (such as auto-antibodies, complement levels, etc.) with possible exploratory exposure response analysis, will be performed when approximately 30 subjects per arm (including subjects from Part 1 and Part 2) have reached Study Day 85 (12 weeks) of treatment or have discontinued prior to reaching study Day 85. Analysis will be performed by an unblinded Sponsor team, while maintaining blind at the site and subject level. Based on the results, the dose levels and sample size may be modified.
- Ongoing assessment of safety will be performed by an independent Data Monitoring Committee (DMC) and an internal unblinded safety monitoring team. Both entities may make recommendations to the Sponsor regarding conduct of study and dose adjustment based on safety observations.

Overall study design

Part 1
- Limited to approximately 30 to 50 subjects (6-10 per arm).
- Interim analysis for safety and RO once 30-50 subjects have reached Day 29 (4 weeks).
- These subjects will continue study treatment beyond the interim analysis for safety and RO and will be treated for up to 24 weeks, and followed for 6 additional weeks after treatment is completed or discontinued. Treatment could be shorter if dose arm(s) are dropped.

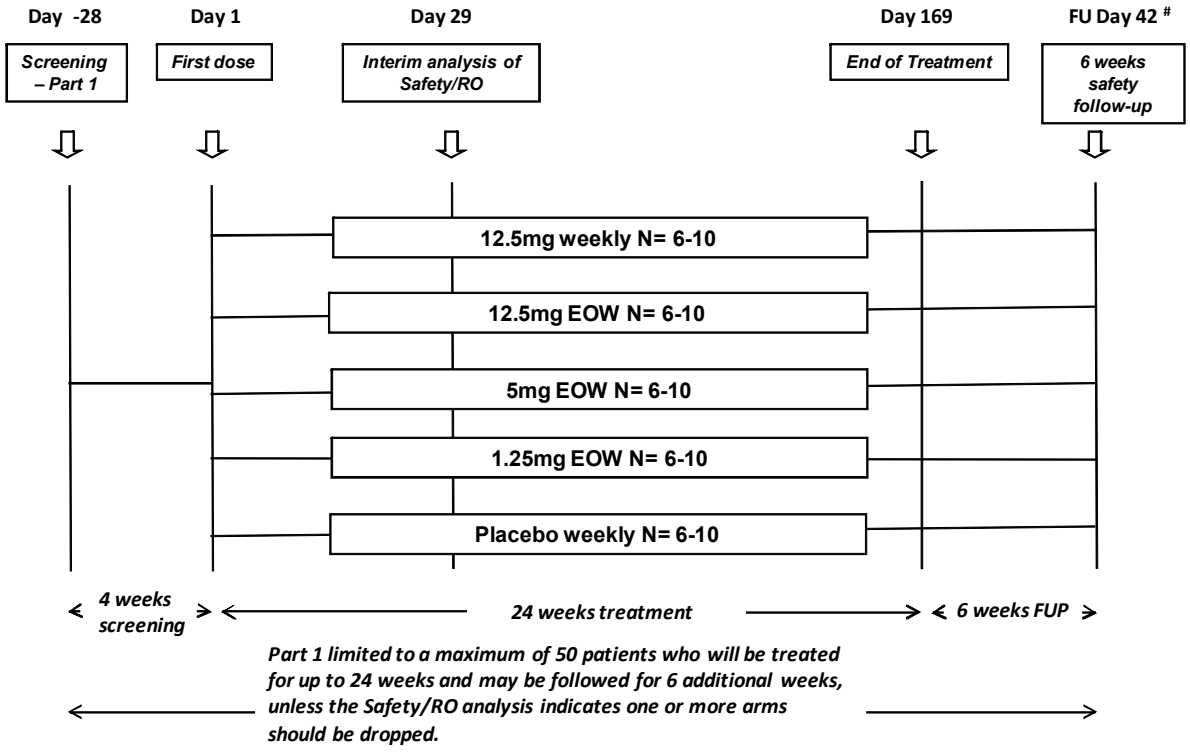
Part 2
- Will start once cumulative safety profile is considered acceptable and RO data for 6-10 subjects per arm for >28 days are available and the interim analysis from Part 1 is completed. Results of the interim analysis in Part 1 and DMC reviews may result in treatment arm(s) modifications.
- Each treatment arm will enroll approximately 70 subjects, including subjects from Part 1.
- Part 2 will have an interim analysis for futility once approximately 30 subjects per arm complete Day 85 (12 weeks), or have discontinued. As in the interim analysis from Part 1, results of the interim analysis in Part 2 and DMC reviews may result in treatment arm(s) modifications.
- All subjects could be treated for up to 24 weeks and followed for 6 additional weeks after treatment is completed or discontinued. Treatment could be shorter if dose arm(s) are dropped.

Long-Term Extension
- Subjects completing Day 169 (24 weeks) on study medication may be eligible to enter an optional long-term extension (LTE) period.
- The LTE period will remain blinded but will no longer have a placebo arm.
  - Subjects will remain on their originally-assigned treatment arm unless they were on placebo.
  - Subjects initially randomized to placebo arm will be automatically re-randomized into one of the existing active arms at Day 169 (24 weeks).

Intense safety monitoring by the DMC, in collaboration with an internal safety monitoring team, will be performed during Part 1 and continue during Part 2.

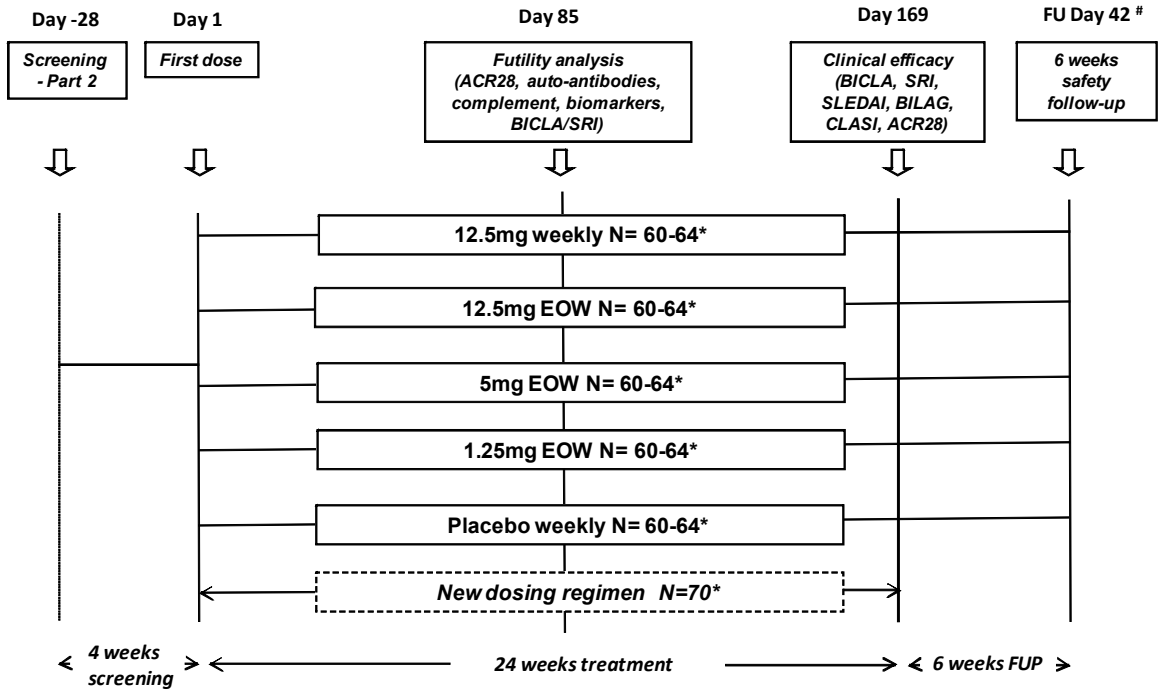
DMC and unblinded internal safety monitoring activities will continue during long-term extension.

Study Design Schematic - Short-term Period (Part 1)



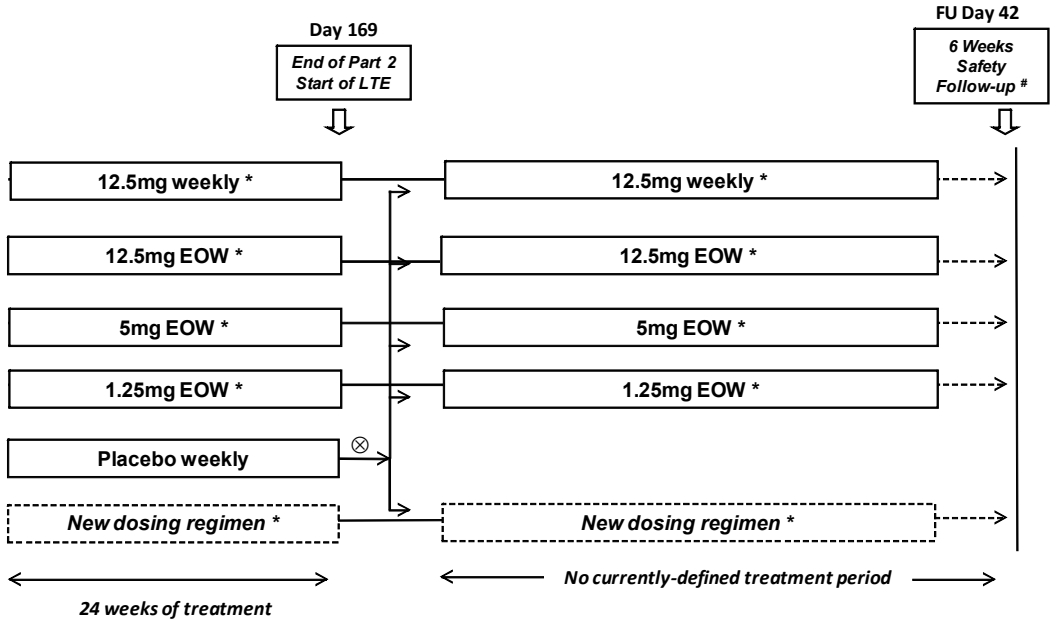
Will not apply to subjects entering LTE.

Study Design Schematic - Short-term Period (Part 2)



** Treatment arm may or may not be included based on Part 1 Day 29 Interim Analysis.*
 # Will not apply to subjects entering LTE.

Study Design Schematic - Long-term extension Period



** Treatment arm may or may not be included based on Interim Analyses.*
⊗ Subjects in the placebo arm will be re-randomized to existing active treatment arms at Day 169.
 # FU Day 42 to occur after last dose of study medication, whether last dose is in short term or long term periods.

Duration of Study:

Short-term Period: 28 days (4 weeks) of screening, 168 days (24 weeks) of treatment, 42 days (6 weeks) of safety follow-up, for a total of approximately 238 days (34 weeks). Subjects randomized into either Part 1 or Part 2 will be treated for up to 24 weeks and will have the same procedures performed and will follow the same visit schedule. If subject is eligible and opts to continue into LTE, the 42-day follow-up visit will not be performed after the short-term period is completed and subject will enter LTE directly. If subject opts not to enter LTE then a follow-up visit will be completed 42 days after end of treatment. At the time of writing there is no defined end date to the long-term extension period, however, the LTE provision may be further adjusted based on results from the ongoing lulizumab development program. Subjects discontinuing treatment during the LTE period will complete the follow-up visit approximately 6 weeks after receiving their last dose of study medication.

Number of Subjects:

Approximately 450 subjects will need to be screened to randomize approximately 350 subjects. Utilizing a 1:1:1:1:1 randomization scheme resulting in approximately 70 subjects in the each treatment arm. If the day 85 interim analysis suggests an additional dose arm at a lower dose level needs to be added, then up to 40 additional subjects may be randomized.

Approximately 125 sites will participate in this study, which will be conducted globally and should include, but will not be limited to, participation of countries located in North America and Europe.

Study Population: Male and female subjects, ages 18-70 years inclusive, satisfying the SLE classification criteria of the American College of Rheumatology (1982), as revised by the College in 1997, with elevated titer of anti-nuclear antibodies at Screening, active features of SLE, including at least one adjudicated BILAG B or greater due to arthritis and/or inflammatory skin disease. Unless intolerant, subjects must be on background therapy for 12 weeks, on a stable dose for at least 8 weeks, with at least one steroid sparing agent, including azathioprine (AZA), leflunomide, methotrexate (MTX), anti-malarial agents, mycophenolate mofetil/ mycophenolic acid, which must remain on stable dose throughout the study. Prednisone is not required; however, if subject is taking prednisone (or prednisone-equivalent), the maximum dose must not exceed 30mg/day of prednisone (or prednisone equivalent) at screening for a subject to be eligible and must be at a maximum of 10mg/day for at least 5 days prior to Day 1. Subjects must not have SLE manifestations or other disorders expected to require increase in corticosteroids (CS) during the study.

Women of childbearing potential (WOCBP) must not be nursing or pregnant and must be using an acceptable method of contraception for at least 4 weeks before dosing. WOCBP must have a negative pregnancy test within 24 hours prior to dosing with study medication

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for IM128027

Medication	Potency	IP/Non-IP
BMS-931699	12.5mg/mL	IP

Study Assessments:

- Efficacy assessments: will include BILAG-2004 Index, SLEDAI 2K, Physician's Global Assessment of Disease Activity (MDGA), Subject's Global Assessment of Disease Activity (PGA), ACR28 - joint count, FACIT - F, CLASI, SLICC/ACR Damage Index, SF-36, Coomb's test-direct.
- Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests. The incidence of observed adverse events will be tabulated and reviewed for potential significance and clinical importance. Ongoing assessment of safety will be performed by an independent Data Monitoring Committee (DMC). The DMC may make recommendations to the Sponsor regarding conduct of study based on safety observations.

- Pharmacokinetic parameters: Ctrough will be derived from serum BMS-931699 concentration versus time data.
- [redacted]

Statistical Considerations:

Sample Size: The sample size calculation is based on power to compare the proportion of subjects who achieve BICLA response (the BICLA response rate) at Day 169 between BMS-931699 and placebo arms. With a one-sided continuity corrected chi-squared test at significance level 0.05, data from 70 randomized and treated subjects per arm will provide at least 89% power to detect a 25% increase in the BICLA response rate in the active treatment arms (ie. 50% response rate in BMS active arms) compared to the placebo and provide 74% power to detect 20% increase in the BICLA response rate in the active treatment arm (ie, 45% response rate in BMS active arm) compared to the placebo, assuming that the placebo arm has 25% response rate which is reasonable based on the EMBLEM phase 2 trial result.[1] No adjustment will be made for multiplicity. Subjects who discontinue treatment/study prior to Day 169 will contribute to the data that will be analyzed for BICLA response at Day 169 (discontinuation will indicate no BICLA response). Therefore, no adjustment will be made for discontinuations.

The primary efficacy analysis will be conducted on all randomized patients who received at least one dose of the study drug. In order to get 70 randomized and treated subjects per arm, an adequate numbers of subjects need to meet the inclusion/exclusion criteria at screening.

If the interim analysis for futility and dose adaption suggests an additional dose arm at a lower dose level needs to be added, then up to 40 additional subjects may be randomized.

Endpoints for Short term Period:

Primary Endpoint

- Proportion of subjects who achieve BICLA response (BICLA response rate) at Day 169.

Secondary Endpoints

Safety

- Incidence and severity of all Adverse Events (AEs), Serious AEs (SAEs), and pre-established Events of Special Interest
- Incidence and severity of clinically significant changes in vital signs
- Incidence and severity of clinically significant ECG abnormalities
- Incidence and severity of clinically significant abnormalities in general laboratory tests

Efficacy

- Proportion of subjects who meet response criteria for the SLE Responder Index [SRI(4), SRI(5) and SRI(6)] at Day 169
- Proportion of subjects who meet response criteria for the SLE Responder Index [SRI(4), SRI(5) and SRI(6)] at Day 85
- Proportion of subjects with BICLA response at Day 85
- Change from baseline in CLASI score at Day 85 and Day 169
- Percentage of subjects with an improvement of >4 or a decrease of >50% from baseline in their CLASI score at Day 85 and Day 169

- Change from baseline in arthritis, as assessed by ACR28-joint count of tender and swollen joints at Day 85 and at Day 169
- The change from baseline in the following other indices SLE activity over time:
  - The overall BILAG-2004 score
  - The overall SLEDAI-2K score
  - The overall MDGA score
- The cumulative corticosteroid and immunosuppressant use over time

Pharmacokinetic

- Ctrough: Trough level serum concentration of BMS-931699 at time points specified in Table 5.5.1-1.

Immunogenicity

- Proportion of subjects with BMS-931699 induced antibody response over time points specified in Table 5.5.1-1.

[redacted]

Endpoints for Long term Extension Period:

During the LTE period, the following endpoints will be assessed cumulatively (safety) and over time (efficacy).

Safety Endpoints

- Incidence and severity of all Adverse Events (AEs), Serious AEs, and pre-established Events of Special Interest
- Incidence and severity of clinically significant abnormalities in general laboratory tests

Efficacy Endpoints

- Proportion of subjects who achieve BICLA response (BICLA response rate)
- Proportion of subjects who meet response criteria for the SLE Responder Index (SRI) [SRI(4), SRI(5) and SRI(6)]
- CLASI score
- ACR 28 joint count of tender and swollen joints
- Overall BILAG-2004 score
- Overall SLEDAI-2K score
- Overall MDGA score
- The cumulative corticosteroid and immunosuppressant use
- Proportion of patients reaching a Major Clinical Response and Partial Clinical Response
- Fatigue, based on the FACIT
- Quality of life, based on SF-36

Pharmacokinetic Endpoints

- Ctrough: Trough level serum concentration of BMS-931699 at time points specified in Section 5.5.

[redacted]

Immunogenicity

- Proportion of subjects with BMS-931699 induced antibody response

Analyses for the Short-term Period:

Primary analysis:

The Chi-square tests will be used to compare the BICLA response rates at Day 169 between each of the active treatment arms and the placebo arm. The Chi-square p-value will be provided for each comparison between the active treatment and the placebo arm. In addition, the difference of the response rates between each active treatment and placebo will be estimated and their corresponding 90% confidence interval will be calculated. No adjustment will be made for multiplicity.

Secondary analysis:

Efficacy analysis:

- Proportion of subjects who meet response criteria for the SLE Responder Index [SRI(4)], SRI(5) and SRI(6)] at Day 169
- Proportion of subjects who meet response criteria for the SLE Responder Index [SRI(4)], SRI(5) and SRI(6)] at Day 85
- Proportion of subjects with BICLA response at Day 85
- Percentage of subjects with an improvement of > 4 or a decrease of > 50% from baseline in their CLASI score at Day 85 and Day 169

For each of the above endpoints, the estimate and its corresponding 90% confidence interval will be calculated for the difference of the proportions between each active treatment arm and the placebo arm at the specified visit, similar to the primary analysis.

For each of the following endpoints, the mixed effect model will be fit with treatment and visit as the fixed effects and measurements within each subject as the repeated measurements. The baseline value will be added into the model as a covariate if necessary. Based on the mixed effect model, the estimate and 90% confidence interval will be calculated for the difference between each active treatment and the placebo at each specified visit.

- Change from baseline in CLASI score at Day 85 and Day 169
- Change from baseline in arthritis, as assessed by ACR28-joint count of tender and swollen joints at Day 85 and at Day 169
- The change from baseline in the following other indices SLE activity over time:
  - The overall BILAG-2004 score
  - The overall SLEDAI-2K score
  - The overall MDGA score

In addition, the cumulative corticosteroid and immunosuppressant use over time will be summarized.

***Safety analysis*:**

All recorded adverse events will be listed and tabulated by system organ class, preferred term and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical

examination findings, and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed. The pre-established Events of Special Interest will be listed and summarized.

PK analysis:

Ctrough will be summarized by dose and study day.

Immunogenicity analysis

Proportion of subjects with BMS-931699-induced antibody response and titers over time will be summarized.

[redacted]

Interim analysis:

Interim Analysis for Safety/RO at Day 29

When at least 6 subjects per arm have reached Day 29, an interim analysis (IA) for safety and RO will be performed. The safety analysis will focus on incidence and severity of all adverse events (AEs), serious AEs and pre-established Events of Special Interest such as infection AEs and any other safety analysis requested by DMC. For RO: the median RO at Day 29 for each treatment arm will be calculated. Based on the results of this interim analysis, a decision will be taken regarding the doses that will be carried forward into Part 2 of the study. Specifically, dosing regimens originally included in Part 1 may be discontinued and/or new dosing regimens may be added according to the following criteria:

Safety:

The DMC in conjunction with an unblinded internal monitoring team may require one or more doses to be discontinued if stopping criteria are met or other safety signals arise that the Medical Monitor and/or DMC consider of sufficient concern.

Receptor Occupancy:

- If median RO of any dose is < 20%, the sponsor may consider dropping that dose;
- If the median RO for all doses is > 90%, the sponsor may consider adding or replacing a dose in Part 2 of the study to ensure an adequate pharmacodynamic range (dose not to exceed 12.5 mg weekly).

Dose decrease and/or reduction of frequency of administration may also be considered if RO results fall outside the parameters indicated above. This adjustment may occur for safety reasons or in case unforeseen RO profiles observed in SLE patients. The decision to adjust dose and/or frequency will be taken after review of the data by the clinical team.

Interim analysis for futility and dose adaptation at Day 85:

After 30 subjects per treatment arm (including the subjects from Part 1) have completed at least 84 days of the treatment period or discontinued the treatment, an interim analysis will be conducted to assess the futility of the BMS-931699 dose arms and the overall safety. The results of the interim analysis will be reviewed by an unblinded sponsor team who will provide recommendations to the blinded study team. The blinded study team will make the decision. The unblinded BMS team may recommend to:

- Maintain the current design;
- Drop a certain dose arm(s) and equally randomize the remaining unallocated subjects to the remaining arms;
- Stop the study if all dose arms need to be dropped for safety or futility reasons.

The interim analysis for futility and dose adaption will be performed on the BICLA response at Day 85 and Day 169, of those 30 subjects per arm who have completed 85 days of treatment or discontinued the treatment, using

a Bayesian predictive approach.[2] This analysis assumes that the BICLA response at Day 85 and at Day 169 in the subjects who have not yet been observed will be similar to those observed for the subjects included in the interim analysis at Day 85 and Day 169, respectively. As such, the unobserved data will be simulated from the predictive distribution conditional on the interim data and the prior distribution of the treatment difference (using a non-informative prior). Under the Bayesian framework, the posterior distribution of the treatment difference (BMS-931699 active dose – Placebo) will be constructed to determine the predictive probability of a successful outcome (ie, reach statistical significance) at Day 169. Based on computer simulations of the operating characteristics of the study design, the futility threshold in this interim analysis is set to 0.2. For the comparison of interest, if the predictive probability of a successful outcome at the planned end of the trial falls below 0.2, that BMS-931699 dose arm is deemed futile in terms of BICLA response. However, the final futility will also incorporate the results from SRI(4), ACR28 and some biomarkers (C3, C4, ANA and anti-dsDNA).

The proposed stopping rules at the interim analysis, based on the futility assessment and the overall safety assessment, are as follows:

- Rule 1: Drop the futile dose arm(s) and the dose arm cannot be dropped until the lower dose arm has been dropped.
- Rule 2: Drop the dose arm(s) with safety issues identified;
- Rule 3: If safety issues are identified in all dose arms or all dose arms are futile, stop the study.

In case dosing arms are dropped following the interim analysis, the remaining unallocated subjects will be randomized into the remaining arms.

If the predictive probability of success for each active arm versus placebo is greater than or equal to 0.9, then the BMS team may also recommend adding an additional dose arm at lower dose level than current active doses to explore a suboptimal dose.

In that case, the remaining unallocated subjects with up to 40 additional subjects will be randomized into the remaining arms and the new dose arm based on the new randomizations schedule.

Analyses for the long-term extension period:

The LTE period starts when a subject receives at least one post Day 169 dose. The analysis based on this period is descriptive in nature.

Populations of Analysis

All Subjects who received at least one dose post Day 169.

Demographics and Baseline Characteristics

Categorical parameters will be summarized using frequency counts and percentages. Continuous parameters will be summarized through means, SD, median, and range. The baseline (Day 1) is defined as the start of study medication (the same as baseline in Double-blind period). The baseline results will be based on LTE analysis population.

Efficacy Analyses

For continuous secondary endpoints (e.g. SLEDAI, MDGA etc.) point estimates and 90% confidence intervals for mean change from baseline to subsequent time points (in LTE period) within each treatment groups will be provided. For binary endpoints (BICLA Response, SRI(X) etc.), point estimates and 90% confidence intervals (CIs) will be provided using normal approximation within each treatment group. The assessment windows for LTE period will be based on the first LTE dose date; the baseline to assess responses or changes still refers to the Day 1 assessment (the same as baseline in Short-term Period). The results will be presented by treatment groups. All Analyses will be based on as-observed data; hence no imputation will be implemented. No statistical testing including p-value computation will be performed.

Safety Analyses

The evaluation of long term safety of the selected dose(s) will be based on clinical adverse events, vital signs and laboratory abnormalities reported during the LTE period. Frequency distributions and individual listings of all

adverse events and laboratory marked abnormalities will be generated based on As Treated population. The results will be presented by treatment groups.

Immunogenicity

The incidence of a positive response of anti-BMS-931699 antibodies during the LTE period will be summarized by treatment groups.

Pharmacokinetic Analyses

The descriptive summary of PK parameters will be provided by visits and by treatment groups during the LTE period.

Pharmacodynamic Analyses

The descriptive summary of selected PD and selected biomarkers will be provided by visits and by treatment groups during the LTE period.

Outcomes Research Analyses

Not applicable.

The details of the analyses, endpoints and grouping schemes (treatment groups) will be provided in the long-term statistical analysis plan (LTE SAP).

[redacted]

[redacted]

1.2 Research Hypothesis

BMS-931699 will have greater clinical efficacy compared to placebo on the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) score, when added to stable background standard of care in patients with active manifestations of systemic lupus erythematosus (SLE) including, at a minimum, elevated antinuclear antibodies, arthritis, and/or cutaneous manifestations satisfying the BILAG "A" or "B" criteria.

1.3 Objectives(s)

1.3.1 Primary Objectives

To compare the proportion of patients who achieve BICLA response (BICLA response rate) at Day 169.

BICLA is defined as:

- British Isle Lupus Assessment Group improvement, defined as BILAG As at Baseline improved to B/C/D, and BILAG Bs at baseline improved to C/D, and no BILAG worsening in other BILAG organ systems such that there are no new BILAG As or greater than 1 new BILAG B; and
- No worsening in the SLEDAI-2K total score compared to Baseline (defined as no increase in SLEDAI total score); and
- No worsening in the physician's global assessment (MDGA) of disease activity ("no worsening" is defined as less than 10% worsening, equivalent to a 10mm increase on a 100mm visual analog scale [VAS]) compared to Baseline.
- No changes in concomitant medications according to the following criteria:
  - No increase of or addition of a new immunosuppressant agent (azathioprine, mycophenolic acid/mycophenolate mofetil, methotrexate, anti-malarial, leflunomide) over baseline levels.
  - No increase in corticosteroid dose above baseline level outside of those allowed per protocol.

1.3.2 Secondary Objectives

Short-term period Part 1 only:

- To evaluate the safety and RO when 6 to 10 subjects per arm reach 29 days (4 weeks).

Short-term period Part 1 and Part 2:

To assess:

- The safety and tolerability of treatment with BMS-931699 in patients with active SLE
- The proportion of patients who meet response criteria for the SLE Responder Index(4) [SRI(4)], SRI(5) and SRI(6) at Day 169.

  Note: An SRI(X) Response is defined as:

  - a reduction in Day 1 SLEDAI-2K disease activity score of ≥ X points;
  - no worsening of disease (defined as an increase of ≥ 30mm on a 100mm VAS from Day 1 as measured by the MDGA; and
  - no new BILAG-2004 Index A organ system score and no more than one new or worsening BILAG-2004 Index B organ system scores
- The proportion of patients with SLE Responder Index [SRI(4), SRI(5) and SRI(6)] at Day 85.
- The proportion of patients with a BICLA response at Day 85.
- The improvement in the extent of cutaneous and mucous membrane activity, as measured by the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) at Day 85 and Day 169

- Joint tenderness and swellings as measured by the by American College of Rheumatology (ACR)28 at Day 85 and Day 169
- The other indices of SLE activity measured at Days 29, 57, 85, 113, 141 and 169 including:
  - The change from baseline in overall BILAG-2004 score. A major response is defined as described in Yee et al 2010 (A=12, B=8, C=1, D/E=0).[11]
  - The change in overall Systemic Lupus Erythematosus Disease Activity Index 2K score (SLEDAI 2K)
  - The change from baseline in Physician's Global Assessment of disease activity (MDGA) score
- The systemic exposure of BMS-931699 in patients with SLE
- The cumulative corticosteroids use and immunosuppressants use over time
- The immunogenicity of BMS-931699
- Serum biomarkers C3, C4, anti-double-stranded deoxyribonucleic acid (anti-dsDNA), anti-nuclear antibody (ANA) and other autoantibodies at Day 85 and Day 169
- The pharmacodynamics (PD) of BMS-931699, including assessments potentially associated with target engagement [including receptor occupancy (RO)].

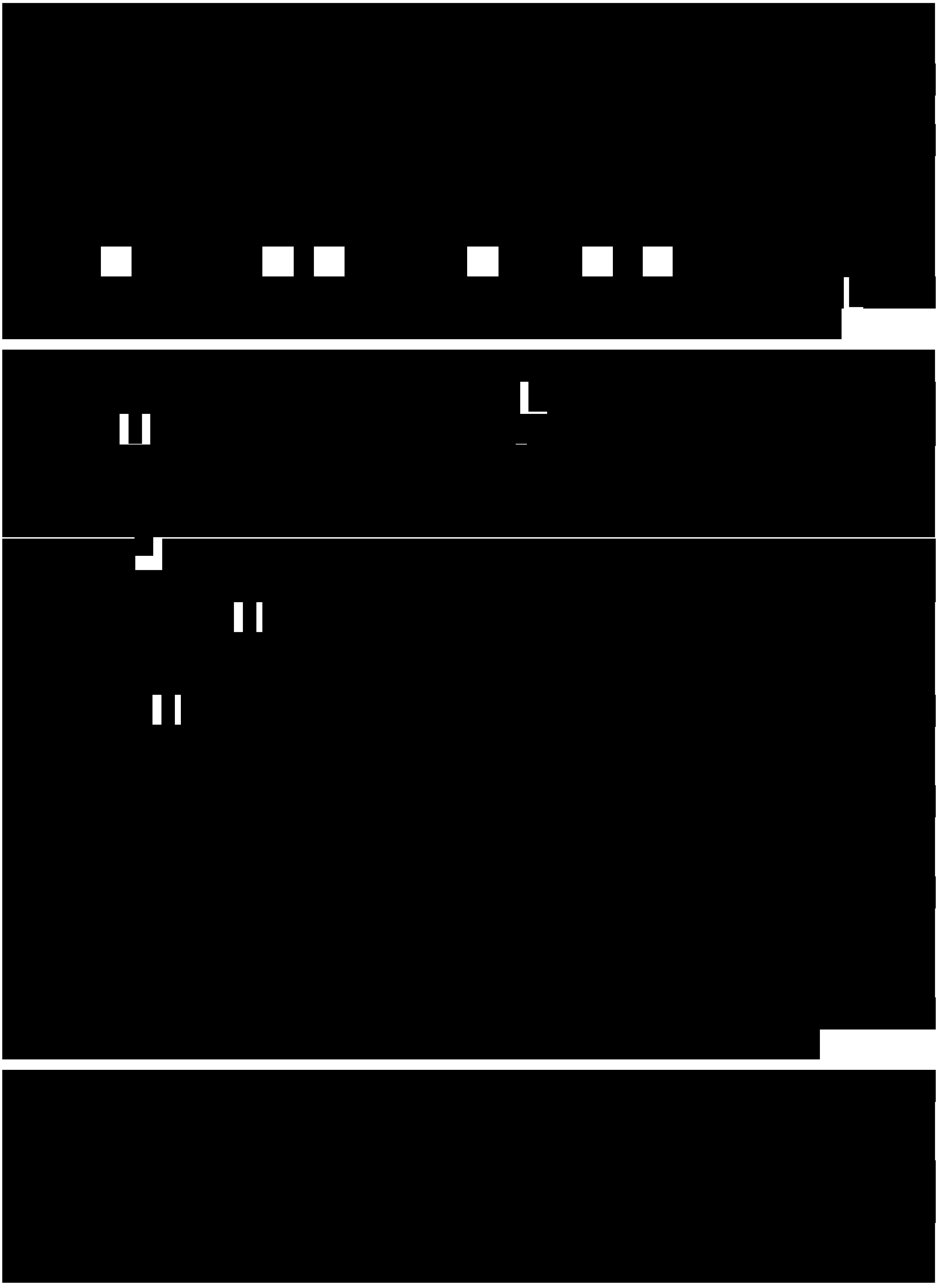
  Note: Although all efforts must be made to collect all RO samples required per protocol, it may not be possible for a site to obtain samples from subjects located in certain participating regions due to stability and processing issues. Site **MUST** consult with the Medical Monitor prior to deciding not to collect RO samples.

[redacted]

1.3.4 Long-Term Extension Period Objectives

Assess the long term clinical safety, tolerability and efficacy of lulizumab pegol.

[redacted]



[redacted]

similar to the reported plasma volume, indicating very limited extravascular distribution. The [redacted]

[redacted]

[redacted][16]

[redacted] [redacted]

[redacted]

[redacted]

The MAD study IM128003 was performed in 24 subjects (3 cohorts of 8 subjects) treated for

[redacted]

[redacted]

[redacted]

Intense safety monitoring will be put in place during the entire study (short-term and long-term extension periods), allowing early detection of any safety signals. Specifically, the following measures will be put in place:

- Patients will undergo safety evaluation at each clinic visit.
- Investigator will conduct safety evaluation before dosing.
- Continuous internal data review by unblinded clinical monitoring team.
- Monitoring team to refer to independent external DMC any safety issue deemed to be of relevance.
- Independent external DMC to meet at regular intervals throughout the entire study to review all data (frequency to be determined in conjunction with DMC).
- Stopping rules to be implemented under DMC guidance.

DMC and internal safety monitoring activities initiated in Part 1 will continue into Part 2 and will be ongoing until the end of the study, including the long-term extension.

In summary, the potential overall benefit ratio for BMS-931699 treated subjects in this trial appears favorable. In order to minimize the overall risk to participating subjects, this protocol has inclusion and exclusion criteria appropriate to the population and proposed treatments, exclusionary screening tests [chest x-ray, Quantiferon Gold testing (or other interferon gamma release assay test, such as T-SPOT) wherever appropriate, risk factor/age specific breast screening, medical history], and specific follow-up safety assessments. In addition, the AEs and SAEs will be reviewed on an ongoing basis by the medical monitors and pharmacovigilance group to look for trends and any safety issues.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol,

which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form(s) which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form(s) and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC’s written approval/favorable opinion of the written informed consent form(s) and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

- If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
- Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form(s) must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a Phase 2, parallel-arm, randomized, double-blinded, multicenter, international study, with an adaptive design.

The study will comprise a short-term period (Part 1 and Part 2), and a long-term extension (LTE) period.

Part 1 of the short-term period will focus on assessing safety and RO and will be limited to a maximum of 50 patients (approximately 6-10 patients/arm) who will be included in the Safety/RO interim analysis (IA). These patients will continue study treatment beyond the IA for Safety/RO and be treated for up to 24 weeks and be followed for 6 additional weeks after treatment is completed. Treatment could be shorter if IA for Safety/RO analysis indicates one or more arms should be dropped.

Part 2 of the short-term period will start once cumulative safety profile is considered acceptable and RO data for 6-10 subjects per cohort dosed for >28 days is available and the interim analysis from Part 1 is completed. Approximately 300 subjects will be randomized into this part of the study (number of patient to be randomized into Part 2 may increase based on the results of the futility interim analysis).

All subjects will undergo screening evaluations to determine eligibility and allow down titration of prednisone (or prednisone equivalent) prior to administration of study medication. The screening period will have a duration of approximately 28 days (+/- 2 days). All eligibility criteria must be met prior to Day 1. In the event of technical difficulties leading inconclusive assessments that would go beyond the allowed window, the study medical monitor must be consulted prior to conducting Day 1. On Day 1, eligibility of subjects will be confirmed and eligible subjects will receive their first dose of study medication.

Dose may be adapted based on results of the planned interim analyses from Part 1 and Part 2, as follows:

- Safety and RO interim analysis: safety and RO analysis will be performed when approximately 6 to 10 subjects per arm have reached Study Day 29. Based on the results of this analysis, dose arms(s) may be adjusted or may be dropped.
- Interim analysis for futility and dose adaptation on BICLA response, SRI response, ACR28 and some SLE biomarkers (such as auto-antibodies, complement levels, etc.) with possible exploratory exposure response analysis, will be performed when approximately 30 subjects per arm have reached Study Day 85 (12 weeks), including subjects from Part 1 and Part 2, of treatment or have discontinued prior to reaching study Day 85). Analysis will be performed by an unblinded Sponsor team, while maintaining blind at the site and subject level. Based on the results, the dose levels and sample size may be modified.
- Ongoing assessment of safety will be performed by an independent Data Monitoring Committee (DMC) and an internal unblinded safety monitoring team. Both entities may make recommendations to the Sponsor regarding conduct of study and dose adjustment based on safety observations.

Following interim analyses and DMC reviews, dose arm(s) may be modified based on the results, as follows:

- If one or more arms are added, future randomizations will include the new arm(s).
- If one or more arms are dropped for safety reasons, randomization into that arm will be terminated and all subjects currently randomized to that or those arm(s) will be discontinued from receiving study medication.
- If one or more arms are dropped due to inadequate RO, there will be no new randomizations into that dose arm; subjects currently randomized may continue at the Investigator discretion.

The **long-term extension (LTE) period** is optional and will include eligible subjects who have completed Day 169 (week 24) of treatment and consent to participate. This period of the study will remain blinded but will no longer have a placebo arm. Eligible subjects will remain on their

originally-assigned dose arm, unless they were on the placebo arm during the short-term period. Placebo-arm subjects will be re-randomized into one of the existing active arms at Day 169 (24 weeks). Re-randomization of the placebo subjects will be done by IVRS and only the unblinded pharmacist/drug preparer will know the new randomization arm. The LTE will remain blinded to the study team and study personnel.

The long-term extension period will not have interim analyses for dose adaptation. However, the BMS unblinded safety committee will continue to review the safety data and discuss it with the DMC (also unblinded), as needed. During their evaluation of adverse events, if a significant safety concern is identified, these two committees may propose that one or more dose arms are dropped. If one or more dose arms are dropped for safety reasons, all subjects currently receiving that or those dose(s) will be discontinued from receiving study medication.

The study design schematics are presented in Figure 3.1-1, Figure 3.1-2, Figure 3.1-3, and Figure 3.1-4.

Figure 3.1-1: Overall Study Design

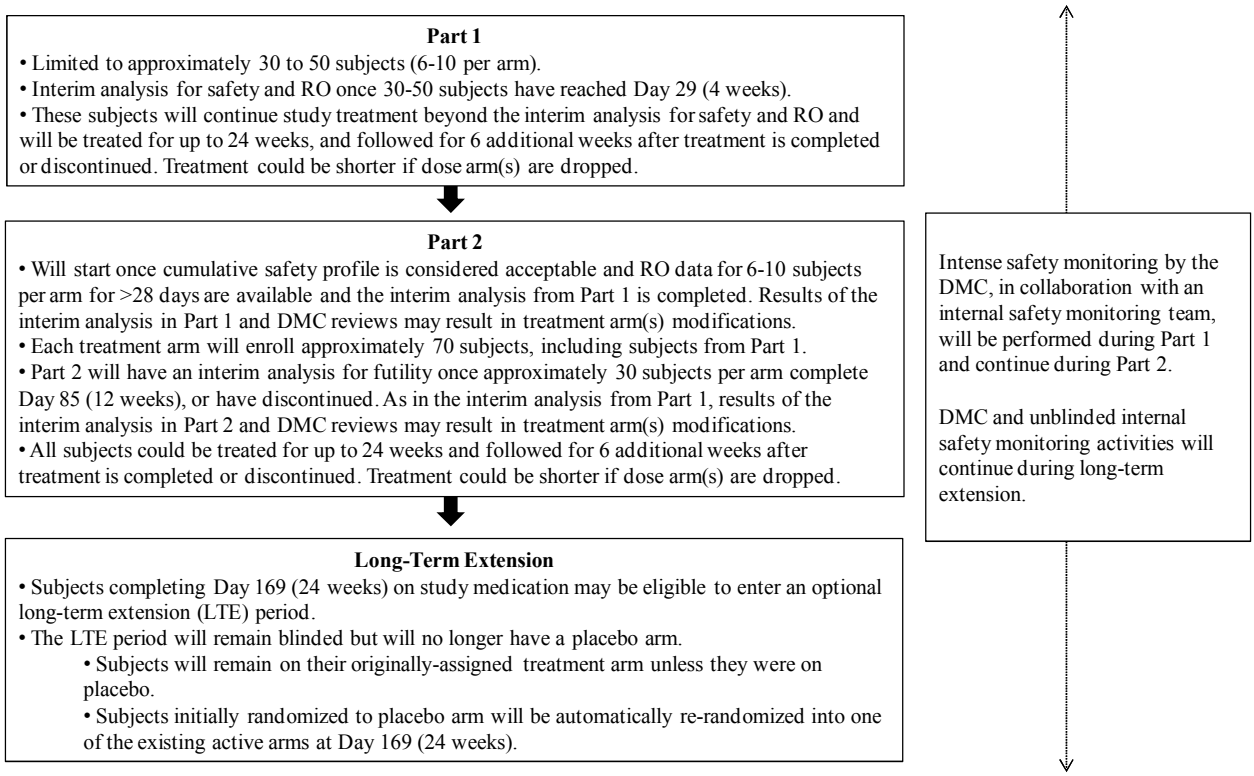
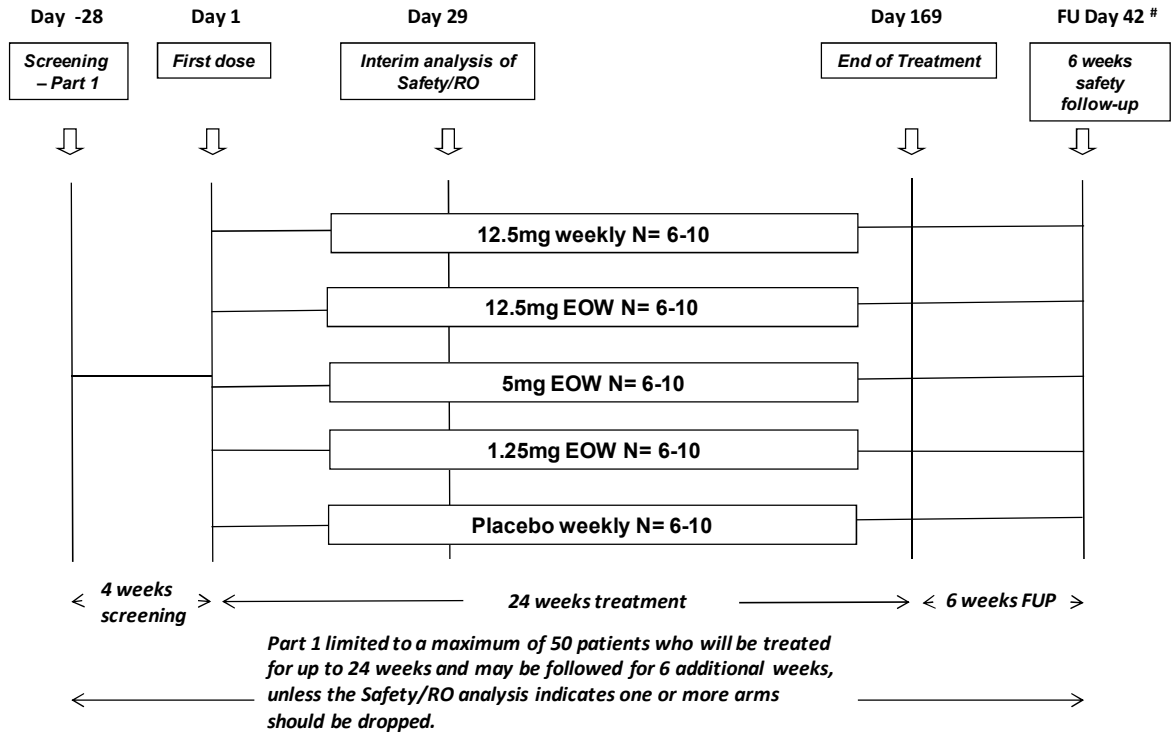
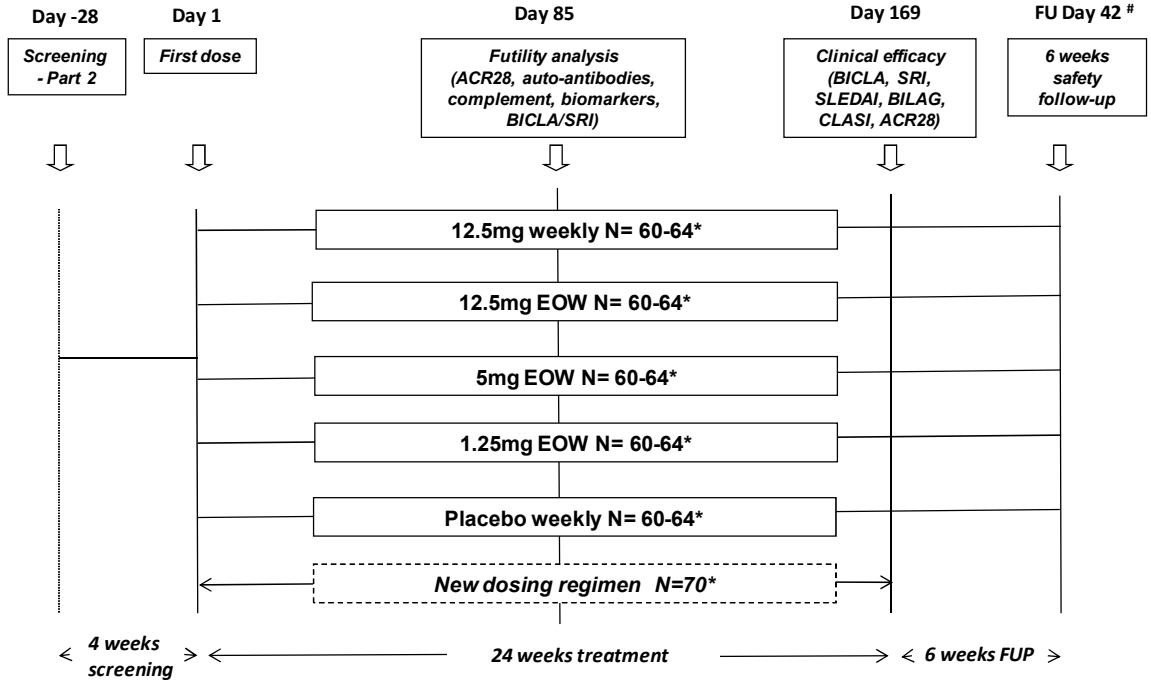


Figure 3.1-2: Study Design Schematic - Part 1



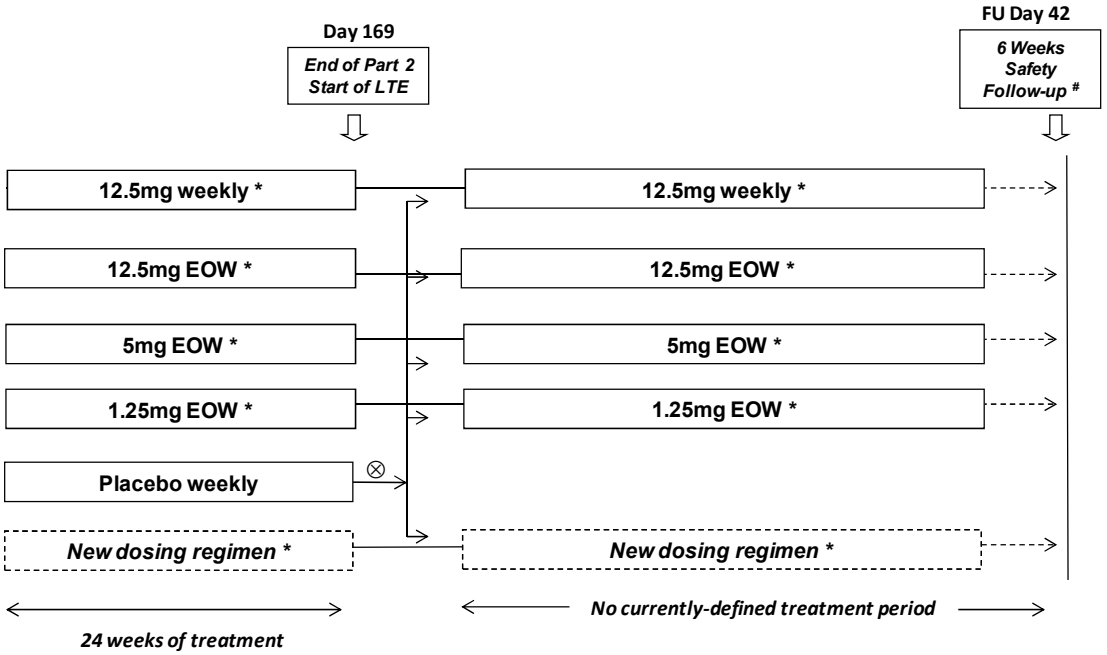
Will not apply to subjects entering LTE.

Figure 3.1-3: Study Design Schematic - Part 2



** Treatment arm may or may not be included based on Part 1 Day 29 Interim Analysis.*
 # Will not apply to subjects entering LTE.

Figure 3.1-4: Long-Term Extension Schematic



** Treatment arm may or may not be included based on Interim Analyses.*
⊗ Subjects in the placebo arm will be re-randomized to existing active treatment arms at Day 169.
 # FU Day 42 to occur after last dose of study medication, whether last dose is in short term or long term periods.

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations will be performed at selected times throughout the study. Subjects will be closely monitored for adverse events throughout the study. Blood will be collected for pharmacokinetic (PK) and pharmacodynamic measurements as well as for safety monitoring.

The approximate duration of the short-term period (Parts 1 and 2) of the study is 238 days (34 weeks), including: 28 days (4 weeks) of screening, 168 days (24 weeks) of treatment, and 42 days (6 weeks) of safety follow-up. If subject is eligible and opts to continue into LTE, the 42-day follow-up visit will not be performed after the short-term period is completed and subject will enter LTE directly. If subject opts not to enter LTE then a follow-up visit will be completed 42 days after end of treatment. At the time of writing there is no defined end date to the long-term extension period, however, the LTE provision may be further adjusted based on results from the ongoing lulizumab development program. Subjects discontinuing treatment during the LTE period will complete the follow-up visit approximately 6 weeks after receiving their last dose of study medication.

Subjects randomized in the short-term period (either Part 1 or Part 2) will be treated for up to 24 weeks, will have the same procedures performed and will follow the same visit schedule. All subjects will account for the approximately 350 subjects planned to be randomized in this study.

Approximately 125 sites will participate in this study, which will be conducted globally and should include, but will not be limited to, participation of countries located in North America and Europe.

Subjects who discontinue from the study will have one follow-up visit, approximately 42 days (6 weeks) after receiving their last dose of study medication, to perform safety assessments. During this period, when subjects are no longer receiving study drug, it is recommended that they are not treated with other biologic therapy, due to the compound's half-life. However, this decision remains at the investigator's discretion. If the study drug becomes commercially available, and if the subject chooses to receive treatment with the commercial product, then the subsequent post-dose follow-up visits are not required.

3.2 Post Study Access to Therapy

At the time of writing there is no defined end date to the LTE period, however, the LTE provision may be further adjusted based on results from the ongoing lulizumab pegol development program. At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug. Study drug may be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS supplied study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; d) BMS terminates development of the drug; or e) therapeutic alternatives become available in the local market.

3.3 Study Population

Men or women (not nursing or pregnant), ages 18-70 years inclusive, who meet the ACR criteria for the classification of Systemic Lupus Erythematosus (see Appendix 3).

For entry into the short-term period of the study, the following criteria MUST be met prior to dosing on Day 1. No exceptions will be granted.

For entry into the long-term extension, subjects must remain on study medication, complete the short-term period (up to 24 weeks of treatment), and sign a new informed consent.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects must be willing to participate in the study and sign the informed consent.

b) Subjects must be willing and able to complete all study specified procedures and visits.

2. Target Population

a) Subjects must have SLE as defined by meeting 4 of the 11 classification criteria of the American College of Rheumatology for the classification of SLE, either sequentially or coincident. The 4 criteria need not be present at study entry, but have occurred at some time during the course of the disease and be documented.

b) Subject Re-screening: This study permits the re-screening of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated). If re-screened, the subject must be re-consented.

Note (1): If a subject is being considered for re-screening, a full screening visit must be performed again.

Note (2): A subject can only be re-screened once (eg, if re-screening for the same subject fails, no additional re-screening is allowed).

c) At screening:

i) Subjects must have elevated ANA ≥ 1:80 via immunofluorescent assay at the central laboratory or anti-dsDNA or anti-Sm above the normal level as determined by the central laboratory.

Note: For inclusion criterion 2c-i: If central laboratory results are negative and positive results are documented at the site, a single repeat of the central laboratory values is allowed. If the central laboratory repeat is negative, the patient is not eligible to be randomized.

ii) Subjects must have a SLEDAI ≥ 6 to be eligible. At least 4 of the points must be attributable to clinical criteria including at least one of the following clinical parameters: arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, vasculitis and excluding points from lupus headache and organic brain syndrome. Must be confirmed by the External Adjudication Committee.

Note: On Day 1, the SLEDAI 2K must be ≥4 including points from at least one of the following clinical components: arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, vasculitis, and fever and excluding parameters which require central laboratory results (hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia and leukopenia). Points from lupus headache and organic brain syndrome are excluded.

iii) Subjects must have at least one of the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the External Adjudication Committee:

(1) BILAG A or B score in the Mucocutaneous body system

(2) BILAG A or B score in the Musculoskeletal body system due to active polyarthritis defined as follows:

(a) "BILAG A": severe arthritis (BILAG #41) manifested by observed active synovitis in ≥ 2 joints with marked loss of functional range of movements and significant impairment of basic activities of daily living, that has been present on several days cumulatively over the past 4 weeks, including at the time of the screening visit. Basic ADLs are defined as the following activities which require assistance or assistive devices (at least one must be present and documented in source): ambulation, toileting, grooming including bathing, dressing, feeding oneself (not responsive to steroids up to 10 mg/day, antimalarials, NSAIDs).

(b) "BILAG B": Moderate arthritis or tendonitis or tenosynovitis (BILAG #42) defined as tendonitis/tenosynovitis or active synovitis in ≥ 1 joint (observed or through history) with some loss of functional range of movements which lead to some loss of functional range of motion as manifested by effects on instrumental ADLs (such as cooking, driving, using the telephone or computer, shopping, cleaning, etc.) which has been present on several days over the last 4 weeks and is present at the time of the screening visit.

(3) if only one "B" and no "A" score is present in the Mucocutaneous body system or in the Musculoskeletal body system due to arthritis, then at least one B must be present in the other body systems for a total of 2 "B" BILAG body system scores.

iv) Unless intolerant, subjects must be currently receiving at least one of the following steroid-sparing agents for a minimum of 12 weeks, and at stable dose for at least 8 weeks (56 days) prior to signing consent:

Azathioprine (AZA), chloroquine, hydroxychloroquine, methotrexate (MTX), leflunomide, mycophenolate mofetil/mycophenolic acid*. Subjects must remain on stable dose throughout the study[#].

*Subjects who are receiving mycophenolic acid/mycophenolate mofetil may participate in the study only if mycophenolate mofetil therapy is given as a maintenance therapy and up to a maximum of 2 g/day (or mycopheloate acid dose equivalent); in subjects of African ancestry, 3 g/day (or mycopheloate acid dose equivalent) may be administered at the Investigator's discretion.

v) Prednisone is not required; however, if subject is taking prednisone (or prednisone-equivalent), dose cannot exceed 30 mg/day at screening for a subject to be eligible and must be stable at a maximum of 10 mg/day for at least 5 days prior to Day 1 (randomization). Refer to Appendix 1 for a list of prednisone-equivalents.

vi) Any other immunossuppressive or biologic drug will require washout periods indicated in Appendix 2 prior to signing consent.

vii) If subjects receive chronic therapy with NSAIDs (including marketed COX-2 inhibitors), doses must be stable for 14 days prior to first dose of study medication on Day 1 (randomization) and are recommended to remain stable throughout the study.

Note: NSAIDs should be withheld for at least 12 hours prior to visits where BILAG, SLEDAI 2K, joint counts, CLASI and MDGA will be assessed.

3. Age and Reproductive Status

a) Males and Females, ages 18 to 70 years, inclusive

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) BMS-931699 plus 5 half-lives of study drug

BMS-931699 (7 days) plus 30 days (duration of ovulatory cycle) for a total of 65 days post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) BMS-931699 plus 5 half-lives of the study drug (7 days) plus 90 days (duration of sperm turnover) for a total of 125 days post-treatment completion.

f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of one method of highly effective contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Subjects with drug-induced SLE, rather than "idiopathic" SLE.

b) Subjects with other autoimmune disease [(for example rheumatoid arthritis (RA), multiple sclerosis (MS)].

Note: Subjects with type I diabetes mellitus, thyroid autoimmune disease and secondary Sjögren syndrome are eligible.

c) Subjects with primary anti-phospholipid antibody syndrome as the sole or primary feature of their SLE or SLE-like syndrome should be excluded. However, subjects with secondary anti-phospholipid syndrome may be included in the study, unless they have had a serious thrombotic event (pulmonary embolism, stroke, deep vein thrombosis) within one year prior to signing consent. Subjects on chronic anti-coagulant therapy can be enrolled in the study.

2. Medical History and Concurrent Diseases

a) Any major surgery within 6 weeks of study drug administration (Day 1) or any elective surgery planned during the course of the study.

b) The following subjects will not be allowed in this study:

i) Subjects with any history or risk for tuberculosis (TB), specifically subjects with:

(1) Current clinical, radiographic or laboratory evidence of active TB

(2) History of active TB within the last 3 years, unless there is documentation that prior anti-TB treatment was appropriate in duration and type according to current World Health Organization Guidelines.

(3) Latent TB defined as Positive QFG or other diagnostic test in the absence of clinical manifestations, unless subject has received at least 1 month treatment with Isoniazid, or other agents recommended by local Health Authority guidelines, and an interferon gamma release assay (IGRA) test, eg, QFG or T-Spot, is negative before Day 1.

(4) Positive QFG test (or other diagnostic test) at screening or within 3 months prior to Day 1 is acceptable as long as there is documentation of a negative result by Day 1. - *Criterion no longer applicable per Protocol Amendment no.6*

ii) Subjects with active or unstable lupus neuropsychiatric manifestations, including but not limited to any condition defined by BILAG "A" criteria, with the exception of mononeuritis multiplex and polyneuropathy, which are allowed.

iii) Subjects with active, severe, lupus nephritis (WHO class III, IV) which requires or may require treatment with cytotoxic agents or high dose corticosteroids. Subjects with prior, controlled renal disease with residual proteinuria up to 3g/day or a urine protein/creatinine ratio of 3 mg/mg or 339 mg/mmol are allowed.

iv) Subjects with herpes zoster that resolved less than 2 months prior to screening.

v) Subjects with evidence (as assessed by the Investigator) of active or latent bacterial or viral infections at the time of potential screening, including subjects with evidence of Human Immunodeficiency Virus (HIV) infection as defined by positivity of HIV-1 and HIV-2 antibody.

vi) Subjects currently on hydroxychloroquine or chloroquine with evidence of retinopathy within 6 months of screening or who have had no ophthalmologic evaluation within one year of screening and will not have this examination done or

who are unwilling or unable to have regular ophthalmologic examinations while participating in the study.

c) Concomitant illness that, in the opinion of the investigator, is likely to require additional systemic glucocorticosteroid therapy during the study, (eg, asthma) is exclusionary. However, treatment for asthma with inhalational corticosteroid therapy is allowed.

d) Female subjects with a breast cancer screening suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations.

e) Subjects with a history of cancer within the last five years (other than non-melanoma skin cell cancers cured by local resection). Existing non-melanoma skin cell cancers must be removed prior to randomization (Day 1 treatment). Carcinoma in situ, treated with definitive surgical intervention, is allowed.

f) Subjects with any acute and/or chronic serious bacterial or viral infection (such as pneumonia, renal infection and sinusitis). Documentation of resolution must be available in medical chart prior to Day 1 (randomization).

g) Donation of blood to a blood bank or in a clinical study (except a screening visit) within 4 weeks of study drug administration (within 2 weeks for plasma only).

h) Blood transfusion within 4 weeks of study drug administration.

i) Inability to be venipunctured and/or tolerate venous access.

j) Any other sound medical, psychiatric and/or social reason as determined by the investigator.

3. Physical and Laboratory Test Findings

a) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG or clinical laboratory determinations beyond what is consistent with the target population.

b) Positive hepatitis-B surface antigen

c) Positive hepatitis-C antibody with positive Recombinant ImmunoBlot Assay (RIBA) or Polymerase Chain Reaction (PCR)

d) White blood cells (WBC) < 1,200/mm^3 (1.2 x 10^9/L)

e) Platelets < 50,000/mm^3 (50 x 10^9/L)

f) Hemoglobin < 8g/dL or < 7g/dL if due to hemolytic anemia related to SLE

g) Proteinuria > 3.0g/day (3000 mg/day) or equivalent level of proteinuria as assessed by protein/creatinine ratio (3 mg/mg or 339 mg/mmol).

h) serum creatinine > 2.0 mg/dL

i) Active urinary sediment defined as the following:

i) RBC casts

j) Serum alanine aminotransferase (ALT) > 2x upper limit of normal (ULN), unless explicitly related to lupus based on the Investigator's judgment.

k) Serum aspartate aminotransferase (AST) > 2xULN, unless explicitly related to lupus based on the Investigator's judgment.

l) Positive urine screen for illegal drugs of abuse, except if these drugs are prescribed by the treating physician (must be documented), and except for other drugs that are not illegal within the country or region.

m) Any other laboratory test results that, in the opinion of the Investigator, might place subject at unacceptable risk for participating in this study.

4. Allergies and Adverse Drug Reaction

a) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity).

5. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

c) Inability to comply with restrictions and prohibited activities/treatments as listed in Section 3.4

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, famales under the age of 55 years must have a documented serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40 mlU/ml at any time during the washout period, the woman can be considered postmenopausal.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

3.3.4 Criteria for Long-Term Extension

Subjects who enter the short-term period according to the eligibility criteria outlined in Sections 3.3.1 and 3.3.2, and who complete 24 weeks on study medication are eligible for participation in the LTE period. The LTE period will remain blinded but will no longer be placebo controlled, as subjects completing Day 169 in the placebo arm will be re-randomized to existing active arms.

A separate informed consent must be signed to enter the LTE period.

The class and dose of background therapies is recommended to remain the same as in the short term period. However, temporary rescue therapy with prednisone (or prednisone equivalent) to transiently manage SLE disease activity may be instituted. The increase in prednisone should not exceed a total daily dose of 20 mg, and must return to the previous stable dose within 14 days. Subjects requiring more than 14 days of rescue therapy will be discontinued.

The use of cyclophosphamide, any intravenous, any intra-articular or biologic agent remains prohibited during LTE. Any changes to or new concomitant therapies must be recorded on the CRF.

[redacted]

[redacted]

3.4.2 Other Restrictions and Precautions

Active SLE and its treatment are associated with increased risk of infection. Subjects should be provided information about the signs of the most common serious infections (eg, pneumonia, sepsis) and must have the knowledge and means to access appropriate medical care.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment and/or participation in the study
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Unblinding a subject for any reason (emergency or non-emergency)
- Development of new active manifestations of lupus requiring treatment with any non-protocol approved medications during the study.
- Inability or subject's failure to comply with the protocol requirements.
- Subject who misses more than 3 consecutive weekly doses.
- Pregnancy
- Treated with prednisone (or prednisone equivalent) at a total daily dose exceeding 20 mg and/or for more than 7 days (short-term period) or more than 14 days (long-term extension period).

Patients should discontinue from study, perform End of Treatment and Follow-up Day 42 visits, and receive standard of care according to local guidelines.

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. If any female subject becomes pregnant she will be immediately discontinued from the study.

All subjects who discontinue investigational product should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate CRF page.

3.6 Post Study Drug Follow up

In this study, assessment of lupus disease activity is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

BMS-931699 or a lookalike placebo will be administered weekly as a SC single injection solution. Table 4-1 below indicates the total dose, formulation strength, and number of vials for each treatment arm.

Table 4-1: Treatment Administration

Treatment	Total Daily Dose	Formulation Strength	Number of Vials
1	1.25 mg SC EOW	12.5mg/mL	1
2	5 mg SC EOW	12.5 mg/mL	1
3	12.5 mg SC EOW	12.5mg/mL	1
4	12.5 mg SC Weekly	12.5mg/mL	1
5	Placebo	Placebo	NSS

On Day 1, each subject will receive a single SC dose of either BMS-931699 or placebo.

There are no restrictions related to food and fluid intake associated with BMS-931699 known at this point.

Product description and storage information is described in Table 4-2.

Table 4-2: Study Drugs for BMS-931699

Product Description Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per label)
BMS-931699-1* Injection. The composition of the drug product is 12.5 mg/mL BMS-931699 in 20 mM phosphate, pH 5.9, with 5% (w/v) sorbitol.	12.5 mg/mL	IP	Open Label	3 cc vial with 13mm opening, 1-panel, open label. Appearance clear to slightly opalescent, colorless to pale yellow solution, 3 cc vial with 13mm opening, 1-panel, open label. Appearance clear to slightly opalescent, colorless to pale yellow solution, which may contain a few white or translucent particles.	Store refrigerated 2-8°C (36-46 °F). Protect from light, protect from freezing.

* The clinical label will reflect the product name as "BMS-931699-01" to be linked with the product description on the vial.

For study drugs not provided by BMS and obtained commercially by the site or subject, storage should be in accordance with the product label.

Preparation instructions will be provided separately to the site.

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product is BMS-931699 Injection.

4.2 Non-investigational Product

There are no non-investigational products in this study.

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Please refer to section 9.2.2 for information on investigation product record retention and Section 4.8 for return and destruction instructions.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Preparation for Subcutaneous (SC) Use:

For SC dosing, no dilution of the drug product solution (12.5 mg/mL) will be required for doses of 12.5mg. However, doses of 5mg and 1.25mg will require dilution. A commercially available appropriately sized sterile needle and appropriate syringe should be used for withdrawal and administration (refer to the pharmacy reference instruction document for further details on the subcutaneous preparation and administration for materials and instructions, provided separately).

The placebo for BMS-931699 injection is normal saline solution, which is administered in a similar fashion as described for the BMS-931699 injection. Normal saline to use as placebo will not be provided by the Sponsor.

After withdrawal into an appropriate sized syringe, the product must be administered within 4 hours. If not dosed immediately, filled syringes should be kept at 2°- 8° C (36°- 46° F) with protection from light prior to use.

Study personnel will administer the dose to the subject. The primary point of injection should be one of the upper arms; however other points of injections are acceptable. The subjects should be monitored for at least 1 hour after each injection for potential reactions.

4.4 Method of Assigning Subject Identification

Subjects will be randomized to receive either BMS-931699 or placebo according to a computer-generated randomization scheme prepared by a Randomization Coordinator within the Drug Supply Management Department of BMS Research and Development.

During the Screening visit, the investigative site will call into the enrollment option of the Interactive Voice Response System (IVRS) designated by BMS for assignment of a 5-digit subject number that will be unique across all sites. Enrolled subjects, including those not dosed, will be assigned sequential subject numbers starting with 00001, eg, 00001, 00002, 00003.... 00010. The patient identification number (PID) will ultimately be comprised of the site number and subject number. For example, the first subject screened (ie, enrolled) at site number 1, will have a PID of 0001 00001. Once it is determined that the subject meets the eligibility criteria following the Screening visit, the investigative site will call the IVRS to randomize the subject into the treatment period.

4.5 Selection and Timing of Dose for Each Subject

4.5.1 Double-blind Administration of BMS-931699 or Placebo

On Day 1, subjects will be randomized to one of the following dosing arms in a 1:1:1:1:1 randomization scheme:

- BMS-931699 at 12.5 mg weekly sub-cutaneous (SC) injection
- BMS-931699 at 12.5 mg every other week (EOW) SC injection
- BMS-931699 at 5 mg EOW SC injection
- BMS-931699 at 1.25 mg EOW SC injection
- Placebo SC injection (short-term period only)

The Pharmacist (or qualified drug preparation person) will know the randomized assignments and will prepare the appropriate dose of active BMS-931699 or placebo accordingly. The prepared drug must be supplied to study personnel in a manner such that neither study personnel nor subjects will be aware of whether they receive active drug or placebo.

Every randomized subject will be required to come to the clinic/research center weekly to be dosed. This will ensure double-blind is maintained despite the variability of regimens. Subjects randomized to weekly subcutaneous injections of either placebo or BMS-931699 will be dosed weekly as per schedule and subjects randomized to one of the every other week arms will be alternating between receiving a subcutaneous injection of BMS-931699 one week and one of placebo the following week.

Every randomized subject will be required to remain on site for at least 1 hour after each dose to ensure safety.

4.5.1.1 Administration Window

A subject's scheduled dosing may be administered within ± 2 days of the target day to adjust for the subject's and/or the site personnel's convenience.

Refer to Section 4.5.2.1 for dose modifications in the presence of an adverse event.

4.5.2 Dose modifications

4.5.2.1 BMS-931699 or Placebo

Dose Modifications in the Absence of Adverse Events

In the absence of adverse events, subjects will complete their scheduled injection as prescribed by protocol. A subject's scheduled dosing may be administered within ± 2 days of the target day to adjust for the subject's and/or the site personnel's convenience.

- If the study medication cannot be administered within **2** days of the target date, that scheduled dose should be skipped, which means subject will miss one (1) dose. The next dose of study medication should then be administered on the next targeted administration day (± 2 days) as originally planned. For example, the Day **15** dose could not be administered until Day **17** and subject comes to the study site to receive it on Day **19**. The planned Day **15** dose should not be given at Day **19** and the next dose will be administered on Day **22** (± 2 days). In this example, one missed dose will be reported in the eCRF.

Dose Modifications for Adverse Events

If there is evidence of toxicity (eg, abnormal laboratory tests or clinical adverse events) that, in the judgment of the Investigator, could place the subject at increased risk, study drug administration should be interrupted. Subjects may be considered eligible to receive further study medication treatment only if full resolution of the adverse event is documented, as follows:

- If the adverse event completely resolves and the study medication is administered within **2** days of the target date, the next dose should be administered on the originally planned dosing day with no missed doses.
- If the adverse event completely resolves but study medication cannot be administered within **2** days of the target date, that scheduled dose should be skipped (which means subject will miss one (1) dose). The next dose of study medication should then be administered on the next targeted administration day as originally planned (± 2 days). For example, the Day **15** dose could not be administered until Day **17** and adverse event resolution occurs on Day **19**. The planned Day **15** dose should not be given at Day **19** and the next dose will be administered on Day **22** (± 2 days). In this example, one missed dose will be reported in the eCRF.

4.5.3 Corticosteroids (Prednisone or Prednisone Equivalent) Dosing

- Prior to Randomization: Corticosteroids (prednisone or prednisone equivalent; refer to Appendix 1) may be used in accordance with the Investigator's clinical judgment and best standard of care. A maximum daily dose of 30mg/day is acceptable to be eligible for the

study and start screening; however, daily dose must be tapered down to a maximum of 10mg/day for at least 5 days prior to Day 1 (randomization day).

- Study Day 1 (randomization day): subjects requiring the use of prednisone (or prednisone equivalent) will be on a maximum dose of 10mg/day.
- Post Day 1 (after initiation of study therapy):
  - For subjects who flare or need to increase their prednisone (or prednisone equivalent) to control disease activity a one-time increase of up to a maximum daily dose of 20 mg/day for up to 2 consecutive days will be allowed to transiently manage disease activity.
  - A subject who requires a total daily dose of prednisone (or prednisone equivalent) exceeding 20 mg/day or who has another flare after the first rescue therapy, will be considered a treatment failure.
  - A subject who meets the treatment failure criteria as described above may continue on study medication; however, a subject requiring more than 20 mg/day of prednisone (or prednisone equivalent) for more than 7 days in the short-term period, or more than 14 days in the long-term extension period, will be discontinued.

Tapering of steroids during the course of the study is encouraged and should be evaluated at all visits. Once subject has received the first dose of study drug, prednisone (or prednisone-equivalent) may be tapered down at the discretion of the Investigator.

4.5.4 Rescue Therapy

4.5.4.1 Short- Term Period

A one-time increase of up to a maximum daily dose of 20 mg/day for up to 2 consecutive days will be allowed to transiently manage disease activity and will not be considered a treatment failure.

- A subject who requires a total daily dose of prednisone (or prednisone equivalent) exceeding 20 mg/day or who has another flare after the first rescue therapy, will be considered a treatment failure.
- A subject who meets the treatment failure criteria based on prednisone use may continue on study medication; however, a subject requiring more than 20 mg/day of prednisone (or prednisone equivalent) for more than 7 days in the short-term period, will be discontinued.

The use of rescue therapies other than prednisone (or prednisone equivalent), such as cyclophosphamide, any intravenous, any intra-articular or biologic agent is prohibited.

Any changes to or new concomitant therapies must be recorded on the CRF.

4.5.4.2 Long-Term Extension Period

The class and dose of background therapies is recommended to remain the same as in the short term period. However, temporary rescue therapy with prednisone (or prednisone equivalent) to transiently manage SLE disease activity may be instituted. The increase in prednisone should not

exceed a total daily dose of 20 mg, and must return to the previous stable dose within 14 days. Subjects requiring more than 20 mg/day for more than 14 days of rescue therapy will be discontinued from the LTE.

The use of rescue therapies other than prednisone (or prednisone equivalent), such as cyclophosphamide, any intravenous, any intra-articular or biologic agent remains prohibited during LTE.

Any changes to or new concomitant therapies must be recorded on the CRF.

4.6 Blinding/Unblinding

4.6.1 Blinding at the Study Sites

The subjects and clinical assessor(s) will not be aware of which treatment is being administered to the subjects enrolled in the study. The pharmacist (or qualified drug preparation person) will be unblinded to study medication (BMS-931699 or placebo).

The pharmacist (or qualified drug preparation person) will know the randomization assignments and prepare the appropriate dose of active BMS-931699 or placebo accordingly. The prepared drug must be supplied to study personnel in a manner such that neither study personnel nor subjects will be aware of whether they receive active drug or placebo.

4.6.2 Unblinding of the Study Sites

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigatory always has ultimate authority for the decision to unblind. The Principal Investigator should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

For this study, the method of unblinding for emergency purposes is IVRS.

For information on how to unblind in an emergency, consult the IVRS manual.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind.

Any request to unblind a subject for non-emergency purposes should be discussed with the Medical Monitor.

In case of an emergency, the Investigator(s) has unrestricted access to randomization information via the Interactive Voice Response System (IVRS) and is capable of breaking the blind through the IVRS system without prior approval from sponsor. Following the unblinding the Investigator shall notify the Medical Monitor and/or Study Director.

4.7 Treatment Compliance

Subject will be dosed at the study site where documentation of injection and compliance will be maintained.

4.8 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible BMS Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.9 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

Arrangements for the return of study drug will be made by the responsible Study Monitor.

Retained Samples for Bioavailability / Bioequivalence

Not applicable

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Study assessments and procedures are presented in Table 5.1-1, Table 5.1-2 and Table 5.1-3. **These study assessments apply to all subjects, whether they are included in Part 1 or Part 2 of this study.**

Table 5.1-1: Screening Procedural Outline (IM128027)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	A subject is considered enrolled/screened only when a protocol specific informed consent is signed.
Enroll subject (contact IVRS)	X	
Inclusion/Exclusion Criteria	X	
Medical history	X	Include any toxicities or allergy related to previous treatments.
ACR criteria for SLE form	X	See Appendix 3
BILAG-2004 Index	X	See Appendix 4
SLEDAI-2K	X	See Appendix 5
Physician's Global Assessment of Disease Activity	X	
ACR28 - joint count	X	
CLASI	X	See Appendix 6
Coomb's test-direct	X	
Stabilize/Withdraw prohibited medications (if necessary)	X	
Safety Assessments	X	
Physical Examination (PE)	X	Include breast physical exam. See Section 5.3.4 of the protocol for more details
Physical Measurements	X	Includes height and weight
Vital Signs	X	Includes body temperature, respiratory rate, seated and standing blood pressure and heart rate. Blood pressure and heart rate should be measured after the subject has been resting quietly for at least 5 minutes.
Electrocardiogram (ECGs)	X	ECGs should be recorded after the subject has been supine for at least 5 minutes.
Chest x-ray (CXR)	X	No need to repeat if chest x-ray performed within 6 months of screening and documentation of the results is available at the site.

Table 5.1-1: Screening Procedural Outline (IM128027)

Procedure	Screening Visit	Notes
Confirm and document that breast cancer and cervical cancer screening are up to date according to local guidelines (females only)	X	
Laboratory safety tests	X	Includes blood and urine samples. Subjects are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests.
Spot urine for protein/creatinine ratio	X	
TB screening	X	In accordance with BMS standard testing. See Section 5.3.3 of the protocol for more details.
Hepatitis B surface antigen and Hepatitis C antibody	X	
CMV and EBV	X	
Serum complement (C3, C4)	X	
ANA, Anti ds-DNA antibodies and Sm auto-antibodies	X	
HIV	X	
Urine Drug Test	X	
Pregnancy Test (for WOCBP only)	X	Serum pregnancy test to be performed only if urine test is positive or un-interpretable
Adverse Event Reporting	X	
Monitor for Serious Adverse Events	X	All SAEs must be collected from the date of subject's written consent until 42 days post discontinuation of dosing or completion of subject's participation in the study if the last scheduled visit occurs at a later time.

Table 5.1-2: Short-Term Procedural Outline (IM128027)

Procedure / Visit Day (± 2 days is allowed for all visits, including Day 1)	**D 1**	**D 15**	**D 29**	**D 57**	**D 85**	**D 113**	**D 141**	**EOT / D 169**	**FU D 42* (FUP no.1 visit)**	**Dosing Every Week (in addition to Visits assessing disease activity)**	**Notes**
Confirm inclusion and exclusion criteria are met prior to dosing	X										
Efficacy Assessments											
BILAG-2004 Index	X		X	X	X	X	X	X	X		See Appendix 4
SLEDAI 2K	X		X	X	X	X	X	X	X		See Appendix 5
Physician's Global Assessment of Disease Activity (MDGA)	X		X	X	X	X	X	X	X		
Subject's Global Assessment of Disease Activity (PGA)	X		X	X	X	X	X	X	X		
ACR28 - joint count	X		X	X	X	X	X	X	X		
FACIT - F	X	X	X	X	X	X	X	X	X		See Appendix 9
CLASI	X		X	X	X	X	X	X	X		See Appendix 6
SLICC/ACR Damage Index	X							X			See Appendix 7
SF-36	X		X	X	X	X	X	X	X		See Appendix 8
Coomb's test-direct	X		X	X	X	X	X	X	X		
Safety Assessments											
Targeted PE	X	X	X	X	X	X	X	X	X		See Section 5.3.4 of the protocol for more details

Table 5.1-2: Short-Term Procedural Outline (IM128027)

Procedure / Visit Day (± 2 days is allowed for all visits, including Day 1)	**D 1**	**D 15**	**D 29**	**D 57**	**D 85**	**D 113**	**D 141**	**EOT / D 169**	**FU D 42* (FUP no.1 visit)**	**Dosing Every Week (in addition to Visits assessing disease activity)**	**Notes**
Spot urine for protein / creatinine ratio	X		X	X	X	X	X	X	X		
Vital Signs	X	X	X	X	X	X	X	X	X	X	Includes body temperature, respiratory rate, seated and standing blood pressure and heart rate. Blood pressure and heart rate should be measured after the subject has been resting quietly for at least 5 minutes.
ECGs	X [a]				X			X			[a] ECG must be performed prior to dosing on Day 1
Urine Pregnancy Test (WOCBP only)	X[b]	X	X	X	X	X	X	X[c]	X		[b] Negative pregnancy test must be confirmed within 24hrs prior to dosing. [c] WOCBP patients must be sent home with a home pregnancy kit to self-performed approximately 28days after the Day 169 visit. - Serum pregnancy test to be performed only if urine test is positive or un-interpretable
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Table 5.1-2: Short-Term Procedural Outline (IM128027)

Procedure / Visit Day (± 2 days is allowed for all visits, including Day 1)	**D 1**	**D 15**	**D 29**	**D 57**	**D 85**	**D 113**	**D 141**	**EOT / D 169**	**FU D 42* (FUP no.1 visit)**	**Dosing Every Week (in addition to Visits assessing disease activity)**	**Notes**
Laboratory safety tests	X	X	X	X	X	X	X	X	X		Include blood and urine samples. Subjects are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests.
CMV and EBV					X			X			
Adverse Event Reporting											
Monitor for Non-Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	
Monitor for Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	All SAEs must be collected from the date of subject's written consent until 42 days post discontinuation of dosing or completion of subject's participation in the study if the last scheduled visit occurs at a later time.
PK Assessments											
PK Sampling	X	X	X	X	X	X	X	X	X		See Table 5.5.3 for additional PK collection instructions.

Table 5.1-2: Short-Term Procedural Outline (IM128027)

Procedure / Visit Day (± 2 days is allowed for all visits, including Day 1)	**D 1**	**D 15**	**D 29**	**D 57**	**D 85**	**D 113**	**D 141**	**EOT / D 169**	**FU D 42* (FUP no.1 visit)**	**Dosing Every Week (in addition to Visits assessing disease activity)**	**Notes**
Immunogenicity (anti-BMS-931699 antibody)	X	X	X		X			X	X		
[redacted]											[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]		[redacted]		[redacted]			[redacted]			
[redacted]	[redacted]				[redacted]			[redacted]			
[redacted]	[redacted]				[redacted]			[redacted]			
[redacted]	[redacted]				[redacted]			[redacted]			
[redacted]	[redacted]		[redacted]		[redacted]			[redacted]			[redacted]
[redacted]	[redacted]		[redacted]		[redacted]			[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]			[redacted]			[redacted]

Table 5.1-2: Short-Term Procedural Outline (IM128027)

Procedure / Visit Day (± 2 days is allowed for all visits, including Day 1)	**D 1**	**D 15**	**D 29**	**D 57**	**D 85**	**D 113**	**D 141**	**EOT / D 169**	**FU D 42* (FUP no.1 visit)**	**Dosing Every Week (in addition to Visits assessing disease activity)**	**Notes**
Serum cytokines and [redacted]	[redacted]	[redacted]	[redacted]		[redacted]			[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]			[redacted]			
[redacted]	[redacted]		[redacted]		[redacted]			[redacted]	[redacted]		
[redacted]											
[redacted]	[redacted]										
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]

Abbreviations: D = Day, EOT = End of Treatment

* Only to be performed if subject is discontinued early or if subject is not entering the LTE after completing 24-weeks of study medication

Table 5.1-3: Long-term Extension Procedural Outline (IM128027)

Procedure / Visit Day (± 2 days is allowed for all visits, including LTE Day 1)	**LTE Day 1**[1]	**Monthly Visits**[2]	**Every 3 Months Visits**[2]	**EOT in LTE**	**FU Day 42 After EOT**	**Dosing Every Week (in addition to Office Visits)**[3]	**Notes**
[redacted]	[redacted]						
Efficacy Assessments							
BILAG-2004 Index	X*	X		X	X		See Appendix 4
SLEDAI 2K	X*	X		X	X		See Appendix 5
Physician's Global Assessment of Disease Activity (MDGA)	X*	X		X	X		
Subject's Global Assessment of Disease Activity (PGA)	X*	X		X	X		
ACR28 - joint count	X*	X		X	X		
FACIT - F	X*	X		X	X		See Appendix 9
CLASI	X*	X		X	X		See Appendix 6
SLICC/ACR Damage Index	X*		X	X			See Appendix 7
SF-36	X*	X		X	X		See Appendix 8
Coomb's test-direct	X*	X		X	X		
Safety Assessments							
Targeted PE	X*	X		X	X		See Section 5.3.4 of the protocol for more details
Spot urine for protein / creatinine ratio	X*	X		X	X		

Table 5.1-3: Long-term Extension Procedural Outline (IM128027)

Procedure / Visit Day (± 2 days is allowed for all visits, including LTE Day 1)	**LTE Day 1**[1]	**Monthly Visits**[2]	**Every 3 Months Visits**[2]	**EOT in LTE**	**FU Day 42 After EOT**	**Dosing Every Week (in addition to Office Visits)**[3]	**Notes**
Vital Signs	X*	X		X	X	X	Includes body temperature, respiratory rate, seated and standing blood pressure and heart rate. Blood pressure and heart rate should be measured after the subject has been resting quietly for at least 5 minutes.
Urine Pregnancy Test (WOCBP only)	X*	X		X	X		[b] Negative pregnancy test must be confirmed within 24hrs prior to dosing. [c] WOCBP patients must be sent home with a home pregnancy kit to self-performed approximately 28days after receiving their last dose of study medication. - Serum pregnancy test to be performed only if urine test is positive or un-interpretable
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	

Table 5.1-3: Long-term Extension Procedural Outline (IM128027)

Procedure / Visit Day (± 2 days is allowed for all visits, including LTE Day 1)	LTE Day 1[1]	Monthly Visits[2]	Every 3 Months Visits[2]	EOT in LTE	FU Day 42 After EOT	Dosing Every Week (in addition to Office Visits)[3]	Notes
Laboratory safety tests	X*	X		X	X		Include blood and urine samples. Subjects are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests.
Adverse Event Reporting							
Monitor for Non-Serious Adverse Events	X*	X		X	X	X	
Monitor for Serious Adverse Events	X*	X		X	X	X	All SAEs must be collected from the date of subject's written consent until 42 days post discontinuation of dosing or completion of subject's participation in the study if the last scheduled visit occurs at a later time.
PK Assessments							
PK Sampling	X*		X*	X	X		* PK Samples will be collected every 3 months during the LTE period, based on 1st dose received in LTE. PK samples will also be collected at EOT whenever it occurs, despite of visit schedule.

Table 5.1-3: Long-term Extension Procedural Outline (IM128027)

Procedure / Visit Day (± 2 days is allowed for all visits, including LTE Day 1)	**LTE Day 1**[1]	**Monthly Visits**[2]	**Every 3 Months Visits**[2]	**EOT in LTE**	**FU Day 42 After EOT**	**Dosing Every Week (in addition to Office Visits)**[3]	**Notes**
Immunogenicity (anti-BMS-931699 antibody)	X*		X**	X	X		** Immunogenicity Samples will be collected every 3 months during the LTE period, based on 1st dose received in LTE. Immunogenicity samples will also be collected at EOT whenever it occurs, despite of visit schedule.
[redacted]							[redacted]
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]		[redacted]				
[redacted]	[redacted]		[redacted]				
[redacted]	[redacted]		[redacted]				[redacted]
[redacted]	[redacted]		[redacted]				
[redacted]	[redacted]		[redacted]				
[redacted]							
[redacted]	[redacted]						

Table 5.1-3: Long-term Extension Procedural Outline (IM128027)

Procedure / Visit Day (± 2 days is allowed for all visits, including LTE Day 1)	LTE Day 1[1]	Monthly Visits[2]	Every 3 Months Visits[2]	EOT in LTE	FU Day 42 After EOT	Dosing Every Week (in addition to Office Visits)[3]	Notes
[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]

Abbreviations: D = Day, EOT = End of Treatment

1 Study procedures performed on Day 169 of the Short-Term period will be used as the starting point for LTE Day 1 procedures. They do not need to be performed twice. These are marked with an asterisk star (*).

2 Starting point for calculating the visits in LTE is the day subject performs Day 1 of the LTE.

3 Weekly SC injection required until Futility Interim Analysis. Frequency may change after the Futility Interim Analysis.

5.1.1 Retesting During Screening

5.1.2 Period

A single-retesting of laboratory parameters and/or other assessments during Screening period will be permitted (in addition to any parameters that require a confirmatory value), only if medically indicated, if there is evidence a laboratory sample was mislabeled, was inadequately processed and/or deteriorated in transit to the central laboratory.

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state. This will also apply to subjects who are being re-screened.

5.2 Study Materials

The site will provide all required materials for the tests performed locally (ie, relevant clinical laboratory tests). The site will have available a well-calibrated scale for recording body weight, a 12-lead ECG machine, and a calibrated sphygmomanometer and thermometer for vital signs assessments. The site will have urine collection containers, a centrifuge, a heated plaque, a monitored and alarmed refrigerator, and freezer (-20°C or below), as well as containers and dry ice for shipment and storage of blood and urine samples. The site will provide all materials required for accurate source documentation of study activities.

BMS will provide a BMS-approved protocol and any amendments or administrative letters (if required), and investigator brochure. Case report forms (electronic or hard copy) will be provided by BMS. Ten centimeter rulers will be provided by BMS for measurement of the Physician and Subject's Global Assessment of disease activity on the Case Report Form.

All Investigator sites within this study will use an Electronic Data Capture (EDC) tool to submit study data to BMS. Electronic Case Report Forms (eCRFs) will be prepared for all data collection fields at Investigator sites, except for fields specific to Pregnancy Forms. Pregnancy Forms will be submitted to BMS using paper CRFs. Subject Quality of Life Questionnaires will be completed by the subject and the information will then be entered with the EDC tool by the investigational site staff. Physician Global Assessment of disease activity worksheet will be completed by the investigator and will then be entered with the EDC tool. Subject completed Quality of Life Questionnaires will be retained at the investigational site.

Study supplies and documents (eg, electronic Case Reports Forms, patient drug logs, etc.) will be provided to the study center by BMS. Urine pregnancy test kits, laboratory specimen collection kits and instructions for collection will be provided by central laboratory vendor. IVRS worksheets and instruction manuals will be provided by the IVRS vendor.

5.3 Safety Assessments

On Day 1, the results of all assessments must be reviewed to assure that eligibility requirements are met before contacting the Central Randomization System for the subject's randomization assignment.

Subjects who discontinue from the double-blind treatment period should have "End of Treatment Visit" procedures performed and should return to the clinical for the "Follow-Up Visit" approximately 42 days after the "End of Treatment Visit". All procedures required for these visits should be completed as well as collection of concomitant medication information.

All assessments should be performed or administered prior to study drug administration unless otherwise indicated. Furthermore, patient's assessments (ie FACIT-F, SF-36 and Subject's Global Assessment) must be performed prior to all other assessments.

Every effort must be made to ensure the same evaluator will complete the assessments for each subject at all visits.

Only data for the procedures and assessments specified in this protocol should be submitted to BMS on a case report form. Additional procedures and assessments may be performed as part of your institutional or medical practice standard of care; however, data for these assessments should remain in the subject's medical record and should not be provided to BMS, unless specifically requested from the sponsor.

Safety Outcome Measures: Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests. The incidence of observed adverse events will be tabulated and reviewed for potential significance and clinical importance.

Ongoing assessment of safety will be performed by an independent Data Monitoring Committee (DMC) and an internal safety monitoring team. Both entities may make recommendations to the Sponsor regarding conduct of study and dose adjustment based on safety observations.

Titers of anti-CMV and EBV antibodies will be obtained at baseline, 12 weeks and 24 weeks to monitor for viral reactivation.

5.3.1 Imaging Assessment for the Study

Not applicable.

5.3.2 Laboratory Test Assessments

For the short-term period (Part 1 and Part 2), a central laboratory will perform the analyses and will provide reference ranges for these tests.

[redacted]

Clinical Laboratory Testing

Blood and/or urine samples will be obtained prior to injection at all visits from each subject entered in this study. **Any laboratory test result that the Investigator considers clinically relevant should be recorded on the appropriate Adverse Event page of the CRF** (see Section 6.3 Laboratory Test Result Abnormalities).

For the Lipid Panel, a fasting sample is required. At least 10 hours prior to the collection time, subjects should not consume food; only water is allowed. Subjects with an abnormal Lipid Panel may be referred back to their primary care provider for further management if warranted.

Urine or serum pregnancy tests will be performed within 24 hours prior to dosing, for all WOCBP. If any female subject becomes pregnant she will be immediately discontinued from the study.

If a WOCBP advises the investigational staff that she has had amenorrhea for ≥ 12 consecutive months while the study is ongoing and menopause is a diagnostic consideration, a serum follicle stimulating hormone (FSH) level should be taken and testing performed at the central laboratory to determine if her FSH level is > 40 mIU/mL. After the level has been confirmed and the diagnosis of menopause has been determined by a treating physician, pregnancy testing at each visit will no longer be required for the subject as she is no longer of child-bearing potential.

If additional or follow-up monitoring of subject safety, eg, potential toxicity or features of active SLE is required, the investigator may obtain samples for additional laboratory tests if deemed necessary after discussion with the BMS study team.

Hematology (CBC)

Hemoglobin	Hematocrit
Platelet count	Total WBC count, including differential
RBC	Total Iron Binding Capacity

Manual differential (separate smear) and Reticulocyte count

Blood Chemistry (Chemistry Panel):

Sodium	Creatinine
Potassium	Blood urea nitrogen (BUN)
Chloride	Total bilirubin
Total Protein	Direct Bilirubin
Albumin	Alanine aminotransferase (ALT)
Calcium	Aspartate aminotransferase (AST)
Phosphorous	Gamma-glutamyltransferase (GGT)
Glucose	Alkaline phosphatase

Creatine Kinase

Lipid Panel (Fasted Sample Mandatory):

Total-Cholesterol	HDL-Cholesterol
LDL-Cholesterol	Triglycerides

Coomb's test-direct

Tuberculosis test (performed at screening only)

Urine drug screen (performed at screening only)

Serum complement:

C3

C4

Urine sample (clean catch):

pH Protein

Glucose Blood

Microscopic examination for Cells, Casts, Bacteria

Spot urine collection:

Urine protein

Urine creatinine

Hepatitis screen (performed at screening only):

Hepatitis B surface antigen

- if positive, reflex to HBV DNA PCR (Hepatitis B Virus PCR)
- Hepatitis B core antibody
- if positive, reflex to HBV DNA PCR (Hepatitis B Virus PCR)
- Hepatitis C Virus antibody
- if low- positive, reflex to HCV RNA PCR (Hepatitis C Virus), quantitative

Subjects with positive PCR (defined as ANY detected virus, not as > LLQ) will be designated as Screen Failure.

HIV screen: antibody anti-HIV 1 and 2 (performed at screening only):

Cytomegalovirus (CMV) (Short-Term Treatment period only)

Epstein-Barr virus (EBV) (Short-Term Treatment period only)

Pregnancy Tests: Urine/serum pregnancy tests (minimum sensitivity 25 IU/L of β-HCG) must be performed for all WOCBP within 24 hours prior to dosing. If any female subject becomes pregnant, she will be discharged from the study. Urine pregnancy tests will be processed locally.

FSH test will be performed for female subjects who become menopausal after entry into the trial.

Immunoglobulin Determination:

Quantitative Immunoglobulins (IgG, IgA, IgM)

Autoimmune Serology:

Anti-nuclear antibody

Anti-double stranded (ds) DNA antibodies

Antiphospholipid antibodies (IgG, IgA, IgM)

Anti-Ro (SS-A) antibodies

Anti-La (SS-B) antibodies

Anti-RNP antibodies

Anti-Sm antibodies

Serum Proteomics (cytokines, chemokines): Serum SST tube

Whole Blood RNA Collection: Blood samples in PAXgene® tubes

Urine Proteomics Collection: 100mL urine (Short-Term period only)

Leukocyte phenotype: Peripheral blood sample (Short-Term period only)

PBMC collection (except in Asia and South Africa since transition time between site and analyzing laboratory is expected to exceed the stability of the sample). (Short-Term period only)

Receptor Occupancy (RO): Peripheral blood sample

Immunogenicity determination: Anti-BMS-931699 antibody

In addition, the investigator will obtain samples for additional laboratory tests if deemed necessary for monitoring subject safety, eg, potential toxicity or features of active SLE.

Blood and Urine Specimen Collection, Processing and Shipping

Detailed instructions on the collection, processing and shipping of all blood and urine samples will be provided to the Investigator in a separate manual at or before the time of study initiation.

5.3.3 Tuberculosis Screening and Chest X-Ray

A chest x-ray (CXR) and physical examination (PE) are considered part of the process to assess a subject's eligibility as outlined in Section 3.3.2.

CXR at the screening visit is required if not already performed within 6 months of obtaining written informed consent or if documentation is not on file.

In addition to a complete physical examination and medical history to evaluate exposure to tuberculosis, all subjects will have a screening test, an interferon gamma release assay [(IGRA) eg, T-spot®, QuantiFERON®], preferably performed centrally. If unable to obtain central lab results (eg, repeated test due to indeterminate result), an IGRA test could be obtained locally, after consultation with the study medical monitor.

Subjects with a positive screening test will not be eligible for the study unless they have completed at least four (4) weeks of treatment for latent TB prior to dosing of study drug, and the

subject has a negative chest X-ray done at screening that reveals no evidence of active TB and a negative IGRA test (Quantiferon or T-Spot) is confirmed prior to Day 1.

5.3.4 Physical Examination

Complete and/or interim physical examinations may be performed by a Doctor of Medicine (MD), or someone who is authorized to perform the examinations by training and has been delegated this task by the principal investigator. While the interim physical examination may not be as comprehensive as the initial full examination, key aspects of the interim examination should evaluate important body systems as clinically indicated. These body systems can include lymph nodes, liver, spleen, and breast at the discretion of the examiner. An interim physical examination may note any changes in the subject's condition (body systems) since the last assessment and does not preclude examination of any of the body systems as clinically indicated.

Every effort should be made to ensure the same evaluator will complete the physical examination for each subject at all visits throughout the study. Documentation of who performed the examination is to be recorded in source notes.

5.4 Efficacy Assessments

Clinical assessments of response should be performed by the same assessor(s) and at approximately the same time of day throughout the duration of the study.

5.4.1 Primary Efficacy Assessment

5.4.1.1 Short-Term Period

Primary efficacy assessment is a composite endpoint, the BICLA, which includes BILAG-2004, SLEDAI-2K (30 day)[20], Physician Global Assessment of disease activity (MDGA) and no treatment failure. The BILAG-2004 index was selected as the central score on the basis of its comprehensiveness, ability to capture partial improvement, and the clinical relevance of its scoring system. BILAG assessments will be performed by the investigators, and grades will be determined by an independent central reader group.

5.4.1.2 Long-Term Extension Period

Primary efficacy assessments during the long-term extension will be the same as in the short-term period, in order to assess long-term durability of response.

5.4.2 Secondary Efficacy Assessments

5.4.2.1 Short-Term Period

Training and instruction on BILAG 2004 index assessment will be provided and discussed at the Investigator's Meeting or at workshops. The response measure (BILAG) will be reviewed and discussed with the investigational staff at the Investigator Meeting or other forum as a method of standardizing the grading between the investigational staffs. All Investigative site personnel performing BILAG evaluations must be trained and certified.

The BILAG index measures and reports disease activity in different organs/systems separately. The BILAG score is calculated for each of nine systems depending on the clinical features

present and whether they are new, worse, the same or improving in the last 4 weeks compared with previously. A BILAG "A" represents the presence of one or more serious features of lupus. A BILAG "B" represents more moderate features of the disease. A BILAG "C" includes only mild symptomatic features. A BILAG "D" represents only prior activity with no current symptoms due to active lupus. A BILAG "E" represents an organ that has never been involved. Assessments used to determine BILAG score must be performed by the Investigator, or a BILAG certified (an individual who has passed the BMS sponsored BILAG Certification Test) Sub-Investigator. The Sub-Investigator may be a Doctor of Medicine (MD), or someone who is authorized to perform the examinations by training and has been delegated this task by the principal investigator. Changes in therapy based on any clinical or laboratory assessment must be approved by the Investigator or a MD/DO Sub-Investigator.

5.4.2.2 Long-Term Extension Period

Secondary efficacy assessments during the long-term extension will be the same as in the short-term period, in order to assess long-term durability of response.

[redacted]

5.5 Pharmacokinetic Assessments

5.5.1 Short-Term Period

Pharmacokinetics of BMS-931699 will be derived from serum concentration versus time data.

The pharmacokinetic parameters to be reported include Ctrough (ng/mL), which will be measured from serum samples collected as defined Table 5.5.3.

Additional blood samples will be obtained according to Table 5.5.3, which specifies pre-dose samples as well as post-dose samples on Day 46 and Day 48. If both post-dose samples cannot be obtained at these times (ie, Days 46 + Day 48), the 2 samples may be obtained on (Days 60 + Day 62) OR (Days 74 + Day76).

Population PK (PPK) analysis maybe performed using PK data from the current proposed study in SLE patients. Results of the PPK analysis may also be used to characterize the exposure-response (E-R) relationship in BMS-931699 by means of the individual model predicted exposure and efficacy/safety data. Further, the effect of covariates (demographic and clinical) on efficacy/safety may be explored in the E-R analyses. Results of the PPK and E-R analyses will be reported separately if performed.

5.5.2 Long-Term Extension Period

Immunogenicity and PK blood samples will be obtained every three months during the LTE period.

5.5.3 Pharmacokinetics: Collection and Processing

Table 5.5.3 lists the sampling schedule to be followed for the assessment of pharmacokinetics. Further details of blood collection and processing will be provided to the site in the procedure manual.

Table 5.5.3: Pharmacokinetic Sampling Schedule for BMS-931699

Study Day of Sample Collection	Event	Time (Relative To BMS-931699 Dose) Hour: Min	BMS-931699 Pharmacokinetic Blood Sample	BMS-931699 Immunogenicity Sample
1	Pre-dose	00:00	X	X
15	Pre-dose	00:00	X	X
29	Pre-dose	00:00	X	X
43	Pre-dose	00:00	X	
46 (± 1 day)[a]		72:00	X	
48 (± 1 day) [a]		120:00	X	
50	Pre-dose	00:00	X	
57	Pre-dose	00:00	X	
64	Pre-dose	00:00	X	
71	Pre-dose	00:00	X	
78	Pre-dose	00:00	X	
85	Pre-dose	00:00	X	X
113	Pre-dose	00:00	X	
141	Pre-dose	00:00	X	
169/End of Treatment		168:00	X	X
Long-term extension	Pre-dose	Every 3 months	X	X
Follow up Day 42 after EOT		42 Days after end of treatment	X	X
AE[b]			X	X

[a] Day 46 and Day 48 post-dose PK samples are planned for the same dosing interval. A dosing interval is the time between two doses, in this study, dosing interval is a week. Sites should plan ahead with patients to ensure these samples are collected during the same dosing interval. If patients cannot have post-dose PK samples collected on Day 46 and Day 48, the 2 samples may be obtained on (Day 60 +Day 62) OR (Day 74 + Day 76). The exact dosing time and sampling time should be recorded accordingly.

[b] PK and immunogenicity samples to be drawn for subjects who experience an AE leading to discontinuation of study treatment.

5.5.4 Pharmacokinetic Sample Analyses

The serum samples will be analyzed for BMS-931699 by a validated LC-MS/MS assay. Pharmacokinetic samples collected from a subject who received placebo will not be analyzed.

In addition, serum samples will be archived for potential exposure biomarker response analysis, if the need arises and to the extent possible.

5.5.5 Immunogenicity Assessments

The immunogenic potential of the study medication will be assessed based on levels of anti-BMS-931699 antibodies. Serum samples will be obtained at visits defined in Table 5.1-3. Only samples from the active treatment arms will be analyzed.

Validated sensitive, electrochemiluminescence (ECL) immunoassay method will be used to measure titers of anti- BMS-931699 antibodies in serum.

5.5.6 Labeling and Shipping of Biological Samples

Detailed instructions for the pharmacokinetic blood collection, labeling, processing, storage, and shipping will be provided to the site in the laboratory manual.

[redacted]

[redacted]

[redacted]

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

> Related: There is a reasonable causal relationship between study drug administration and the AE.
>
> Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be

questioned regarding the specific occurrence of one or more AEs). BMS, as sponsor of the study, commits to declare safety events in accordance with the regulation in force in each country.

6.1 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details.

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)

- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 42 days of discontinuation of dosing.

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that whenever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

If any female subject becomes pregnant she will be immediately discontinued from the study.

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details.).

6.6 Potential Drug Induced Liver Injury (DILI)

Whenever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
   AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

6.7.1 AE's of Special Interest

Although there are no identified risks for BMS-931699, BMS has developed a list of events of special interest for the BMS-931699 program based on the known biologic class effects, the mechanism of action of BMS-931699, overall potential consequences of immunosuppression, and preliminary data from unblinded clinical trials. Event categories of special interest for this study may include, but are not limited to:

- Infections
- Autoimmunity
- Malignancies
- Injection-related reactions

Note: Another event of special interest based on the biologic class effect, albeit not an adverse event in itself, is Immunogenicity, which will be monitored during the entire study. Adverse events in subjects who develop anti-BMS-931699 antibodies will be monitored as AE's of special interest.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

An external Data Monitoring Committee (DMC) will be used in this study. The Committee's scope of responsibility will be limited to monitoring safety by masked treatment group; Committee may request treatment codes and/or efficacy summaries if indicated for safety/benefit assessment. The Committee will comprise 1 biostatistician and 2 clinicians with expertise in SLE.

Data summaries and listings will be provided to the DMC to facilitate their safety and efficacy assessment at the regularly scheduled times as well as on an ad hoc basis if needed. DMC data monitoring will commence when 5 subjects have been dosed. From that time, DMC monitoring will be performed approximately every 6-8weeks (during Part 1) and quarterly during Part 2 (with the agreement of DMC and BMS, this schedule may be changed depending on the rate of subject accrual). The DMC will review safety data including serious adverse events and events of special interest (eg, infections), focusing on early signal detection. The DMC will also evaluate the rates of observed increases of clinical disease activity of SLE and opportunistic infections compared to the background rates expected in this study population based on a review of the relevant literature. Further details on the content and methods of data reports to the DMC will be outlined in the Charter of that Committee along with the processes and procedures the committee will follow.

In collaboration with the DMC, an unblinded internal safety monitoring team will review the safety data throughout the study and will provide recommendations to the blinded study team.

An Adjudication Committee will be used in this study. Scope of responsibility will include, but will not be limited to, adjudication of SLE eligibility criteria, new "A" and "B" BILAG flares and cross-validation of the instruments used in this study to assess the disease being studied.

Further details on the content and methods of data reports by the Adjudication Committee will be outlined in the Charter of that Committee along with the processes and procedures the Committee will follow.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The sample size calculation is based on power to compare the proportion of subjects who achieve BICLA response (the BICLA response rate) at Day 169 between BMS-931699 dose arm and placebo arm. With a one-sided continuity corrected chi-squared test at significance level 0.05, data from 70 randomized and treated subjects per arm will provide at least 89% power to detect a 25% increase in the BICLA response rate in the active treatment arm(s) [(ie, 50% response rate in BMS active arm(s)] compared to placebo, and provide 74% power to detect a 20% increase in the BICLA response rate in the active treatment arm(s) [(ie, 45% response rate in BMS active arm)] compared to placebo, assuming that the placebo arm has 25% response rate which is reasonable based on the EMBLEM phase 2 trial results[21]. No adjustment will be made for multiplicity. Subjects who discontinue treatment/study prior to Day 169 will contribute to the data that will be analyzed for BICLA response at Day 169 (discontinuation will indicate no BICLA response). Therefore, no adjustment will be made for discontinuations.

The primary efficacy analysis will be conducted on all randomized patients who received at least one dose of the study drug. In order to get 70 randomized and treated subjects per arm, an adequate number of subjects will need to meet the inclusion/exclusion criteria at screening.

If the interim analysis for futility and dose adaptation suggests that an additional dose arm (at a lower dose level) needs to be added, then up to 40 additional subjects may be randomized.

8.2 Populations for Analyses

- All Enrolled Subjects, defined as all subjects who sign an informed consent;
- All Randomized Subjects, defined as all subjects who are randomized to a treatment;
- All Treated Subjects, defined as all subjects who receive at least one dose of study treatment;
- Biomarker Analysis Population, defined as all subjects that receive any study medication and have at least 1 post-treatment biomarker measurement.
- Pharmacokinetic Population, defined as all subjects who receive any study medication and have any available concentration-time data.
- Immunogenicity Population, defined as all subjects who receive study drug and have at least 1 post treatment immunogenicity measurement.

All subjects who receive at least one dose of study treatment (all treated subjects) will be included in the safety analysis population and the efficacy analysis population. However, the subjects from Part 1 who are randomized to a treatment arm that is discontinued based on the Part 1 Safety/RO analysis will be excluded from the efficacy analysis. More details will be provided in the statistical analysis plan.

8.3 Endpoints for Short Term Period

8.3.1 Primary Endpoint(s)

The primary objective (to compare the BICLA response rate at Day 169) will be measured by the following primary endpoint:

Proportion of subjects who achieve BICLA response (BICLA response rate) at Day 169.

8.3.2 Secondary Endpoint(s)

8.3.2.1 Efficacy Endpoints

- Proportion of subjects who meet response criteria for the SLE Responder Index(4) [SRI(4)], SRI(5) and SRI(6) at Day 169
- Proportion of subjects who meet response criteria for the SLE Responder Index(4) [SRI(4)], SRI(5) and SRI(6) at Day 85
- Proportion of subjects with BICLA response at Day 85
- Change from baseline in CLASI score at Day 85 and Day 169
- Percentage of subjects with an improvement of >4 or a decrease of >50% from baseline in their CLASI score at Day 85 and Day 169
- Change from baseline in arthritis, as assessed by American College of Rheumatology (ACR) 28-joint count of tender and swollen joints at Day 85 and at Day 169
- The change from baseline in the following other indices SLE activity over time:
  - The overall BILAG-2004 score
  - The overall SLEDAI-2K score
  - The overall MDGA score
- The cumulative corticosteroid and immunosuppressant use over time

8.3.2.2 Safety Endpoints

- Incidence and severity of all Adverse Events (AEs), Serious AEs, and pre-established Events of Special Interest
- Incidence and severity of clinically significant changes in vital signs
- Incidence and severity of clinically significant electrocardiogram (ECG) abnormalities
- Incidence and severity of clinically significant abnormalities in general laboratory tests

8.3.2.3 Pharmacokinetic Endpoints

Ctrough: Trough level serum concentration of BMS-931699 at time points specified in Section 5.5.

[redacted]

[redacted]

8.3.2.5 *Immunogenicity*

Proportion of subjects with BMS-931699 induced antibody response at visit specified in Table 5.5.3.

[redacted]

8.4 Endpoints for Long-term Extension Period

During the LTE period, the following endpoints will be assessed cumulatively (safety) and over time (efficacy).

8.4.1 *Safety Endpoints*

- Incidence and severity of all Adverse Events (AEs), Serious AEs, and pre-established Events of Special Interest
- Incidence and severity of clinically significant abnormalities in general laboratory tests

8.4.2 *Efficacy Endpoints*

- Proportion of subjects who achieve BICLA response (BICLA response rate)
- Proportion of subjects who meet response criteria for the SLE Responder Index (SRI) [SRI(4), SRI(5) and SRI(6)]

- CLASI score
- ACR 28 joint count of tender and swollen joints
- Overall BILAG-2004 score
- Overall SLEDAI-2K score
- Overall MDGA score
- The cumulative corticosteroid and immunosuppressant use
- Proportion of patients reaching a Major Clinical Response and Partial Clinical Response
- Fatigue, based on the FACIT
- Quality of life, based on SF-36

8.4.3 Pharmacokinetic Endpoints

Ctrough: Trough level serum concentration of BMS-931699 at time points specified in Section 5.5.

[redacted]

8.4.5 Immunogenicity

Proportion of subjects with BMS-931699 induced antibody response at visits defined in Table 5.1-3

8.5 Analyses for the Short-Term Period

8.5.1 Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated. Summary statistics for age, body weight, height, and Body Mass Index (BMI) will be tabulated.

8.5.2 Efficacy Analyses

Primary efficacy analysis:

The Chi-square tests will be used to compare the BICLA response rates at Day 169 between each of the active treatment arms and the placebo arm. The Chi-square p-value will be provided for each comparison between the active treatment and the placebo arm. In addition, the difference of the response rates between each active treatment and the placebo will be estimated and their corresponding 90% confidence interval will be calculated. No adjustment will be made for multiplicity.

Secondary efficacy analysis:

- Proportion of subjects who meet response criteria for the SLE Responder Index(4) [SRI(4)], SRI(5) and SRI(6) at Day 169

- Proportion of subjects who meet response criteria for the SLE Responder Index(4) [SRI(4)], SRI(5) and SRI(6) at Day 85
- Proportion of subjects with BICLA response at Day 85
- Percentage of subjects with an improvement of > 4 or a decrease of > 50% from baseline in their CLASI score at Day 85 and Day 169

For each of the above endpoints, the estimate and its corresponding 90% confidence interval will be calculated for the difference of the proportions between each active treatment arm and the placebo arm at the specified visit, similar to the primary analysis.

For each of the following endpoints, the mixed effect model will be fit with treatment and visit as the fixed effects and measurements within each subject as the repeated measurements. The baseline value will be added into the model as a covariate if necessary. Based on the mixed effect model, the estimate and 90% confidence interval will be calculated for the difference between each active treatment and the placebo at each specified visit.

- Change from baseline in CLASI score at Day 85 and Day 169
- Change from baseline in arthritis, as assessed by ACR28-joint count of tender and swollen joints at Day 85 and at Day 169
- The change from baseline in the following other indices SLE activity over time:
  - The overall BILAG-2004 score
  - The overall SLEDAI-2K score
  - The overall MDGA score

In addition, the cumulative corticosteroid and immunosuppressant use over time will be summarized.

8.5.3 Safety Analyses

All recorded adverse events will be listed and tabulated by system organ class, preferred term and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings, and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed. The pre-established Events of Special Interest will be listed and summarized.

8.5.4 Pharmacokinetic Analyses

Ctrough will be summarized by dose and study day.

[redacted]

[redacted]

8.5.7 Outcomes Research Analyses

Not applicable.

8.5.8 Other Analyses

8.5.8.1 Immunogenicity Analysis

Proportion of subjects with BMS-931699 induced antibody response and titers over time will be summarized.

8.6 Interim Analyses

8.6.1 Interim Safety/RO Real Time Analysis at Day 29

When at least 6 patients per treatment arm have either reached Study Day 29 or discontinued, an interim analysis (IA) for safety and RO will be performed. The safety analysis will focus on incidence and severity of all adverse events (AEs), serious AEs and pre-established Events of Special Interest such as infection AEs and any other safety analysis requested by DMC. For RO: the median RO at Day 29 for each treatment arm will be calculated. Based on the results of this interim analysis, a decision will be taken regarding the doses that will be carried forward into Part 2 of the study. Specifically, dosing regimens originally included in Part 1 may be discontinued and/or new dosing regimens may be added according to the following criteria:

Safety:

The DMC in conjunction with an unblinded internal monitoring team may require one or more doses to be discontinued if stopping criteria are met or other safety signals arise that the Medical Monitor and/or DMC consider of sufficient concern.

Receptor Occupancy:

- If median RO of any dose is < 20%, the sponsor may consider dropping that dose
- If the median RO for all doses is > 90% the sponsor may consider adding or replacing a dose in Part 2 of the study to ensure an adequate pharmacodynamic range (dose not to exceed 12.5 mg weekly)

Dose decrease and/or reduction of frequency of administration may also be considered if RO results fall outside the parameters indicated above. This adjustment may occur for safety reasons or in case unforeseen RO profiles observed in SLE patients. The decision to adjust dose and/or frequency will be taken after review of the data by the clinical team.

8.6.2 Interim Analysis for Futility and Dose Adaption at Day 85

After 30 subjects per treatment arm (including the subjects from Part 1) have completed at least 84 days of the treatment period or discontinued the treatment, an interim analysis will be conducted to assess the futility of the BMS-931699 dose arms and the overall safety. The results of the interim analysis will be reviewed by an unblinded sponsor team who will provide recommendations to the blinded study team. The blinded study team will make the decision. The unblinded BMS team may recommend to:

- maintain the current design;
- drop a certain dose arm(s) and equally randomize the remaining unallocated subjects to the remaining arms;
- stop the study if all dose arms need to be dropped for safety or futility reasons.

The interim analysis for futility and dose adaption will be performed on the BICLA response at Day 85 of those 30 subjects per arm and BICLA response at Day 169 of those subjects who have completed 168 days of treatment or discontinued the treatment using a Bayesian predictive approach.[22] This analysis assumes that the BICLA at Day 85 and at Day 169 in the subjects who have not yet been observed will be similar to what were observed for the subjects included at the interim analysis at Day 85 and Day 169, respectively. As such the unobserved data will be simulated from the predictive distribution conditional on the interim data and the prior distribution of the treatment difference (using a non-informative prior). Under the Bayesian framework, the posterior distribution of the treatment difference (BMS-931699 active dose – Placebo) will be constructed to determine the predictive probability of a successful outcome (ie, reach statistical significance) at the planned end of the trial for each dose arm. Based on computer simulations of the operating characteristics of the study design, the futility threshold in this interim analysis is set to 0.2. For the comparison of interest, if the predictive probability of a

successful outcome at the planned end of the trial falls below 0.2, that BMS-931699 dose arm is deemed futile in terms of BICLA response. However, the final futility will also incorporate the results from SRI(4), ACR28 and some biomarkers (C3, C4, ANA and anti-dsDNA).

The proposed stopping rules at the interim analysis, based on the futility assessment and the overall safety assessment, are as follows:

- Rule 1: Drop the futile dose arm(s) and the dose arm cannot be dropped until the lower dose arm has been dropped.
- Rule 2: Drop the dose arm(s) with safety issues identified;
- Rule 3: If safety issues are identified in all dose arms or all dose arms are futile, stop the study.

In case dosing arms are dropped following the interim analysis, the remaining unallocated subjects will be randomized into the remaining arms.

If the predictive probability of success for each active arm versus placebo is greater than or equal to 0.9, then the BMS team may also recommend adding an additional dose arm at lower dose level than current active doses to explore the suboptimal dose.

In that case, the remaining un-allocated subjects with up to 40 additional subjects will be randomized into the remaining arms and the new dose arm based on the new randomizations schedule.

[redacted]

8.7.1 Analysis for the Long-Term Extension Period

The LTE period starts when a subject receives at least one post Day 169 dose. The analysis based on this period is descriptive in nature.

8.7.1.1 Populations of Analysis

All Subjects who received at least one dose post Day 169.

8.7.1.2 Demographics and Baseline Characteristics

Categorical parameters will be summarized using frequency counts and percentages. Continuous parameters will be summarized through means, SD, median, and range. The baseline (Day 1) is defined as the start of study medication (the same as the baseline in the short-term period). The baseline results will be based on LTE analysis population.

8.7.1.3 Efficacy Analyses

For continuous secondary endpoints (eg, SLEDAI, MDGA etc.) point estimates and 90% confidence intervals for mean change from baseline to subsequent time points (in LTE period) within each treatment groups will be provided. For binary endpoints (BICLA Response, SRI(X) etc.), point estimates and 90% confidence intervals (CIs) will be provided using normal

approximation within each treatment group. The assessment windows for LTE period will be based on the first LTE dose date; the baseline to assess responses or changes still refers to the Day 1 assessment (the same as the baseline in the short-term period). The results will be presented by treatment groups. All analyses will be based on as-observed data; hence no imputation will be implemented. No statistical testing including p-value computation will be performed.

8.7.1.4 Safety Analyses

The evaluation of long term safety of the selected dose(s) will be based on clinical adverse events, vital signs and laboratory abnormalities reported during the LTE period. Frequency distributions and individual listings of all adverse events and laboratory marked abnormalities will be generated based on As Treated population. The results will be presented by treatment groups.

8.7.1.5 Immunogenicity

The incidence of a positive response of anti-BMS-931699 antibodies during the LTE period will be summarized by treatment groups.

8.7.1.6 Pharmacokinetic Analyses

The descriptive summary of PK parameters will be provided by visits and by treatment groups during the LTE period.

8.7.1.7 Pharmacodynamic Analyses

The descriptive summary of selected PD and selected biomarkers will be provided by visits and by treatment groups during the LTE period.

8.7.1.8 Outcomes Research Analyses

Not applicable.

The details of the analyses, endpoints and grouping schemes (treatment groups) will be provided in the long-term extension statistical analysis plan (LTE SAP).

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment/screening.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form .For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

External Principal Investigator designated at protocol development

National Coordinating Investigator

Study Steering Committee chair or their designee

Subject recruitment (eg, among the top quartile of enrollers)

Involvement in trial design

Regional representation (eg, among top quartile of enrollers from a specified region or country)

Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
Medical Research	Those scientific activities which cannot be reasonably anticipated at the time of trial design, for which we would like to collect and/or retain samples from study participants. Examples of Medical Research include, but are not limited to, new assay development and validation, companion diagnostic development, new hypotheses in the interaction of drug and the human body, and exploration of emerging science in the understanding of disease.

10.1 List of Abbreviations

Term	Definition
ACR	American College of Rheumatology
ADA	anti-drug antibodies
ADLs	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANC	absolute neutrophil count
Anti-Sm	Anti-Smith antibodies
APC	antigen presenting cells
APL	antiphospholipids
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AZA	azathioprine
β-HCG	beta-human chorionic gonadotrophin
BA/BE	bioavailability/bioequivalence
BICLA	BILAG-based Composite Lupus Assessment
BID, bid	bis in die, twice daily
BILAG	British Isles Lupus Assessment Group
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca^{++}	calcium
Cavg	average concentration
CBC	complete blood count

Term	Definition
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
CHO	chinese hamster ovary
CI	confidence interval
CIA	collagen-induced arthritis
$C1^-$	chloride
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLcr	creatinine clearance
CLT	total body clearance
CLTp	total plasma clearance
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CMV	cytomegalovirus
CNS	central nervous system
cpm	counts per minute
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
CS	corticosteroids
Ctrough	trough observed plasma concentration
CV	coefficient of variation
CXR	chest x-ray
CYP	cytochrome p-450
dAb	domain antibody
D/C	discontinue
DC	dendritic cell
dL	deciliter
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ds-DNA	double-stranded deoxyribonucleic acid

Term	Definition
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
EA	extent of absorption
EAE	experimental autoimmune encephalitis
EBV	Epstein-Barr virus
EC50	effective concentration of drug or antibody which induces a response halfway between the baseline and maximum after a specified exposure time
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
eg	exempli gratia (for example)
ePPND	enhanced prenatal/postnatal toxicology
ESR	Expedited Safety Report
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue
FBDS	formulated bulk drug substance
FDA	Food and Drug Administration
FIH	first in human
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO_3^-	bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate

Term	Definition
HRT	hormone replacement therapy
IA	Interim Analysis
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IFN	interferon
IL	interleukin
IM	intramuscular
IMP	investigational medicinal products
IND	Investigational New Drug
IRB	Institutional Review Board
IU	International Unit
K	slope of the terminal phase of the log concentration-time curve
K_3EDTA	potassium ethylenediaminetetraacetic acid
K^+	potassium
kg	kilogram
KLH	keyhole limpet hemocyanin
L	liter
LBA	ligand binding assay
LCV	lymphocryptovirus
LLOQ	lower limit of quantification
LOD	limit of detection
LTE	Long-Term Extension
mAb	monoclonal antibody
MABEL	minimal anticipated biological effect level
MAD	multiple ascending dose
MBP	myelin basic protein

Term	Definition
MCB	master cell bank
MDGA	Physician's Global Assessment of Disease Activity
mg	milligram
Mg^{++}	magnesium
min	minute
mL	milliliter
mmHg	millimeters of mercury
MOA	mode of action
MOG	myelin oligodendrocyte glycoprotein
MR	medical research
MRT	mean residence time
MS	multiple scelorosis
MTD	maximum tolerated dose
MTΞ	methotrexate
MW	molecular weight
μg	microgram
N	number of subjects or observations
Na^{+}	sodium
N/A	not applicable
Ng	nanogram
NHV	normal healthy volunteer
NIMP	non-investigational medicinal products
NOAEL	no observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drug
NSS	Normal saline solution
OVA	ovalbumin
PBMC	peripheral blood mononuclear cell
PBS	phosphate buffered saline
PD	pharmacodynamics
PGA	Subject's Global Assessment of Disease Activity

Term	Definition
PK	pharmacokinetics
POC	proof of concept
QC	quality control
QFG	QuantiFERON-TB Gold assay
R^2	coefficient of determination
RA	rhumatoid arthritis
RBC	red blood cell
RO	receptor occupancy
SAD	single ascending dose
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SF-36	Short Form (36)
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC/ACR Damage Index	Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index
SOP	Standard Operating Procedures
SRI	SLE Responder Index
ST	serine and threonine
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
TCR	T-cell receptor
TDAR	T-cell dependent antibody response
T-HALF	Half life
TID, tid	ter in die, three times a day
Tmax, TMAX	time of maximum observed concentration
TNF	tumor necrosis factor
T-Regs	regulatory T-lymphocytes

Term	Definition
ULN	upper limit of normal
VAS	visual analog scale
VH	variable regions of the heavy chain of a human antibody
VL	variable regions of the light chain of a human antibody
Vss	volume of distribution at steady-state
WHO	World Health Organization
WOCBP	women of childbearing potential
WT	wild type

APPENDIX 1 COMMONLY USED CORTICOSTEROID EQUIVALENTS

Medication	Dose Equivalence
Prednisone	20mg
Cortisone	100mg
Hydrocortisone	80mg
Prednisolone	20mg
Methylprednisolone	16mg
Triamcinolone	16mg
Budesonide	4mg
Dexamethasone	3mg
Bethamethasone	2.4mg

APPENDIX 3 THE 1982 REVISED CRITERIA FOR CLASSIFICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS[1,2]

Criterion	Definition
1) Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2) Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3) Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4) Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5) Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6) Serositis	a) Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion OR b) Pericarditis--documented by ECG or rub or evidence of pericardial effusion
7) Renal disorder	a) Persistent proteinuria greater than 0.5 grams per day or greater than 3 + if quantitation not performed OR b) Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8) Neurologic	a) Seizures--in the absence of offending drugs or known metabolic disorder derangements; eg, uremia, ketoacidosis, or electrolyte imbalance OR b) Psychosis--in the absence of offending drugs or known metabolic derangements, eg, uremia, ketoacidosis, or electrolyte imbalance
9) Hematologic disorder	a) Hemolytic anemia--with reticulocytosis OR b) Leukopenia--less than 4,000/mm3 total on 2 or more occasions OR c) Lymphopenia--less than 1,500/mm3 on 2 or more occasions OR d) Thrombocytopenia--less than 100,000/mm3 in the absence of offending drugs
10) Immunologic disorder	a) Anti-DNA: antibody to native DNA in abnormal titer OR b) Anti-Sm: presence of antibody to Sm nuclear antigen OR c) Positive finding of anti-phospholipid antibodies based: 1) an abnormal serum level of IgG or IgM anti-cardiolipin antibodies, 2) a positive test result for lupus anticoagulant using a standard method, or 3) a false positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test.
11) Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

* The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

Protocol Number: IM128027
IND Number: 110,787
EUDRACT Number 2014-002184-14
Date: 28-Apr-2015

Protocol IM128027: A Phase 2, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of lulizumab pegol vs Placebo on a Background of Limited Standard of Care in the Treatment of Subjects with Active Systemic Lupus Erythematosus

Amendment Number 06
Site Number: All

Study Director/Central Medical Monitor
Lara Pupim, MD, MSCI
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Bristol-Myers Squibb Research and Development
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This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

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Changes to the Protocol:

1. Title Page and Protocol Header: updated generic name of the investigational drug from anti-cd28dab to lulizumab pegol
2. Synopsis, Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): updated to add the generic name lulizumab pegol and to include the LTE.
3. Synopsis, Research Hypothesis; Section1.2 Research Hypothesis: corrected a typographical error to cutaneous from cutanenous
4. Synopsis, Objectives: updated to separate the Short-Term Period Objectives from those of the LTE
5. Synopsis, Primary Objective; Section 8.3.1 Primary Endpoints: deleted the fragment "following 24-week treatment with BMS-931699 or placebo administered on a stable background therapy", as BICLA will be assessed at Day 169 for subjects who have completed Day 169 or discontinued, ie subjects who have discontinue will count as non-responders.
6. Synopsis, Secondary Objectives; Section 1.3.2 Secondary Objectives: clarified the objectives of Parts 1 and 2 of the study and added objectives for the LTE
7. Synopsis, Study Design, Duration of the Study:
   a) updated to clarify the dose adaptation plans and to include the LTE
   b) updated Study Schematics to include the LTE
   c) added a new figure, Study Design Schematic - Long-Term Extension Period, to show the LTE schema
   d) added new paragraphs to describe the LTE and clarify when the 42 days Follow Up visit will be performed
   e) Synopsis, Number of Subjects: updated to clarify when the number of participating subjects could be increased
8. Synopsis, Study Population: corrected 1 month to 8 weeks of stable background therapy and updated to clarify the allowed background therapy for consistency with protocol
9. Synopsis, Study Assessments:
   a) reorganized for category to increase clarity
   b) “soluble receptors” removed from the biomarkers being assessed
   c) updated the list of biomarkers being assessed to increase clarity
10. Synopsis, Sample Size and Section 8.1 Sample Size Determination: updated to clarify how Discontinuations will be managed in the analysis
11. Synopsis, Endpoints and Analyses: updated for clarity and to support the LTE

12. [redacted]

13. [redacted]

[redacted]

15. Section 1.3.1 Primary Objectives:
    a) deleted the fragment "following 24-week treatment with BMS-931699 or placebo administered on a stable background therapy", as BICLA will be assessed at Day 169 for subjects who have completed Day 169 or discontinued, ie subjects who have discontinue will count as non-responders.
    b) added mycophenolate acid/mycophenolate mofetil and leflunomide to the list of immunosuppressant agents that must remain stable
16. Section 1.3.2 Secondary Objectives:
    a) deleted the fragment "following 24-week treatment with BMS-931699 or placebo administered on a stable background therapy", as objectives will be assessed for subjects who have completed Day 169 or discontinued, ie subjects who have discontinue will count as non-responders.
    b) removed “pain” as only tenderness and swelling are assessed in the ACR28 used in this study.

[redacted]

18. Section 1.3.4 Long-Term Extension Period Objectives: new section to support the LTE
19. Section 1.5 Overall Risk/Benefit Assessment:
    a) updated to include the LTE
    b) updated to clarify the acceptable tuberculosis screening tests
20. Section 3.1 Study Design and Duration:
    a) updated to clarify the dose adaptation plans, to clarify duration of screening period and Day 1 visit window and, to include the LTE
    b) updated Figure 3.1-1 Overall Study Design to include the LTE
    c) added a new figure, Figure 3.1-4 Long-Term Extension Schematic, to show the LTE schema
    d) added new paragraphs to describe the LTE and clarify when the 42 days Follow Up visit will be performed
21. Section 3.2 Post Study Access to Therapy: updated to specify that the LTE has no end date at this point but that this could change based on results obtained from the development program of lulizumab pegol
22. Section 3.3 Study Population: added sentence summarizing the requirements for entry into the LTE.

23. Section 3.3.1 Inclusion Criteria:
    a) corrected criterion 2.c)i) to clarify the targeted patient population
    b) corrected criterion 2.c)iv) to add mycophenolate acid/mycophenolate mofetil as a permitted immunosuppressant agent and also include leflunomide (for consistency with the synopsis) and to add the requirement to follow the mycophenolate mofetil (MMF) insert package in case of neutropenia (for subjects taking MMF)
    c) corrected criterion 2.c)v) to clarify that prednisone (or prednisone equivalent) is allowed but not required
    d) corrected criterion 2.c)vi) to clarify that washout periods must be fulfilled prior to signing consent
    e) corrected criterion 2.c)vii) to clarify that the requirement for stable NSAIDs only applies for chronic use and correct a typographical error in the MDGA acronym.
24. Section 3.3.2 Exclusion Criteria:
    a) clarified exceptions to exclusion criterion 1.b) and 1.c)
    b) removed exclusion criterion 2.b)i (4) as it is included in 2.b)i (3)
    c) corrected a typographical error in exclusion criterion 2.b)ii) to mononeuritis from mononeritis
    d) updated exclusion criterion 2.b)v) to clarify the HIV antibodies being tested
    e) clarified exceptions to exclusion criterion 3.l)
25. Section 3.3.4 Criteria for Long-term Extension: new section to include the LTE
26. Section 3.4.1 Prohibited and/or Restricted Treatments; Appendix 2 Washout Times of Medications Based on 5 Half-Lives:
    a) reformatted the section to avoid duplication of information in text and in Appendix 2. For clarity, required washout or recovery times are now all contained in Appendix 2 and not repeated in text.
    b) deleted restriction of mycophenolate mofetil, which is now an acceptable background immunossuppressant in the study.
    c) added the requirement to follow the mycophenolate mofetil (MMF) insert package in case of neutropenia (for subjects taking MMF)
    d) added sentence to clarify when influenza and pneumococcal vaccine can be administered
    e) deleted restriction of planned elective surgery from this section as it is part of the inclusion and exclusion criteria section.
    f) added some clarity around the management of concomitant medications
27. Section 3.5 Discontinuation of Subjects following any Treatment with Study Drug:
    a) clarified the requirement for discontinuation related to excessive use of prednisone (or prednisone equivalent).
    b) added Pregnancy
28. Section 3.5 Discontinuation of Subjects following any Treatment with Study Drug; Section 6.4 Pregnancy: clarified that females that become pregnancy will be immediately discontinued from the study

29. Section 4 Study Drug:
    a) removed the requirement to dose BMS-931699 in the morning
    b) Table 4.1 Treatment Administration: corrected to capture that placebo is not a vial but normal saline solution (NSS)
30. Section 4.3 Storage and Dispensing:
    a) corrected name of document referred to in paragraph 5 from Preparation for Subcutaneous Use to Pharmacy Reference Instruction
    b) removed preparation details that can be found in more details in the Pharmacy Reference Instructions
    c) updated to clarify that subjects must remain at the site for at least 1 hour after each injection, consistent with Section 4.5.1
31. Section 4.4 Method of Assigning Subject Identification: corrected to remove "within each panel" as there are no panels in this study
32. Section 4.5.1 Administration of BMS-931699 or placebo:
    a) added double-blind to heading for clarity
    b) corrected the information pertaining to the 12.5mg weekly dose from BMS-931688 to BMS-931699
    c) added that Placebo injection only applies to the Short-Term period of the study
33. Section 4.5.2 Dose modifications: clarified the management of the dose modifications
34. Section 4.5.3 Corticosteroids (Prednisone or Prednisone Equivalent) Dosing: clarified the management of dose modifications during the study
35. Section 4.5.4 Rescue Therapy: new section added for clarity on protocol allowance as rescue therapy and to define when subjects who require rescue therapy will be discontinued.
36. Section 4.6.2 Unblinding of the Study Sites: removed the last 2 paragraphs since the information was not pertaining to the unblinding of the study sites
37. Section 5.1 Flow Chart/Time and Events Schedule:
    a) Table 5.1-1 Screening Procedural Outline (IM128027): corrected Notes for ACR criteria for SLE form to be Appendix 3
    b) Table 5.1-1 Screening Procedural Outline (IM128027): corrected Procedures to add that breast/cervical cancer screening must also be documented
    c) Table 5.1-1 Screening Procedural Outline (IM128027): removed Ro (SS-A), La (SS-B), RNP and APL from samples collected at screening as these assessments are not required for eligibility
    d) Table 5.1-2 Short-Term Procedural Outline (IM128027): updated to clarify the +/- 2 days window also applies to Day 1 visit
    e) Table 5.1-2 Short-Term Procedural Outline (IM128027): removed Total soluble CD28 from procedures performed during the study
    f) Table 5.1-2 Short-Term Procedural Outline (IM128027): added a footnote to specify when the 42 days Follow Up visit should be conducted
    g) Table 5.1-3 Long-Term Extension Procedural Outline (IM128027): new table to outline procedures for LTE

38. Section 5.2 Study materials: updated to remove the requirement for a refrigerated centrifuge
39. Section 5.3.2 Laboratory Test Assessments: updated to clarify the laboratory tests being assessed, to include the LTE and add HIV screen at the screening visit only (since this was omitted in the initial version of the protocol)
40. Section 5.3.3 Tuberculosis Screening and Chest X-Ray: updated to clarify that a confirmed negative IGRA test is required prior to Day 1
41. Section 5.4.1 Primary Efficacy Assessment: updated to include the LTE
    a) Section 5.4.1.1 Short-Term Period: new section to separate the Short-Term Period Efficacy Assessment from the LTE
    b) Section 5.4.1.2 Long-Term Extension Period: new section added to include the LTE
42. Section 5.4.2 Secondary Efficacy Assessments: updated to include the LTE
    a) Section 5.4.2.1 Short-Term Period: new section to separate the Short-Term Period Efficacy Assessment from the LTE
    b) Section 5.4.2.2 Long-Term Extension Period: new section added to include the LTE
43. Section 5.5 Pharmacokinetic Assessments: updated to include the LTE
    a) Section 5.5.1 Short-Term Period: added new section to separate the Short-Term Period Pharmacokinetic Assessment from the LTE, removed specific timepoints and referred to Table 5.5.1-1 for consistency
    b) Section 5.5.2 Long-Term Extension Period: new section added to include the LTE
44. Section 5.5.1 Pharmacokinetics: Collection and Processing:
    a) renumbered to Section 5.5.3
    b) Table 5.5.1-1 Pharmacokinetic Sampling Schedule for BMS-931699 renumbered to Table 5.5.3-1
    c) Table 5.5.1-1 (renumbered to Table 5.5.3-1) updated to include collection schedule for LTE
    d) added footnote b to Table 5.5.1-1 (renumbered to Table 5.5.3-1) to clarity that for AEs samples are to be drawn only for subjects that experience an AE leading to discontinuation of study treatment
45. Section 5.5.2 Pharmacokinetic Sample Analyses renumbered to Section 5.5.4 Pharmacokinetic Sample Analyses
46. Section 5.5.3 Immunogenicity Assessments: renumbered to Section 5.5.5 and updated for clarity
47. Section 5.5.4 Labeling and Shipping of Biological Samples renumbered to Section 5.5.6 Labeling and Shipping of Biological Samples

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49. Section 5.7.1 Blood-Based (RNA) Assessments: updated to clarify the planned RNA analysis

[redacted]

51. Section 5.8 Outcomes Research Assessment: removed subsection on hospitalization and emergency room visits

52. Section 6 Adverse Events: updated to clarify the reporting of safety events to comply with countries requirements
53. Section 6.1.1 Serious Adverse Event Collecting and Reporting: updated to 42 days (from 30) for consistency with the Time & Event Table, the half-life of lulizumab pegol and the estimated receptor occupancy.
54. Section 6.7.1 AE's of Special Interest:
    a) updated to remove Immunogenicity from the list and clarify how it will be monitored
    b) updated to clarify that Injection-related reactions will be monitored to include local and systemic reactions, instead of Injection-site reactions
55. Section 8.3 Endpoints: renamed 8.3 Endpoints for Short-Term Period to differentiate from Endpoints for the LTE

[redacted]

57. Section 8.4 Endpoints for Long-Term Extension Period: new section to include the LTE
    a) Section 8.4.1 Safety Endpoints: new section to include the LTE
    b) Section 8.4.2 Efficacy Endpoints: new section to include the LTE
    c) Section 8.4.3 Pharmacokinetic Endpoints: new section to include the LTE

    [redacted]

    e) Section 8.4.5 Immunogenicity: new section to include the LTE
58. Section 8.4 Analyses: renumbered and changed to Section 8.5 Analyses for Short-Term Period
    a) Section 8.4.1 Demographics and Baseline Characteristics renumbered Section 8.5.1 Demographics and Baseline Characteristics
    b) Section 8.4.2 Efficacy Analyses renumbered Section 8.5.2 Efficacy Analyses
    c) Section 8.4.3 Safety Analyses renumbered Section 8.5.3 Safety Analyses
    d) Section 8.4.4 Pharmacokinetic Analyses renumbered Section 8.5.4 Pharmacokinetic Analyses

    [redacted]

    g) Section 8.4.7 Outcomes Research Analyses renumbered Section 8.5.7 Outcomes Research Analyses
    h) Section 8.4.8 Other Analyses renumbered Section 8.5.8 Other Analyses
    i) Section 8.4.8.1 Immunogenicity Analysis renumbered to Section 8.5.8.1 Immunogenicity Analysis
59. Section 8.5 Interim Analyses renumbered Section 8.6 Interim Analyses
    a) Section 8.5.1 Interim Safety/RO Real Time Analysis at Day 29 renumbered Section 8.6.1 Interim Safety/RO Real Time Analysis at Day 29
    b) Section 8.5.2 Interim Analysis for Futility and Dose Adaption at Day 85 renumbered Section 8.6.2 Interim Analysis for Futility and Dose Adaption at Day 85

    [redacted]

[redacted]

61. Section 10.1 List of Abbreviations: updated to add Anti-SM, LTE and NSS and remove MMF
62. Appendix 2 Washout Times of Medications Based on 5 Half-Lives:
    a) renamed Washout or Recovery Times Required Prior to Screening
    b) updated for clarity and consistency with other sections
63. Appendix 5 Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) Disease Activity Questionnaire: corrected the period of time the manifestation must be present within from 10 days to 30 days, for consistency with other sections

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.