Official Title of Study:

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy and Safety of BMS-986165 in Subjects with Systemic Lupus Erythematosus

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Clinical Protocol IM011021

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy and Safety of BMS-986165 in Subjects with Systemic Lupus Erythematosus

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DOCUMENT HISTORY

Document	Date of Issue	Approver(s)	Summary of Change
Original Protocol	23-May-2017	[redacted]	Not applicable
Japan Protocol Amendment 01	23-Aug-2017		Japan specific
Global Revision 01 (Version 2.0)	24-Jan-2018		Updated the Sponsor's protocol template, style, and made typographic corrections throughout the protocol; revised study design including sample size reduction to 360, decreased frequency of 12 mg arm to QD, and changed primary objective to SRI(4) response; clarified and updated certain procedures; revised certain inclusion/exclusion for clarity; revised certain appendices based on updates throughout Innovative Medicines Development
Japan Protocol Amendment 02	28-Mar-2018		Japan specific
Japan Protocol Amendment 03	26-Jun-2018		Japan specific
Global Revision 02 (Version 3.0)	28-Jan-2019		Updated the Sponsor's contact information; made typographic corrections to the protocol; clarified certain procedures; changed LLDAS [redacted] to a secondary endpoint; redefined partial and major clinical response; revised certain inclusion/exclusion criteria for clarity; updated wording in Appendix 3 and Appendix 4 to be consistent across studies of BMS-986165

Document	Date of Issue	Approver(s)	Summary of Change
Global Revision 03 (Version 4.0)	11-Jun-2019	[redacted]	Updated the Document History to include several Japan-specific amendments Restored the Photography assessment in Table 3 (Week 28/Day197 Visit), which was inadvertently omitted in v3.0 [redacted] Clarified Inclusion Criteria regarding: • Loss of functional range of movements and daily activity (SLE Disease Characteristics in Inclusion Criterion 2)e)ii); Section 5.1) • Use of corticosteroid monotherapy (Medications for SLE in Inclusion Criterion 3)b); Section 5.1) • Use of effective methods of contraception (Age and Reproductive Status in Inclusion Criterion 4)f) and 4)g); Section 5.1) Removed language regarding prohibition of P-glycoprotein inhibitors (item #7, Section 6.7.1) based on recent drug-drug interaction data Revised the definition of an overdose to align with a revision of appendices across IMD; overdose is no longer reported automatically as a serious adverse event (Section 8.4) [redacted] Clarified that plasma concentration values (rather than just Ctrough values) will be summarized (Section 9.3.3.1) Aligned APPENDIX 4 language regarding male subjects with female partner(s) of childbearing potential with current safety guidance.

Document	Date of Issue	Approver(s)	Summary of Change
Protocol Amendment 07[a]	30-Jul-2019	[redacted]	South Korea and Taiwan-specific amendment to modify inclusion criterion regarding age and to include hepatitis B surface antibody screening and hepatitis B virus DNA screening and monitoring.
Global Revision 04 im011021-revprot04[b]	15-Apr-2020		Updated the Study Director and Approver information; [redacted] clarified PK sampling windows; synchronized sample size determination with testing hierarchy; updated adjustments for multiplicity.

[a]Revision numbering has been updated to reflect total number of revisions.
[b]Protocol numbering format has been updated. Legacy [redacted] numbering is provided for consistency.

SUMMARY OF CHANGES

Rationale:

The primary purpose of this global revised protocol is to modify the analysis plan and provide clarifications in the protocol.

Key modifications and clarifications are summarized as follows:

- Added clarifying detail to several items in the protocol
- Changed secondary endpoints to be assessed at 48 weeks
- Updated the sampling windows for the collection of pharmacokinetic samples at the Day 1 and Day 85 visits
- Revised certain sub-sections within Statistical Considerations

Substantive changes made to previous versions of the protocol and the rationale for these changes are noted below in the summary of key changes table. All changes applied to the protocol body were applied to the synopsis, as necessary; synopsis changes are not included in the summary of key changes table. Only major additions and deletions are provided in this summary table; all minor grammatical, formatting, stylistic changes, or clarifications as well as organizational changes are not included.

SUMMARY OF KEY CHANGES TO THE REVISED PROTOCOL

Section Number & Title	Description of Change	Brief Rationale
Title Page	Updated sponsor Study Director	Updated with current contact
Document History	Updated sponsor Study Approver	Updated with current contact
Synopsis	Updated all corresponding sections to the main report sections (listed below)	Rationale for changes included below
3 Objectives and Endpoints; Table 7	Revised description of pharmacokinetics objective and endpoint	Clarified that the active metabolite of BMS-986165 is included in the analysis
3 Objectives and Endpoints, 9.3.1.1 Endpoints	Moved Week 48 endpoints (SRI(4), BICLA, LLDAS, CLASI50, and 40-Joint count) to multiplicity-controlled Secondary Endpoints (and corresponding Secondary Objectives) [redacted]	Week 48 endpoints moved into the multiplicity-controlled hierarchy for better alignment with regulatory guidance documents

SUMMARY OF KEY CHANGES TO THE REVISED PROTOCOL

Section Number & Title	Description of Change	Brief Rationale
4.1 Overall Design	Removed the following sentence: The end of the study for sample analysis is defined as 2 years after final clinical study report	To remove inconsistency as future sample analysis may be up to 15 years after the final clinical study report or as per local regulations
5.1 Inclusion Criteria	Removed criterion 4 i)	For consistency with male contraception requirements
5.5.1 Retesting During Screening Period; Rescreening	Updated text for rescreening subjects	Additional rescreening is allowed for subjects who may be otherwise eligible but experience an exceptional circumstance beyond site or subject control.
8.6.2 Sampling Windows	Updated to: •The following windows apply to other samples: **- ±0.25 hour for the 0.5-hour sample** **- ±0.5 hour for the 2-hour sample** - ±1 hour for the 4- and 6-hour samples	Added a pharmacokinetic sampling window for the 0.5-hour collection (Day 1 and Day 85) and modified the 2-hour collection window (Day 1 and Day 85)
8.6.2 Sampling Windows	Updated to: **If samples cannot be taken within the specified time window, every effort should be made to take a sample as soon as possible. Deviations from the sampling windows** must be noted in the source documents.	To instruct sites to collect samples even if they are collected outside of the provided sample windows and document these occurrences.
9.1 Sample Size Determination	Updated text to include description of the BID and QD branches	The power for the initial statistical tests within each branch (BID, alpha=0.04 and QD, alpha=0.01) were added.
9.2 Populations for Analyses	The word “important” changed to “relevant” in per protocol set definition	Updated terminology.

SUMMARY OF KEY CHANGES TO THE REVISED PROTOCOL

Section Number & Title	Description of Change	Brief Rationale
9.3.1.2 Nonresponders	Nonresponder imputation (NRI) section updated	Updated to clarify that this NRI is applicable to the primary and secondary endpoints at Week 32 and Week 48. Further guidance for other endpoints /timepoints will be provided in the SAP.
9.3.1.3 Analysis Methodology	Single randomization stratum combining Region (US, Latin America, Rest of World, Japan [other stratification factors will not be applied in Japan]), CS dose at baseline (≥ 10 mg/day or < 10 mg/day) and SLEDAI-2K at baseline (≥ 10 or < 10) added for logistic regression, Cochran-Mantel-Haenszel and repeated measures analysis	Clarification of how to handle the lack of CS and SLEDAI-2K stratification within Japanese subjects
[redacted]		
9.3.5 Analysis and Reporting	The planned 32-week database lock has been removed.	Since the key secondary endpoints will now be assessed at Week 48 no database lock will occur until all randomized subjects have completed 48 weeks of double-blind treatment (or have discontinued).
APPENDIX 4 Women of Childbearing Potential Definitions and Methods of Contraception	Updated text to specify hormonal contraception must begin at least 30 days prior to initiation of study therapy	To align with informed consent language across all BMS-986165 studies

STUDY ACKNOWLEDGMENT/DISCLOSURE

I understand that this protocol contains information that is confidential and proprietary to Bristol-Myers Squibb Company (BMS). Any supplemental information that may be added to this document is also confidential and proprietary to BMS and must be kept in confidence in the same manner as the contents of this protocol.

I have read the original protocol/revised protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein and will make a reasonable effort to complete the study within the time designated.

I will provide copies of the protocol and access to all information furnished by BMS to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I will provide protocol information to my Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s]. I understand that original protocol/revised protocols must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion by all necessary Health Authorities before implementation unless to eliminate an immediate hazard to subjects.

I agree that the contents of the protocol may not be disclosed to any other person or entity or used for any other purpose without the prior written consent of BMS. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to BMS of any such disclosure.

I agree that the study data derived from this protocol may only be used and disclosed in furtherance of the protocol, for the medical treatment of a study subject or for publication of study results in accordance with the terms of the clinical trial agreement or as otherwise permitted by the terms of the clinical trial agreement.

I agree not to collect or use samples (e.g., tissue, blood, serum, urine) or collect data (other than for diagnostic or treatment purposes) from the study subjects while enrolled in the study, except as expressly permitted by the protocol or the terms of the clinical trial agreement.

I understand that I may terminate or suspend enrollment of the study at any time if it becomes necessary to protect the best interests of the study subjects. Unless otherwise provided in the clinical trial agreement, the study may be terminated at any time by BMS, with or without cause.

Original Protocol: ☐ Revised Protocol: ☒

Protocol Number: IM011021 Site Number:

Date of Protocol or Revised Protocol: 15-Apr-2020

IND Number: 134253 EUDRACT Number: 2017-001203-79

Investigator: Date:

(signature)

(printed name)

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy and Safety of BMS-986165 in Subjects with Systemic Lupus Erythematosus

Study Phase: 2

Rationale:

BMS-986165 is the first, potent, oral tyrosine kinase 2 (TYK2) inhibitor with a novel, highly selective mechanism of action that has the potential to safely and effectively treat a broad spectrum of immune-mediated diseases. Tyrosine kinase 2 activates intracellular signal transducer and activator of transcription (STAT)-dependent transcription and functional responses downstream of receptors for critical immune mediators, such as interleukin (IL)-12, IL-23, and Type I and III interferons (IFNs).[1, 2, 3] These immune and inflammatory signaling pathways are critical in the pathophysiology of various immune-mediated diseases including psoriasis, lupus, spondyloarthritis, inflammatory bowel disease (IBD), dermatomyositis, and Type I interferonopathies.[4,5] BMS-986165 potently inhibits IL-23-, IL-12-, and Type I/III IFN-driven responses and has demonstrated proof of mechanism in mouse models of autoimmunity (psoriasis, colitis, and systemic lupus erythematosus [SLE]) and in healthy humans.[5,6]

The proposed Phase 2 study in subjects with SLE will provide evidence of dose-ranging efficacy of BMS-986165 in this disease. Systemic lupus erythematosus is an ideal condition to evaluate the efficacy of the selective TYK2 inhibitor BMS-986165 for multiple reasons, as follows: 1) the major pathways in the TYK2 signaling cascade (Type I IFN and IL-12/23 and the downstream mediators IFNγ and IL-17) have been implicated in SLE disease pathogenesis;[7] 2) biologic agents targeting the IL-12/23 pathway, or the IFNα (or the Type I IFN) receptor have been shown to be efficacious in Phase 2 studies of SLE[8]; and 3) the ability to measure circulating target-specific (such as suppression of IFN-stimulated gene expression) and disease-specific pharmacodynamic (PD) measures in SLE both before and after treatment allows for establishing exposure-response relationships for PD endpoints in this condition.

The present study is the first study of this TYK2 inhibitor conducted in subjects with SLE and is intended to determine whether the pharmacological effects of TYK2 inhibition are associated with objective clinical improvement in SLE disease activity and related biomarkers. The study is also designed to assess the safety and tolerability of short- and long-term BMS-986165 treatment in subjects with SLE and to determine the dose level that provides the optimal balance of efficacy and safety.

Study Population:

The study will enroll male and female subjects, 18 to 75 years old (inclusive), with SLE defined as follows:

- Meeting the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE[9]

- Being positive for one of the following: antinuclear antibody (ANA) ≥ 1:80 or positive anti-double-stranded deoxyribonucleic acid (dsDNA; indeterminate values are considered positive) or positive anti-Smith (Sm) as determined by the central laboratory
- Having Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score ≥ 6 points and clinical SLEDAI-2K score ≥ 4 (points from organic brain syndrome, headache, alopecia, and mucosal ulcers do not count towards the SLEDAI-2K score for the purposes of inclusion)

Those with drug-induced SLE, certain other immune-mediated diseases, and active, severe lupus nephritis or central nervous system lupus will be excluded. To be randomized on Day 1 and to receive study treatment or placebo, subjects must meet criteria related to active musculoskeletal and/or mucocutaneous disease, with a clinical SLEDAI ≥ 4.

Objectives and Endpoints:

Objective	Endpoint
Primary Efficacy	
• To assess the effect of BMS-986165 on SLE Responder Index (SRI)(4) response at Week 32 in subjects with SLE	• Proportion of subjects who meet response criteria for SRI(4) at Week 32 (Section 8.1)
Secondary Efficacy	
• To assess the effect of BMS-986165 on measures of global and organ-specific clinical responses	• Proportion of subjects who meet response criteria for SRI(4) at Week 48 • Proportion of subjects who achieve a British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) response at Week 48 • Proportion of subjects who achieve Lupus Low Disease Activity State (LLDAS) at Week 48 • Proportion of subjects with a Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score ≥ 10 at baseline who achieve a CLASI response, defined as a decrease of ≥ 50% from baseline CLASI activity score at Week 48 • Change from baseline in the 40-joint count for tender, swollen, and tender + swollen joints at Week 48

Objective	Endpoint
Safety	
• To assess the safety and tolerability of BMS-986165	• Number and proportion of subjects experiencing serious adverse events (SAEs); adverse events (AEs); and abnormalities in laboratory testing, vital signs, and electrocardiograms (ECGs)

[redacted]

Overall Design:

This is a randomized, placebo-controlled, double-blind, multicenter study to evaluate the efficacy and safety of BMS-986165 in subjects with SLE. The study includes a screening period (SP) of up to 4 weeks (28 days); a 48-week (336-day) blinded treatment period (TP); and a 28-day follow-up period (FP), for subjects who do not continue into the long-term extension (LTE) study (IM011074). The total duration will be approximately 56 weeks (392 days). Other details of study design are as follows:

- Randomization will be performed after completion of the SP, on Day 1 of the TP.
- Randomization in a 1:1:1:1 ratio will be performed using interactive response technology (IRT) and will be stratified by screening corticosteroid (CS) dose (≥ 10 mg/day or < 10 mg/day), screening SLEDAI-2K score (≥ 10 or < 10), and geographic region.
- The blind will be maintained during the TP by the use of matched capsules (placebo and 3 mg BMS-986165) provided in blister cards that are identical in appearance while providing the appropriate randomized dose.
- Clinical, laboratory, and photographic evidence of disease activity will be reviewed by blinded external reviewers.
- Safety data will be reviewed by the Data Monitoring Committee.
- The primary analysis of Week 32 efficacy assessments will be performed after all subjects have completed 48 weeks of double-blind treatment (or discontinued from the study).

Number of Subjects:

Approximately 360 subjects will be randomized to receive oral treatment with BMS-986165 12 mg once daily (QD), 6 mg twice daily (BID), 3 mg BID, or placebo BID.

Treatment Arms and Duration:

Study treatment: Subjects in all treatment groups will take oral doses of the investigational product (IP) for 48 weeks during the TP as follows: BMS-986165 12 mg QD, 6 mg BID, 3 mg BID, or placebo BID.

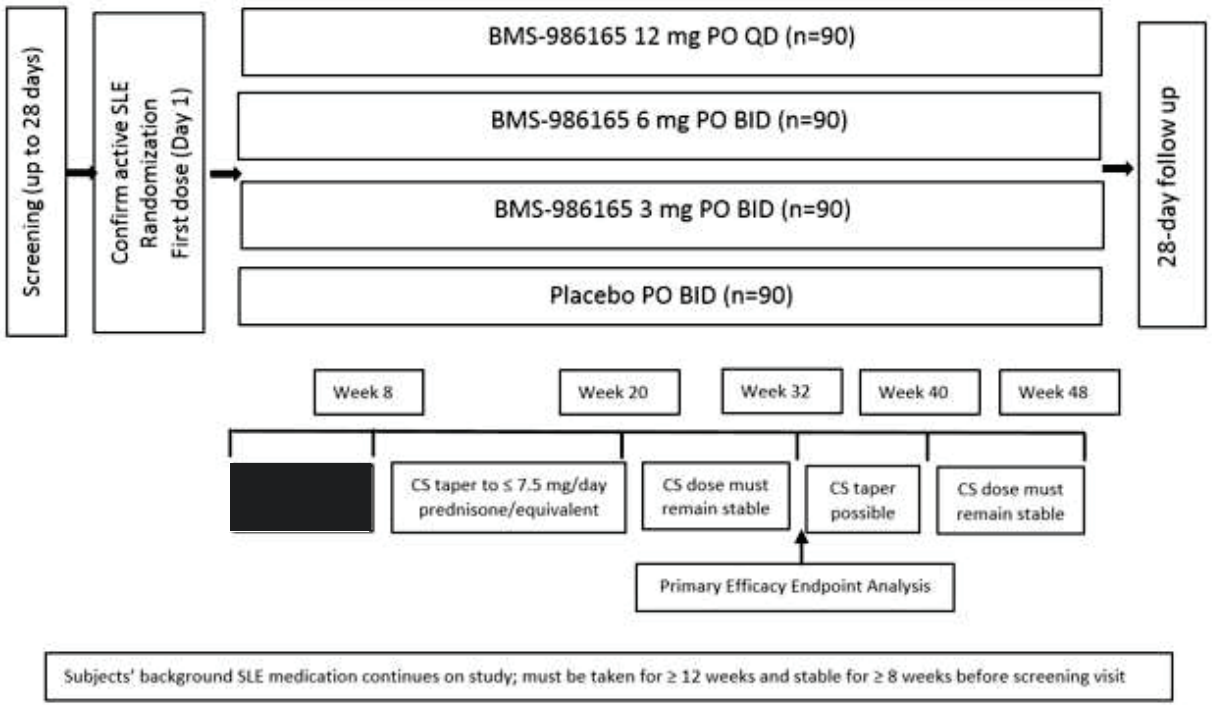
Study Treatment for IM011021

Medication	Potency	IP/Non-IP
BMS-986165	3 mg	IP
Placebo	Not applicable	IP

IP = investigational product

- The total duration of study participation for each subject is up to approximately 56 weeks (392 days), including up to a 4-week (28-day) SP, a 48-week (336-day) TP, and a 4-week (28-day) FP for subjects who do not continue into the LTE study (IM011074).
- In all treatment groups, subjects will take their randomly assigned treatment twice daily as oral capsules in a blinded manner.
- No titration or modification of IP doses is permitted.

1.2 Schema



BID = twice daily; CS = corticosteroid; PO = per os (by mouth); QD = once daily; SLE = systemic lupus erythematosus

1.3 Schedules of Activities

Schedules of procedures are described in Table 1 for screening, Table 2 for the first half of the TP (up to Week 24), and Table 3 for the second half of the TP (after Week 24).

Table 1: Screening Procedural Outline (Protocol IM011021)

Procedure	Screening Visit From Day -28	Notes
Eligibility Assessments		
Informed Consent	X	A subject is considered enrolled only when a protocol-specific informed consent is signed.
Enroll subject	X	Obtain number from IRT; contact IRT to screen fail those not eligible.
Inclusion/exclusion criteria	X	Section 5
Medical history	X	Include any toxicities or allergy related to previous treatments.
SLICC criteria for SLE	X	APPENDIX 5
BILAG-2004 Index	X	APPENDIX 10
SLEDAI-2K	X	APPENDIX 11
Physician's Global Assessment	X	Assessment of disease activity using a 3-point scale
40-joint count	X	Counts for tender, swollen, and tender + swollen joints (Section 8.1)
CLASI	X	APPENDIX 12; photography as needed.
Review concomitant medications	X	Restricted medications are detailed in APPENDIX 7. Medication restrictions at screening are in Section 6.
Safety Assessments		
Physical examination	X	General, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdominal, extremities, neurologic, psychiatric, skin, musculoskeletal
Physical measurements	X	Height and weight
Vital signs	X	Body temperature, respiratory rate, and blood pressure and heart rate; blood pressure and heart rate should be measured seated after at least 5 minutes of rest.
Electrocardiogram	X	Single 12-lead reading, recorded after the subject has been supine for at least 5 minutes
Chest X-ray	X	Can be performed within 6 months of the screening visit with documentation on file
Monitor for SAEs	X	From the signing of informed consent
Breast and cervical cancer screening	X	Investigators are encouraged to ensure screening is up to date according to local guidelines (women only). Because most patients with SLE are young women, screening for cervical and breast cancer prior to randomization is encouraged as per local guidelines due to the small inherent risk of increased malignancy with immunosuppressant agents, but this screening is at the investigator's discretion.
Laboratory Tests		
Hematology, chemistry, urinalysis, and coagulation	X	Includes blood and urine samples; collect after at least 10 hours of fasting.

Table 1: Screening Procedural Outline (Protocol IM011021)

Procedure	Screening Visit From Day -28	Notes
Serology	X	Includes hepatitis C antibody, hepatitis B surface antigen, hepatitis B core antibody, HIV 1 and 2, (Section 5.2)
Tuberculosis screening	X	In accordance with standard testing (details are provided in Section 8.5.2)
Pregnancy test (urine)	X	Women of childbearing potential only
Follicle-stimulating hormone	X	Postmenopausal women only, to confirm status (APPENDIX 4)
Thyroid stimulating hormone	X	Free thyroxine will be assessed only if thyroid-stimulating hormone is abnormal.
Spot urine for protein:creatinine ratio	X	
Serum complement (C3, C4)	X	
Autoantibodies	X	ANA, anti-Ro (SSA), anti-La (SSB), anti-RNP, anti-dsDNA, anti-Sm, antiphospholipid antibodies: anti-cardiolipin, lupus anticoagulant, beta-2 glycoprotein 1
Coomb's test (direct)	X	
Blood sample for gene expression analysis	X	Required for study entry but not used for prospective subject stratification
Blood for inflammation markers	X	Serum and plasma
[redacted]		
Photography	X	Subjects who consented to photography will be photographed at randomization for baseline photographs, including all views per the Photography Manual. Subjects with rash and/or alopecia at screening who consented to photography will be photographed beginning at screening. See Photography Manual for details.

ANA = antinuclear antibodies; anti-Sm = anti-Smith; BILAG = British Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; dsDNA = double-stranded deoxyribonucleic acid; HIV = human immunodeficiency virus; IRT = interactive response technology; RNP = ribonucleoprotein; SAE = serious adverse event; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics

Table 2: Treatment Period Procedural Outline Up to Week 24 (Protocol IM011021)

Procedure	Week 0 D1	Week 2 D15 (±3 d)	Week 4 D29 (±3 d)	Week 8 D57 (±3 d)	Week 12 D85 (±3 d)	Week 16 D113 (±3 d)	Week 20 D141 (±3 d)	Week 24 D169 (±3 d)	Notes
Eligibility/randomization criteria	X								Confirm eligibility criteria and assess randomization criteria (Section 5.3). All procedures to be completed before dosing unless otherwise specified
[redacted]									
Safety Assessments									
Complete PE	X								General, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdominal, extremities, neurologic, psychiatric, skin, musculoskeletal
Targeted PE		X	X	X	X	X	X	X	General, eyes, throat, cardiovascular, lungs, abdominal, extremities, skin, musculoskeletal, and others as clinically indicated
Body weight	X		X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	See note in Table 1
Electrocardiogram	X		X	X	X				See note in Table 1
Concomitant medication use	X	X	X	X	X	X	X	X	
Monitor for AEs and SAEs	X→							→X	SAEs from the signing of informed consent; AEs from time of first dose of the IP
Laboratory Tests									Predose (note in Table 1; Section 8.5.3)
Hematology, chemistry, urinalysis, coagulation	X	X	X	X	X	X	X	X	
Fasting lipid panel	X				X				Predose, after at least a 10-hour fast
Fasting plasma glucose	X				X				After at least a 10-hour fast

Table 2: Treatment Period Procedural Outline Up to Week 24 (Protocol IM011021)

Procedure	Week 0 D1	Week 2 D15 (±3 d)	Week 4 D29 (±3 d)	Week 8 D57 (±3 d)	Week 12 D85 (±3 d)	Week 16 D113 (±3 d)	Week 20 D141 (±3 d)	Week 24 D169 (±3 d)	Notes
Pregnancy test (WOCBP only)	X	X	X	X	X	X	X	X	APPENDIX 4
Spot urine for protein creatinine ratio	X		X	X	X	X	X	X	
Coomb's Test (direct)	X		X	X	X	X	X	X	
hsCRP	X				X			X	
TBNK	X				X			X	
Serum Ig	X		X		X			X	IgM, IgA, IgG, IgE
PK Assessments	X	X	X	X	X			X	Note: Fasting is required for Day 1 and Day 85. See Section 8.6
Biomarker Assessments									
Serum Complement	X	X	X	X	X	X	X	X	C3, C4
Anti-dsDNA autoantibodies	X		X	X	X	X	X	X	
[redacted]									
Blood RNA for IRG and steroid signature, and genome-wide expression	X	X	X	X	X[a]	X	X	X	PD assessment of IRG, steroid signature, and genome-wide expression analysis; predose; (Section 8.9). [redacted] ollection is to be anytime within the window, regardless of dosing time on the day of collection.
[redacted]									

Table 2: Treatment Period Procedural Outline Up to Week 24 (Protocol IM011021)

Procedure	Week 0 D1	Week 2 D15 (±3 d)	Week 4 D29 (±3 d)	Week 8 D57 (±3 d)	Week 12 D85 (±3 d)	Week 16 D113 (±3 d)	Week 20 D141 (±3 d)	Week 24 D169 (±3 d)	Notes
[redacted]									
Efficacy Assessments									NSAIDs must be withheld for ≥ 12 hours before visits.
BILAG-2004 Index	X		X	X	X	X	X	X	
SLEDAI-2K	X		X	X	X	X	X	X	
[redacted]									
Physician's Global Assessment	X		X	X	X	X	X	X	Assessment of disease activity using a 3-point scale (0 to 3)
40-joint count	X		X	X	X	X	X	X	See note in Table 1.
CLASI	X		X	X	X	X	X	X	APPENDIX 12

Table 2: Treatment Period Procedural Outline Up to Week 24 (Protocol IM011021)

Procedure	Week 0 D1	Week 2 D15 (±3 d)	Week 4 D29 (±3 d)	Week 8 D57 (±3 d)	Week 12 D85 (±3 d)	Week 16 D113 (±3 d)	Week 20 D141 (±3 d)	Week 24 D169 (±3 d)	Notes
Photography	X		X	X	X	X	X	X	Subjects who consented to photography will be photographed at randomization for baseline photographs, including all views per the Photography Manual. Subjects with rash and/or alopecia at screening who consented to photography will be photographed beginning at screening. See Photography Manual for details.
Assess suitability for CS taper	(X)	(X)	(X)	X	X	X	X		Taper is not required to start until Week 8. The CS dose must remain stable from Week 20 to 32.
[redacted]									
Patient's Global Assessment	X		X	X	X	X	X	X	Assessment of disease activity using a visual analog scale (APPENDIX 17)
Pain assessment	X		X	X	X	X	X	X	Using a numerical rating scale (APPENDIX 17)
Clinical Drug Supplies									
Randomization	X								Using IRT
Dispense Study Treatment	X →							X	Study treatment dispensed on Day 169 for the continued TP (Table 3)

Table 2: Treatment Period Procedural Outline Up to Week 24 (Protocol IM011021)

Procedure	Week 0 D1	Week 2 D15 (±3 d)	Week 4 D29 (±3 d)	Week 8 D57 (±3 d)	Week 12 D85 (±3 d)	Week 16 D113 (±3 d)	Week 20 D141 (±3 d)	Week 24 D169 (±3 d)	Notes
Study Treatment Administration	X→							→X	
Study Treatment Compliance		X	X	X	X	X	X	X	

AE = adverse event; ANA = antinuclear antibodies; anti-Sm = anti-Smith; BILAG = British Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CS = corticosteroid; dsDNA = double-stranded deoxyribonucleic acid; [redacted] hsCRP = high-sensitivity C-reactive protein; Ig = immunoglobulin; IP = investigational product; IRG = interferon-regulated genes; IRT=interactive response technology; [redacted] NSAID = nonsteroidal anti-inflammatory drug; PD = pharmacodynamic(s); PE = physical examination; PK = pharmacokinetic(s); [redacted] RNA = ribonucleic acid; RNP = ribonucleoprotein; SAE = serious adverse event; [redacted] SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; TBNK = T cells, B cells, and natural killer cells; TP = treatment period; WOCBP = women of childbearing potential

[a]Intensive PD sampling on Day 85 is further described in Table 7.

Table 3: Treatment Period Procedural Outline After Week 24 (Protocol IM011021)

Procedure	Week 28 D197 (±3 d)	Week 32 D225 (±3 d)	Week 36 D253 (±3 d)	Week 40 D281 (±3 d)	Week 44 D309 (±3 d)	Week 48 D337/EOT (±3 d)	FP (28 days after EOT)[a]	Notes
Safety Assessments								
Complete PE		X				X		General, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdominal, extremities, neurologic, psychiatric, skin, musculoskeletal
Targeted PE	X		X	X	X		X	General, eyes, throat, cardiovascular, lungs, abdominal, extremities, skin, musculoskeletal, and others as clinically indicated
Body weight	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	See note in Table 1.
Electrocardiogram		X				X		See note in Table 1.
Concomitant medication use	X	X	X	X	X	X	X	
Monitor for AEs and SAEs	X →	→	→	→	→	→	X	
Laboratory Tests								See note in Table 1.
Hematology, chemistry, urinalysis, coagulation	X	X	X	X	X	X	X	
Fasting lipid panel		X				X		
Fasting plasma glucose		X				X		
Pregnancy test (WOCBP only)	X	X	X	X	X	X	X	See note in Table 1.
Spot urine for protein creatinine ratio	X	X	X	X	X	X	X	
Coomb's Test (direct)	X	X	X	X	X	X	X	
hsCRP		X		X		X		

Table 3: Treatment Period Procedural Outline After Week 24 (Protocol IM011021)

Procedure	Week 28 D197 (±3 d)	Week 32 D225 (±3 d)	Week 36 D253 (±3 d)	Week 40 D281 (±3 d)	Week 44 D309 (±3 d)	Week 48 D337/EOT (±3 d)	FP (28 days after EOT)[a]	Notes
TBNK		X				X		
Serum Ig		X				X	X	IgM, IgA, IgG, IgE
PK Assessments		X				X		See Section 8.6
Biomarker Assessments								
Serum Complement	X	X	X	X	X	X	X	C3, C4
Anti-dsDNA autoantibodies	X	X	X	X	X	X	X	
[redacted]								
Blood RNA for IRG, steroid signature, and genome-wide expression	X	X	X	X	X	X	X	Assessment of IRG, steroid signature, and genome-wide expression; predose (Section 8.9)
[redacted]								

Table 3: Treatment Period Procedural Outline After Week 24 (Protocol IM011021)

Procedure	Week 28 D197 (±3 d)	Week 32 D225 (±3 d)	Week 36 D253 (±3 d)	Week 40 D281 (±3 d)	Week 44 D309 (±3 d)	Week 48 D337/EOT (±3 d)	FP (28 days after EOT)[a]	Notes
Efficacy Assessments								NSAIDs must be withheld for ≥ 12 hours before visits.
BILAG-2004 Index	X	X	X	X	X	X	X	
SLEDAI-2K	X	X	X	X	X	X	X	
[redacted]								
Physician's Global Assessment	X	X	X	X	X	X	X	Assessment of disease activity using a 3-point scale (0 to 3)
40-joint count	X	X	X	X	X	X	X	See note in Table 1.
CLASI	X	X	X	X	X	X	X	APPENDIX 12
Photography	X	X	X	X	X	X	X	Subjects who consented to photography will be photographed at randomization for baseline photographs, including all views per the Photography Manual. Subjects with rash and/or alopecia at screening who consented to photography will be photographed beginning at screening. See Photography Manual for details.
Assess suitability for CS taper		X	X	X		X		CS dose must remain stable Weeks 20–32 and 40–48.
[redacted]								

Table 3: Treatment Period Procedural Outline After Week 24 (Protocol IM011021)

Procedure	Week 28 D197 (±3 d)	Week 32 D225 (±3 d)	Week 36 D253 (±3 d)	Week 40 D281 (±3 d)	Week 44 D309 (±3 d)	Week 48 D337/EOT (±3 d)	FP (28 days after EOT)[a]	Notes
Patient's Global Assessment	X	X	X	X	X	X	X	Assessment of disease activity using a visual analog scale (APPENDIX 17)
Pain assessment	X	X	X	X	X	X	X	Using a numerical rating scale (APPENDIX 17)
Clinical Drug Supplies								
Dispense Study Treatment	X	X	X	X	X			
Study Treatment Administration	X	X	X	X	X	X		
Study Treatment Compliance	X	X	X	X	X	X		

ACR = American College of Rheumatology; AE = adverse event; ANA = antinuclear antibodies; anti-Sm = anti-Smith; BILAG = British Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CS = corticosteroid; dsDNA = double-stranded deoxyribonucleic acid; EOT = End of Treatment; FP = follow-up period; hsCRP = high-sensitivity C-reactive protein; Ig = immunoglobulin; IRG = interferon-regulated gene; [redacted] NSAID = nonsteroidal anti-inflammatory drug; PD = pharmacodynamic(s); PE = physical examination; PK = pharmacokinetic(s); [redacted] RNA = ribonucleic acid; RNP = ribonucleoprotein; SAE = serious adverse event; [redacted] SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; TBNK = T cells, B cells, and natural killer cells; WOCBP = women of childbearing potential

[a] Only for subjects not continuing in the long-term extension study IM011074

2 INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic progressive immune-mediated disease characterized by pleiotropic organ/tissue involvement and clinical manifestations that are varied and widespread. The most commonly affected body systems are mucocutaneous, musculoskeletal, and renal. Progression of the disease is marked by flares requiring therapy modification, and uncontrolled SLE leads to end organ damage and death. SLE prevalence in the United States is estimated at 20 to 150 cases per 100,000, and incidence is estimated at 1 to 25 per 100,000. Women are more frequently affected than men (9:1), as are people of African American and African Caribbean descent, and peak incidence occurs around the third or fourth decade of life. Autoantibodies that define the autoimmune nature of SLE have been identified. However, these autoantibodies are not specific to SLE. This and the variable clinical manifestations of SLE contribute to the complexity of diagnosis and treatment.

Current therapies are unsatisfactory, and include immunosuppressive drugs and corticosteroids (CS), which can temporarily control SLE flares and disease progression. However, the utility of these therapies wanes over time, and their use is associated with substantial undesirable effects that may outweigh any short-term improvements. One goal in the management of SLE is to achieve disease and symptom control while minimizing CS exposure. Treatments include antimalarials, immunosuppressants, biologics including belimumab, and other agents (prescribed off-label). There remains an unmet need for novel, well-tolerated, orally administered therapies that can effectively modify the disease course and control symptoms.

2.1 Study Rationale

BMS-986165 is a potent, highly selective small molecule inhibitor of tyrosine kinase 2 (TYK2), which functions as a critical mediator in signaling pathways that regulate diverse, yet specific, immunomodulatory cellular responses, such as immunity, inflammation, and anti-inflammatory responses. BMS-986165 is the first, potent, oral TYK2 inhibitor with a novel, highly selective mechanism of action that has the potential to safely and effectively treat a broad spectrum of immune-mediated diseases. Tyrosine kinase 2 activates signal transducer and activator of transcription (STAT)-dependent transcription and functional responses downstream of critical immune mediators, such as interleukin (IL)-12, IL-23, and Type I and III interferons (IFNs). BMS-986165 inhibits TYK2 through a novel allosteric mechanism, binding to the unique Janus kinase (JAK) homology 2 (JH2) domain, rather than binding directly to the active site.[1, 2, 3] TYK2 mediates immune and inflammatory signaling pathways critical in the pathophysiology of various immune-mediated diseases including psoriasis, lupus, spondyloarthritis, inflammatory bowel disease (IBD), dermatomyositis, and Type I interferonopathies.[4,5] BMS-986165 potently inhibits IL-23-, IL-12-, and Type I/III IFN-driven responses and has demonstrated proof of mechanism in mouse models of psoriasis, colitis, and lupus; and in healthy human volunteers.[5,6]

The proposed Phase 2 study in subjects with SLE will provide evidence of biologic activity of BMS-986165 in a relevant disease population and will facilitate dose ranging for future studies in SLE and other immune-mediated conditions. SLE is an ideal condition to evaluate the efficacy of the TYK2 inhibitor BMS-986165 for multiple reasons, as follows: 1) The major pathways in the

TYK2 signaling cascade (Type I IFN and IL-12/23 and the downstream mediators IFNγ and IL-17) have been implicated in SLE disease pathogenesis,[7] 2) Biologic agents targeting the IL-12/23 pathway, or the IFNα (or the Type I IFN) receptor are under investigation and have been shown to be efficacious in the treatment of SLE based on some Phase 2 data that have been released. Thus, it is feasible that SLE patients treated with BMS-986165 may derive therapeutic benefit, 3) It is also conceivable that TYK2 inhibition may show improved benefits over existing anti-IFN monoclonal antibody therapies because of combined blocking effects on both the IL-12/23 and Type I IFN pathways,[8] 4) The ability to measure circulating target-specific (such as suppression of IFN-stimulated gene expression) and disease-specific pharmacodynamic (PD) measures in SLE both before and after treatment allows for establishing exposure-response relationships for PD endpoints.

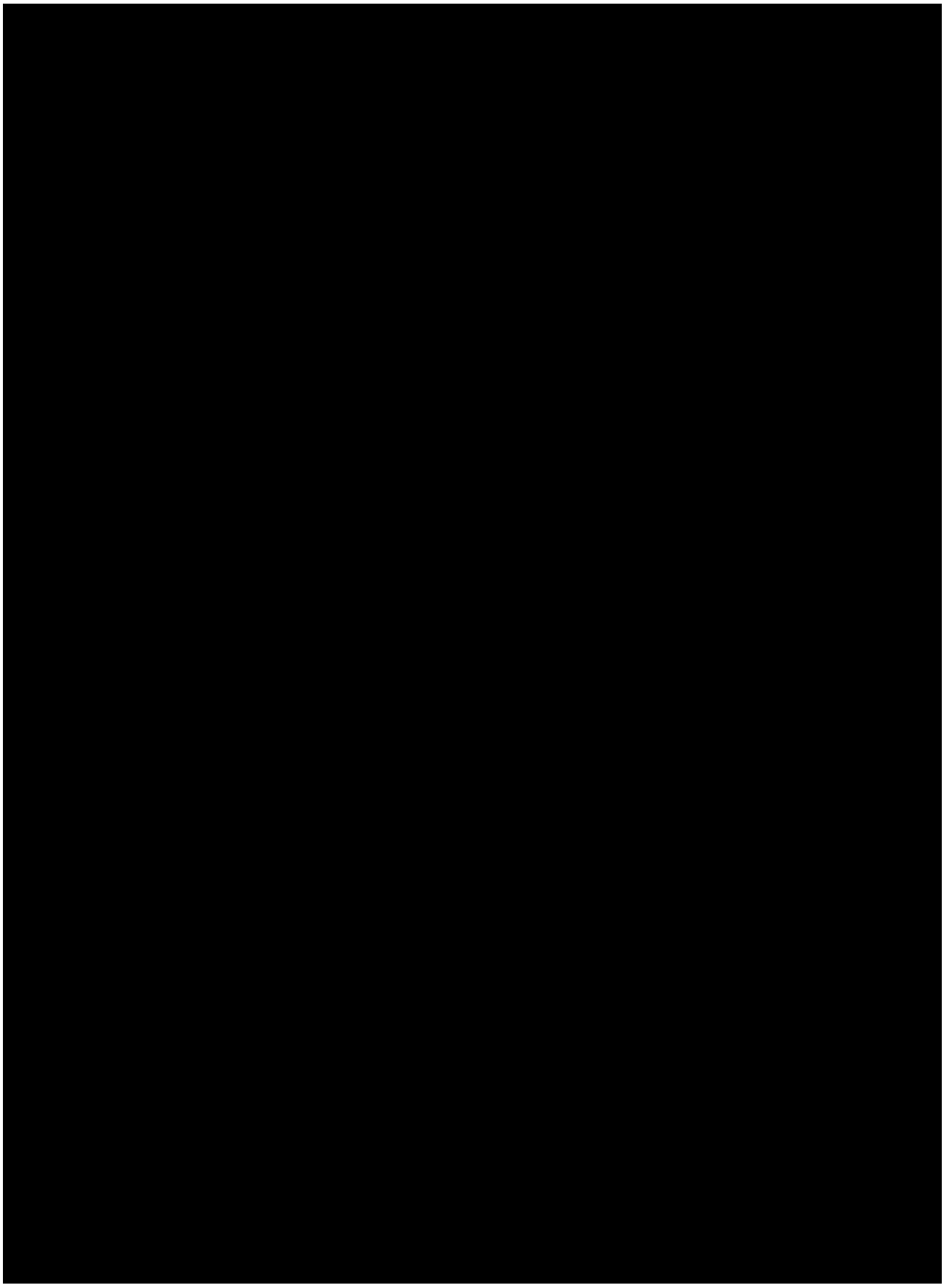
The present study is the first study of this TYK2 inhibitor conducted in subjects with SLE and is intended to determine whether the pharmacological effects of TYK2 inhibition are associated with objective clinical improvement in SLE disease activity and related biomarkers. The study is also designed to assess the safety and tolerability of short- and long-term BMS-986165 treatment in subjects with SLE, and to determine the dose level that provides the optimal balance of efficacy and safety.

Research statement: The proportion of subjects with SLE who meet the response criteria for the SLE Responder Index (SRI[4]) at Week 32 will be greater with at least 1 of the BMS-986165 regimens than with placebo.

2.2 Background

Tyrosine kinase 2 (a member of the JAK family) catalyzes the phosphorylation of STAT proteins downstream of the receptors for the p40-containing cytokines IL-12 and IL-23 as well as the Type I IFN receptor, resulting in the activation of STAT-dependent transcription and functional responses specific for those receptors. BMS-986165 is a first-in-class orally administered small molecule inhibitor of TYK2 that has been shown to be superior to blockade of the Type I IFN receptor in an IFN-dependent mouse model of SLE.

[redacted]



2.2.2 Early Clinical Experience

The clinical data available to date supporting the safety, pharmacokinetics (PK), and PD of BMS-986165 are from 5 Phase 1 studies of BMS-986165 in healthy volunteers (IM011002, IM011015, IM011016, IM011031, and IM011039) and a Phase 2 study in adult subjects with moderate-to-severe psoriasis (IM011011).

Study IM011002 (Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, PK, and PD of BMS-986165 in Healthy Subjects) used 1, 3, 10, 20, and 40 mg doses for the single-dose part and 2, 4, 6, or 12 mg BID or 12 mg once daily (QD) for 14 days for the multiple ascending dose part. All reported adverse events (AEs) were mild or moderate in severity, and approximately half of subjects overall had at least 1 AE that was considered potentially related to study treatment. The most frequently reported AEs with single dosing were headache and dyspepsia. The most frequently reported AEs with multiple dosing were headache, skin rash and acne, and upper respiratory tract infection. Dose-limiting AEs in the form of skin rashes and acneiform lesions were observed. These observations were largely reported for subjects in the 24 mg/day (12 mg BID) group and were reported for most subjects dosed at this level. These events had not been observed earlier in the monkey studies. These AEs were mild or moderate in nature and resolved with topical treatments (corticosteroid applications, benzoyl peroxide cream, clindamycin solution, chlorhexidine ointment). All events requiring treatment responded appropriately and rarely resulted in discontinuation of study drug. Overall, BMS-986165 was found to have an acceptable safety profile, and the acneiform lesions that were seen at the highest doses were manageable with topical treatments, were reversible, and were not serious or severe.

Study IM011016 (Pharmacokinetics and Metabolism of [^{14}C] BMS-986165 in Healthy Male Participants) used a single dose of 24 mg [^{14}C] BMS-986165 containing approximately 100 µCi of total radioactivity. Five of the 6 enrolled subjects reported mild diarrhea (loose stools), and 1 of

the 5 also had mild palpitations and moderate emesis. No deaths or discontinuations due to AEs were reported.

Study IM011015 (The Effect of BMS-986165 on the Pharmacokinetics of Rosuvastatin) used a 12 mg QD dose administered with 10 mg rosuvastatin in 20 healthy subjects and showed that BMS-986165 had no impact on exposure to rosuvastatin. Fifteen of 17 subjects who completed the study experienced an AE of acne, and all these AEs were mild or moderate in severity. Subjects with no or mild acne at baseline developed either mild or moderate acne, whereas subjects with moderate acne at baseline generally experienced less worsening of their acne as the study progressed. In 2 subjects, an AE of moderate acne led to discontinuation of study medication. All events of acne that required treatment responded to topical treatment.

In Study IM011039 (The Effect of BMS-986165 on the Pharmacokinetics of a Combined Oral Contraceptive), healthy subjects received 24 mg/day (12 mg BID). Acneiform lesions (eg, skin rashes or pustules) were seen in all subjects at this dose and the number of events was similar to that in Study IM011002. According to the investigator, subjects typically reported light itching of the skin within 12 hours after the first dose of BMS-986165, followed by the acneiform dermatitis eruptions in face/hairline-scalp, neck, and back on Day 2 or Day 3 of dosing. Less frequently, the breast, arms, or abdomen were involved. The AE intensity was based on the severity of the lesion and the extent of body surface area affected. Bacterial cultures taken from a few of these lesions were negative. All lesions responded well to topical treatment and did not lead to discontinuation of study medication. No new skin eruptions appeared after 3 days after last dose, and all events resolved. All reactions were again mild or moderate and were managed with topical treatments.

Study IM011011 is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the clinical efficacy, safety, and PD of BMS-986165 after 12 weeks of treatment with 4 weeks' follow-up in 267 subjects with moderate-to-severe psoriasis. The study met its primary and secondary efficacy endpoints of clinically relevant improvement in Psoriasis Activity and Severity Index and static Physician Global Assessment scores for 4 of the 5 doses investigated (only the 3 mg every other day dose did not meet the primary endpoint). The most common AEs reported overall were nasopharyngitis, upper respiratory tract infection, diarrhea, and nausea. The majority of the AEs reported in the study were mild or moderate in intensity. The acneiform dermatitis AEs appeared to be dose related, and most were reported for subjects in the 2 highest dose groups. Most of the lesions were completely resolved (a few were almost completely resolved) with topical treatments and did not result in discontinuation of the study treatment. Several of the verbatim reported terms for the acneiform dermatitis group were similar to those previously reported for healthy subjects in Studies IM011002, IM011015, IM011031, and IM011039: "acne on face neck and back," "pustular eruptions in face, neck and back" (sometimes including arms), or "folliculitis;" the similarity of these terms and a clear dose dependency suggest a common etiopathogenesis.

In summary, BMS-986165 has demonstrated promising clinical efficacy in the treatment of patients with moderate-to-severe psoriasis. Acneiform skin reactions have been observed across the early clinical trials of BMS-986165. The reactions appear to be dose related, with the highest incidence at the 12 mg BID dose. All of the reactions have been mild or moderate, nonserious,

reversible, and have rarely led to discontinuation of study treatment. There have been no signs or symptoms of circulatory or respiratory impairment and no suggestions of a systemic hypersensitivity reaction. The acneiform skin reactions requiring treatment have been well managed with topical treatment such as benzoyl peroxide cream, clindamycin solution, chlorhexidine ointment, salicylic acid ointment, or retinoid gel. The likely mechanism(s) behind the acneiform dermatitis is not currently known.

In assessments of PK in Study IM011002, BMS-986165 achieved maximum plasma concentrations (Cmax) approximately 1 to 2 hours after dosing and had a median terminal half-life ranging from 8 to 15 hours across the dose range tested. With single dosing, BMS-986165 exposures appeared to increase in a greater than dose-proportional manner at doses less than 3 mg, and in an approximately dose-dependent manner from 3 to 40 mg. After multiple-day dosing, BMS-986165 accumulation in the 1.4× to 1.9× range was observed at steady state. BMS-986165 is metabolized by multiple metabolic pathways, but it does not inhibit cytochrome P450 (CYP450) enzymes at expected plasma concentrations. When taken with a high-fat meal, BMS-986165 exhibited a lower Cmax and a delayed time to maximum plasma concentration (Tmax) relative to dosing in the fasted state. Although the area under the concentration-time curve extrapolated to infinity (AUC[0-INF]) was decreased by 15% in the fed state relative to the fasted state, this difference was not thought to be clinically meaningful.

A detailed description of the chemistry, pharmacology, efficacy, and safety of BMS-986165 is provided in the Investigator Brochure (IB).

2.3 Benefit/Risk Assessment

At this early stage in the development of BMS-986165 for the treatment of patients with SLE, assessments of benefit and risk rely on nonclinical data and clinical experience in subjects without SLE. The proposed dosing regimens reflect implementation of appropriate safety margins and are within the range of doses tested in the first-in-human (FIH) study and within exposure margins based on comparisons of systemic exposure and body surface area.

The effects of TYK2 inhibition by BMS-986165 have been documented in pharmacology studies, and the potential for benefit in SLE has been suggested by nonclinical studies using a mouse model of SLE; further support is found in mouse models of other immune-mediated diseases. Findings in toxicology studies were consistent with expectations based on the pharmacology of BMS-986165. Thus, the FIH study was conducted with standard safeguards within a range of dose regimens. Even at the highest exposures in healthy subjects, AEs were mild to moderate, reversible, and consistent with expectations based on nonclinical experience.

The risk for PK drug-drug interactions (DDIs) with BMS-986165 was assessed based on regulatory guidelines. At the maximum concentrations expected in this study (in portal vein or systemic circulation, as appropriate), the potential for DDIs involving most transporters is low. BMS-986165 is a breast cancer resistance protein (BCRP) inhibitor with an in vitro 50% inhibitory concentration of 0.31 μM. The impact of BMS-986165 on the exposures of potential concomitant medications that are sensitive BCRP substrates, such as rosuvastatin, is expected to be low. Data from a clinical DDI study that assessed the effect of BMS-986165 on rosuvastatin PK showed less

than 10% increase in exposures of rosuvastatin. Because of potential PK interactions with the transporter P-glycoprotein (P-gp) as substrate, concomitant use of strong inhibitors of P-gp is prohibited throughout the study. Treatment with BMS-986165 is not expected to diminish the effectiveness of contraceptives.

Nonclinical data and clinical experience in healthy subjects in combination with the design and doses selected for the current Phase 2 study indicate an overall favorable risk/benefit assessment for investigating BMS-986165 as an oral treatment of patients with SLE. Detailed information about the known and expected benefits and risks and reasonably anticipated AEs of BMS-986165 is provided in the IB.

3 OBJECTIVES AND ENDPOINTS

Table 4: Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy • To assess the effect of BMS-986165 on the SRI(4) response at Week 32 in subjects with SLE	• Proportion of subjects who meet response criteria for SRI(4) (Section 8.1) at Week 32
Secondary Efficacy • To assess the effect of BMS-986165 on measures of global and organ-specific SLE clinical response	• Proportion of subjects who meet response criteria for SRI(4) at Week 48 • Proportion of subjects who achieve a British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) response at Week 48 after treatment with BMS-986165 or placebo administered on stable background therapy (Section 9.3.1.1) • Proportion of subjects who achieve Lupus Low Disease Activity State (LLDAS) at Week 48 (Section 8.1) • Proportion of subjects with a Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score ≥ 10 at baseline who achieve a CLASI response, defined as a decrease of ≥ 50% from baseline CLASI activity score at Week 48 (Section 8.1) • Change from baseline in the 40-joint count for tender, swollen, and tender + swollen joints at Week 48

Table 4: Objectives and Endpoints

Objectives	Endpoints
Safety • To assess the safety and tolerability of BMS-986165	• Number and proportion of subjects experiencing serious adverse events (SAEs); AEs; and abnormalities in laboratory testing, vital signs, and electrocardiograms (ECGs) throughout the study
Pharmacokinetics • To assess PK of BMS-986165 and its active metabolite (BMT-153261) in subjects with SLE (Section 8.6)	• Plasma concentration of BMS-986165 and BMT-153261
Pharmacodynamics • To assess the effect of BMS-986165 on PD markers (Section 8.9.2)	• Change in mean and median interferon-regulated gene (IRG) expression levels compared to baseline over time and at Week 32 • Change in mean complement (C3, C4) and anti-double-stranded DNA (dsDNA) levels compared to baseline over time and at Week 32 • Assess the effect of BMS-986165 on measures of global SLE clinical response in subjects based on IRG status (ie, high versus low IRG signature) at Week 32
[redacted]	[redacted]

Table 4: Objectives and Endpoints

Objectives	Endpoints
[redacted]	[redacted]
[redacted]	[redacted]

Table 4: Objectives and Endpoints

Objectives	Endpoints
	[redacted]

[redacted]

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, double-blind, multicenter study to evaluate the efficacy and safety of BMS-986165 in subjects with SLE. The primary study endpoint is the proportion of subjects who meet SRI(4) response (see Section 8.1) at Week 32 after treatment with BMS-986165 or placebo administered on stable background therapy. This endpoint will be used to evaluate the research statement (Section 2.1).

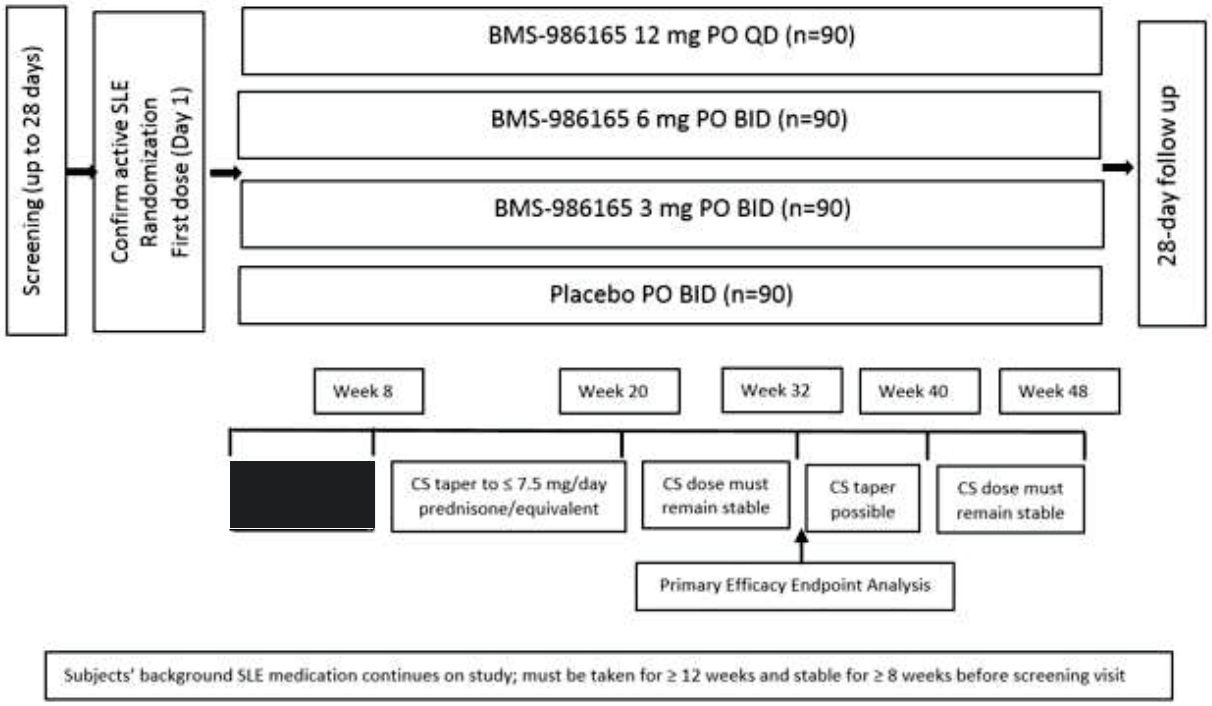
The duration of study participation is approximately 56 weeks (392 days), as follows:

- Screening period (SP): up to 4 weeks (28 days)
- Treatment period (TP): 48 weeks (336 days) of blinded treatment
- Follow-up period (FP): 28 days

Note: The FP is only for subjects who do not continue into the long-term extension (LTE) study (IM011074)

The study design schematic is presented in Figure 1.

Figure 1 Study Design Schematic



BID = twice daily; CS = corticosteroid; PO = per os (by mouth); QD = once daily; SLE = systemic lupus erythematosus

Other aspects of study design are as follows:

- Randomization will be performed after completion of the SP, on Day 1 of the TP.
- Randomization in a 1:1:1:1 ratio will be performed using interactive response technology (IRT) and will be stratified by screening CS dose (≥ 10 mg/day or < 10 mg/day), SLEDAI-2K score (≥ 10 or < 10), and region (United States of America [USA], Latin America, rest of world, and Japan [other stratification factors will not be applied in Japan]).
- The blind will be maintained during the treatment period (TP) by the use of matched capsules (placebo and 3 mg BMS-986165) provided in blister cards that are identical in appearance while providing the appropriate randomized dose.
- Clinical, laboratory, and photographic evidence of disease activity will be reviewed by blinded external reviewers.
- The primary efficacy analysis will be based on Week 32 efficacy assessments.
- CS tapering will be managed as described in Section 6.7.3.

[redacted]

- Subjects will be considered nonresponders for analysis purposes under circumstances as described in Section 9.3.1.2.

- An independent data monitoring committee (DMC) will assess safety and efficacy data.
- Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Subjects will be closely monitored for AEs throughout the study. Blood samples will be collected for PK and PD analyses as well.
- Samples for biomarker assessments will be collected from a subset of subjects (those at USA sites only) on Day 2 or 3 (24 to 72 hours after the first dose).

4.1.1 Data Monitoring Committee and Other External Committees

An external DMC will be used in this study to perform safety monitoring by treatment group.

Unblinded data summaries and listings will be provided to the DMC to facilitate their safety assessment at the regularly scheduled times and on an ad hoc basis if needed. The safety review includes all AEs and events of interest (infections and skin reactions), focusing on early signal detection. Further details on the frequency, content, and methods of data reports to the DMC will be outlined in the DMC charter along with the processes and procedures the committee will follow.

Central Review Services (CRS) will be used in this study. The scope of responsibility will include [redacted] review of SLE eligibility criteri [redacted].

4.2 Number of Subjects

Approximately 360 subjects will be randomized 1:1:1:1 to receive BMS-986165 12 mg QD, 6 mg BID, 3 mg BID, or placebo BID during the TP. Sample size considerations are described in Section 9.1.

4.3 End of Study Definition

The duration of study participation for individual subjects is expected to be approximately 56 weeks (392 days).

The start of the study is defined as first visit for first subject screened. The end of the study is defined as the last visit or scheduled procedure shown in the Schedules of Activities (Section 1.3) for the last subject. Study completion is defined as the final date on which data for the primary endpoint was expected to be collected, if this is not the same. The end of the study for analysis of biomarker samples is mentioned in Section 8.9.

4.4 Scientific Rationale for Study Design

The primary purpose of the study is to determine the optimal dose of BMS-986165 for treatment of subjects with SLE. A placebo control is included to allow the effects of treatment, both desired and adverse, to be appropriately attributed to treatments received. All subjects will be permitted to continue their existing therapies for SLE, and rescue treatments are permitted as needed (with a few protocol-specified limitations) to allow subjects to maintain standard disease control

regardless of the effects of their assigned study treatment. A plan for CS tapering is included to allow subjects to use the lowest dose that meets their needs throughout much of the study, but doses are held stable for 12 weeks before the Week 32 assessments (primary efficacy) and for 8 weeks before the Week 48 assessments to isolate effects of assigned study treatments. A DMC will monitor safety and efficacy findings throughout the study to allow timely management of any concerns that arise. Study visits allow for close monitoring of subjects. The eligibility and randomization criteria are designed to ensure that subjects have the expected level of SLE disease activity and to minimize the risk for serious infections that may be associated with immunosuppressive therapies. Randomization is stratified by the screening CS dose and screening SLEDAI-2K score, and region in order to balance subjects equally across treatment groups based on these characteristics, which may indicate the background severity of disease and/or background level of disease control and will also balance for potential regional differences in SLE background medication.

5 STUDY POPULATION

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.

All screening and randomization evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable. CRS and the PRA medical monitor will review all eligibility criteria for all subjects who are not initially screen-failed by the site. Study designated therapeutic experts outside of the Sponsor and CRO may review eligibility criteria as needed. No subject will be randomized without confirmation of eligibility by CRS and the PRA medical monitor. In addition, [redacted] will assign BILAG grades for all subjects based on information provided by the sites. Procedures conducted as part of the subject's routine clinical management and obtained before signing of informed consent may be utilized for screening purposes, provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedules of Activities (Section 1.3). However, all laboratory testing must be performed by the study-specific central laboratory.

The duration of the screening period (SP) is up to 4 weeks. If eligibility parameters cannot be obtained within this time period, the SP may be extended by up to 5 days if approved by the [redacted] medical monitor. Rules for retesting and rescreening are provided in Section 5.5.

To be eligible for the study, subjects must meet the criteria in Section 5.1. To be randomized into the study on Day 1, subjects must meet the criteria in Section 5.3.

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1) Signed Written Informed Consent

a) Willing to participate in the study and have the ability to give informed consent

b) Willing and able to complete all study-specific procedures and visits

2) SLE Disease Characteristics

a) Diagnosed ≥ 24 weeks before the screening visit

b) Meets the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE[9] APPENDIX 5

c) One of the following: elevated antinuclear antibodies (ANA) ≥ 1:80 or positive anti-dsDNA (positive includes indeterminate results) or positive anti-Smith (anti-Sm) as determined by the central laboratory

d) Total SLEDAI-2K score ≥ 6 points and clinical SLEDAI-2K score ≥ 4 points with joint involvement and/or rash (score must be confirmed by CRS)

i) Lupus headache, alopecia, organic brain syndrome, and mucosal ulcers cannot count toward the points required for screening at entry.

ii) Clinical SLEDAI-2K excludes laboratory abnormalities such as hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia.

e) At least 1 of the following BILAG-based protocol-specific manifestations of SLE [redacted]:

i) BILAG A or B grade in the Mucocutaneous body system. [redacted]

ii) Modified BILAG A or B score in the Musculoskeletal body system [redacted]

iii) If only 1 B and no A grade is present in the Mucocutaneous body system or in the Musculoskeletal body system due to arthritis, then at least 1 B grade must be present in one of the other body systems, for a total of 2 BILAG B body system grades.

3) Medications for SLE

a) Background therapy is required for ≥ 12 weeks before the screening visit and must be at a stable dose for ≥ 8 weeks before the screening visit and remain stable until randomization and throughout study participation. Details for specific medications are as follows:

- Immunosuppressants (combinations of these are NOT permitted):
  - azathioprine (maximum 200 mg/day)
  - 6-mercaptopurine (6-MP)
  - methotrexate (MTX; maximum 25 mg/week; dose and route of administration of MTX may not be changed for 8 weeks before the screening visit and throughout study participation)
  - leflunomide
  - mycophenolate mofetil/mycophenolic acid (MMF). **Note:** Subjects who are receiving MMF may participate in the study only if administered as a maintenance therapy and up to a maximum of 2 g/day (or equivalent); in subjects

of African ancestry, 3 g/day (or equivalent) is acceptable. Treatment may be interrupted due to neutropenia per the product label.

- Antimalarials: chloroquine, hydroxychloroquine, or quinacrine; monotherapy is permitted if the minimum doses are met: chloroquine 125 mg QD, hydroxychloroquine 200 mg QD, or quinacrine 100 mg QD
- Required discontinuation periods for other immunomodulatory drugs (eg, cyclosporine, tacrolimus, etc) or biologic drugs (eg, rituximab, belimumab, tocilizumab, etc) are provided in APPENDIX 7. If a drug is not specifically listed, consult the [redacted] medical monitor for guidance. Usual discontinuation periods are 4 weeks or 5 half-lives, whichever is longer.

b) CS (prednisone or equivalent) background therapy is permitted but not required. For subjects taking CS, the dose must be stable for ≥ 2 weeks before the screening visit, cannot exceed 30 mg/day at screening, and must remain stable until randomization. CS monotherapy is not permitted. Prednisone equivalents are provided in APPENDIX 6.

[redacted]

c) Requirements for subjects who are receiving chronic therapy with nonsteroidal anti-inflammatory drugs (NSAIDs; including marketed cyclooxygenase-2 inhibitors) are as follows; exceptions or changes may be possible with approval by the [redacted] medical monitor:

- Doses must be stable for 14 days before the screening visit and must remain stable until randomization and throughout the study.
- No more than 1 oral NSAID may be used (at a stable dose) during the study and may be combined with topical NSAIDs.
- Use of 1 or more topical NSAIDs is permitted but must follow a stable regimen throughout the study.
- Aspirin is allowed (in addition to a single NSAID and topical NSAIDs) at stable doses no higher than 325 mg/day throughout the study.

4) **Age and Reproductive Status**

a) Men and women aged 18 to 75 years inclusive at the time of screening

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta-human chorionic gonadotropin [β-HCG]) within 24 hours prior to the start of study treatment.

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 treatment(s) (BMS-986165 or placebo) plus 5 half-lives of study treatment (3 days) plus 30 days (duration of ovulatory cycle) for a total of 33 days post treatment completion.

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

f) Investigators shall counsel WOCBP and men who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective or less than highly effective methods of contraception (APPENDIX 4).

g) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (APPENDIX 4) for the duration of treatment with study treatment (BMS-986165 or placebo).

h) Azoospermic males are exempt from contraceptive requirements.

i) N/A per Revised Global Protocol im011021-revprot04

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1) Target Disease Exceptions

a) Drug-induced SLE

b) Subjects with other autoimmune diseases (eg, multiple sclerosis, psoriasis, IBD, etc) are excluded. Subjects with type I autoimmune diabetes mellitus, thyroid autoimmune disease, Celiac disease, or secondary Sjögren's syndrome are not excluded.

c) Subjects with SLE overlap syndromes such as scleroderma and mixed connective tissue disease are excluded. Subjects with an overlap syndrome of SLE with rheumatoid arthritis are not excluded as long as they meet the criteria for the classification of SLE as outlined in the inclusion criteria (Section 5.1, Inclusion Criterion 2).

d) Subjects with antiphospholipid antibody syndrome on stable anticoagulant therapy at an effective dose (eg, if on warfarin, an international normalized ratio [INR] target 2 to 3 or as appropriate for the clinical situation) are allowed if this is not the sole or the predominant feature of their SLE. Subjects with a serious thrombotic event (eg, pulmonary embolism, stroke, deep vein thrombosis) or unexplained pregnancy loss within 1 year before the screening visit are excluded. Subjects with a history of catastrophic antiphospholipid syndrome or saddle embolism are excluded. Subjects with a history of 3 or more unexplained consecutive pregnancy losses would also be excluded.

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

f) Subjects with active, severe lupus nephritis (World Health Organization Class III, IV) that requires or may require treatment with cytotoxic agents or high-dose CS are excluded. Subjects with prior, controlled renal disease with serum creatinine $\leq 2\times$ upper limit of

normal (ULN) and either residual proteinuria up to 3 g/day or a urine protein/creatinine ratio (UPCR) of 3 mg/mg or 339 mg/mmol are allowed. Control of renal disease must be documented with at least 2 measurements of proteinuria or UPCR over the past 6 months.

2) Other Medical Conditions and History

a) Women who are pregnant or breastfeeding

b) Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, immunologic, psychiatric) or local active infection/infectious illness that, as determined by medical judgment, will substantially increase the risk to the subject if he or she participates in the study

c) Any major surgery within the last 30 days before the first dose of study treatment, or any surgery planned during the course of the study

d) Cancer or history of cancer or lymphoproliferative disease within the previous 5 years (other than adequately treated cutaneous basal cell or squamous cell carcinoma with no evidence of recurrence)

e) Class III or IV congestive heart failure as defined by the New York Heart Association (NYHA) or any recent onset of heart failure resulting in NYHA Class III/IV symptoms

f) Acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) and/or any history of significant cerebrovascular disease within 24 weeks before screening

g) Current or recent (within 3 months before randomization) gastrointestinal disease, including gastrointestinal surgery, that could impact the absorption of study treatment

h) Subject with non-SLE concomitant illness, as determined by medical judgment, who is likely to require additional systemic glucocorticosteroid therapy during the study (eg, asthma).

i) Significant blood loss (> 500 mL) or blood transfusion within 4 weeks before randomization

j) Inability to take medication orally

k) Inability to undergo venipuncture and/or tolerate venous access

l) Recent (within 6 months before randomization) drug or alcohol abuse as defined by the Diagnostic Criteria for Drug and Alcohol Abuse in the Diagnostic and Statistical Manual of Mental Disorders IV (APPENDIX 8)

m) Any other sound medical, psychiatric, and/or social reason as determined by medical judgment

3) Prior and Concomitant Therapy

a) Inability to comply with restrictions and prohibited treatments (Section 6.7.1); inability to comply with discontinuation requirements listed in APPENDIX 7

b) Taking more than 1 immunosuppressant

c) Prior exposure to TYK2 inhibitors

d) Prior exposure to anifrolumab, rontalizumab, ustekinumab, or interferon alpha kinoid (INFα Kinoid)

e) Current administration of opioids unless all the following criteria are met:

i) The prescribed dose has been stable for ≥ 4 weeks before screening

ii) The drug is not used on an as-needed basis

iii) The dose is expected to remain stable through the study period

iv) In the opinion of the investigator, the subject's use of opioids will not impact the protocol-specific efficacy and safety assessments

v) The dose does not exceed the equivalent of 30 mg of morphine per day (see APPENDIX 18 for morphine milligram equivalents of commonly used opioids)

f) Other investigational agents must be discontinued at least 12 weeks or 5 half-lives before screening, whichever is longer

4) Findings Related to Possible Infection

a) Evidence of active or latent tuberculosis (TB), as follows:

- Positive chest X-ray for evidence of active pulmonary TB within 6 months before screening
- Subjects with negative chest X-ray within 6 months before screening may be eligible provided any of the following apply:
  - negative IFN gamma release assay (IGRA)
  - positive IGRA and no symptoms of active TB, and have previously (within 5 years) received adequate documented treatment for latent TB, per investigator's medical judgment
  - positive IGRA and no symptoms of active TB, but have NOT previously (within 5 years) received adequate documented treatment, per investigator's medical judgment; subject must initiate prophylactic treatment per local guidelines and may rescreen after 1 month of treatment (if subject is enrolled, the prophylactic TB treatment must continue throughout the study)
  - indeterminate IGRA at screening with no signs or symptoms of active TB must be retested for confirmation. If the second test is again indeterminate, the subject will be excluded from the study. If the retest is positive, the subject should be treated as having latent TB infection. If the retest is negative, subject may be eligible, provided no other exclusion criteria for TB is met

b) Hepatitis C, hepatitis B, or human immunodeficiency virus (HIV) infection as demonstrated by a positive blood screen for hepatitis C antibody (anti-HCV), hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), or HIV-1 and -2 antibody. Subjects who have been vaccinated for hepatitis B (hepatitis B surface antibody [anti-HBs]-positive) are not excluded. Note that anti-HBs is not requested (APPENDIX 9).
Note: Subjects who are newly found to be HIV-positive should be directed to appropriate follow-up care.

c) Currently on any therapy for chronic infection (eg, pneumocystis, cytomegalovirus, herpes simplex, herpes zoster, invasive bacterial or fungal infections, or atypical mycobacteria)

d) History of congenital or acquired immunodeficiency

e) Known active infection, or any major episode of infection requiring hospitalization or treatment with parenteral (intramuscular or IV) antimicrobial agents (eg, antibiotics,

antiviral, antifungal, or antiparasitic agents) within 30 days of randomization, or completion of oral antimicrobial agents within 2 weeks of randomization

f) Previous history of herpes zoster, herpes simplex, or influenza infection within 12 weeks before randomization or a history of disseminated/complicated herpes zoster infection (multidermatomal involvement, ophthalmic zoster, central nervous system involvement, or post-herpetic neuralgia)

g) Administration of a live vaccine within 90 days or an inactivated vaccine within 30 days before randomization. Heat-killed or otherwise inactivated or protein vaccines (eg, influenza and pneumococcal vaccines) may be received at any time on study. Furthermore, live vaccines should not be used during treatment or within the 2 months following last dose, and any other inactivated vaccines (eg, tetanus, etc) should be used according to local guidelines during the TP.

5) Physical and Laboratory Test Findings

a) Clinically significant abnormalities on chest X-ray or ECG

b) Clinically significant abnormalities in laboratory tests including the following:

i) Serum alanine aminotransferase (ALT) > 2× ULN, unless explicitly related to SLE

ii) Serum aspartate aminotransferase (AST) > 2× ULN, unless explicitly related to SLE

iii) Serum total bilirubin > 1.5× ULN, unless explicitly related to SLE or documented Gilbert's syndrome

iv) Hemoglobin < 8 g/dL (80 g/L) or, if due to hemolytic anemia related to SLE, < 7 g/dL (70 g/L)

v) Proteinuria > 3.0 g/day (3000 mg/day) or equivalent level of proteinuria as assessed by UCPR (3 mg/mg or 339 mg/mmol)

vi) Estimated glomerular filtration rate < 30 mL/min

vii) Absolute white blood cell count < $1.2\times 10^3/\mu L$ ($1.2\times 10^9/L$)

viii) Platelet count < $50 \times 10^3/\mu L$ ($50 \times 10^9/L$)

ix) Abnormal free thyroxine (T4) (if the thyroid-stimulating hormone [TSH] is abnormal at screening, a free T4 will be assessed; subjects with abnormal TSH and abnormal free T4 will be excluded but after discussion with the [redacted] medical monitor may be able to rescreen a minimum of 6 weeks after adjustment of thyroid hormone replacement therapy).

c) Any other significant laboratory or procedure abnormalities, as determined by medical judgment, that might pose unacceptable risk to the subject during the study

6) Allergies and Adverse Drug Reaction

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

7) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and BMS approval is required).

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

c) Inability to comply with the study protocol

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.

5.3 Randomization

Eligible subjects must meet the following criteria on Day 1 before randomization and the first dose:

1. The subject continues to satisfy all eligibility criteria.
2. If the subject had rash at screening, the subject must have a total score of the erythema and scale components (excluding mucous membrane ulcerations and nonscarring alopecia) of the CLASI disease activity score of ≥ 3.
3. If the subject had moderate or severe arthritis at screening, the inclusion criteria for BILAG-based protocol-specific manifestations of SLE in Section 5.1, Inclusion Criterion 2)e) must continue to be met.

5.4 Lifestyle Restrictions

No restrictions are required. However, general skin care measures are recommended that are standard for patients with SLE, as follows: use of broad spectrum sunscreen (minimum sun protection factor 15 and with inorganic ingredients [zinc oxide, titanium dioxide]), avoiding sun exposure, wearing sun-protective clothing, avoidance of alcohol-based emollients, avoidance of over-the-counter anti-acne medications and alcohol-based skin care products, and avoidance of perfumed soaps and detergents, and similar measures.

Study treatment may be taken without regard to meals. However, subjects are required to fast for a minimum of 10 hours before visits on which fasting lipid and fasting glucose samples will be drawn (at 2 of these visits [Days 1 and 85], fasting PK samples will also be drawn).

5.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized in the study for any reason. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

5.5.1 Retesting During Screening Period; Rescreening

For laboratory parameters and/or assessments that initially do not meet eligibility requirements, a single retest within the 28-day SP is permitted in an effort to find all possible well-qualified subjects. Consultation with the [redacted] medical monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

The study permits the rescreening (after the end of the initial 4-week SP) of a subject who discontinues the study as a pretreatment failure (ie, the subject fails screening or randomization

and has not been treated). The subject must be reconsented and will be assigned a new identification number, and a full screening visit must be performed again. Other than exceptional circumstances which must be reviewed and approved by the medical monitor, a subject can only be rescreened 1 time. Depending on the timing of rescreening, repetition of some assessments may not be required. Duration of existing treatments and required discontinuation periods shall be considered relative to the given screening visit and/or randomization.

The most current result prior to randomization is the value by which study inclusion will be assessed, as it represents the subject's most current clinical state.

6 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device intended to be administered to a study subject according to the study randomization or treatment allocation

Study treatment includes both investigational [medicinal] product (IP/IMP) and noninvestigational [medicinal] product (non-IP/non-IMP) and can consist of BMS-986165 and placebo. Information about the pharmacology and previous experience with BMS-986165 is provided in Section 2.2.

An IP, also known as IMP in some regions, is defined as 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.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as noninvestigational products. Table 5 shows the study treatments for Protocol IM011021.

Table 5: Study Treatments for IM011021

Product Description/Class and Dosage Form	Potency	IP/Non-IP	Blinded/Open-Label	Packaging/ Appearance	Storage Conditions (per label)	Comments
BMS-986165 oral capsule	(as the free base)	IP	Blinded	Blister card containing 64 active (3 mg BMS 986165) and/or placebo capsules to equal required daily dosing	Store at 2°C to 8°C (36°F to 46°F). Store in original container.	
Placebo matching BMS-986165 oral capsule	Not applicable	IP	Blinded	Blister card containing 64 active (3 mg BMS-986165) and/or placebo capsules to equal required daily dosing	Store at 2°C to 8°C (36°F to 46°F). Store in original container.	
Any of the following: AZA, 6-MP, MTX, leflunomide, MMF; chloroquine, hydroxychloroquine, quinacrine	As prescribed	Non-IP	Open-label	As provided	As indicated	Subjects are to be receiving at least 1 of these at a stable dose for ≥ 8 weeks before the screening visit, throughout the screening period, and throughout the study. See Inclusion 3a (Section 5.1) for further information. Non-IP will not be provided by the Sponsor.
CS: prednisone (or equivalent)	≤ 30 mg/day (or equivalent)	Non-IP	Open-label	As provided	As indicated	CS is not required; if on CS, the dose must be stable for ≥ 2 weeks before the screening visit, and throughout the SP. A dose up to 30 mg/day prednisone or equivalent is permitted at the screening visit (see Inclusion 3b in Section 5.1) and should be tapered according to the protocol guidelines during the treatment period. Information about CS tapering [redacted] is provided in Sections 6.7.3 [redacted]

6-MP = 6-mercaptopurine; AZA = azathioprine, CS = corticosteroid; IMP = investigational medicinal product; IP = investigational product; MMF = mycophenolate mofetil/mycophenolic acid; MTX = methotrexate; SP = screening period

6.1 Treatments Administered

Dose information for each treatment group for the TP is provided in Table 6. Study treatment will be supplied in blister card kits. The capsules will be arranged into sets to be taken in the morning and in the evening, approximately 12 hours apart. If a subject forgets a dose, but remembers within 4 hours of the expected dose, the dose should be taken. If the missed dose is discovered more than 4 hours after it should have been taken, that dose should be not be taken and the next scheduled dose should be taken at the usual time.

Table 6: Selection and Timing of Dose

Study Treatment	Unit dose strength(s)/ Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
12 mg QD BMS-986165	3 mg	4 active capsules QD in the morning; and 4 placebo capsules QD in the evening	Oral
6 mg BID BMS-986165	3 mg	2 active and 2 placebo capsules; BID	Oral
3 mg BID BMS-986165	3 mg	1 active and 3 placebo capsules; BID	Oral
Placebo	Not applicable	4 placebo capsules; BID	Oral

BID = twice daily; QD = once daily

6.2 Method of Treatment Assignment

At the time of the screening visit, immediately after informed consent is obtained and before any study-related procedures are performed, the investigative site will access the enrollment option using IRT for assignment of a subject number (including subjects not subsequently randomized or treated). This number will be unique across all sites. Enrolled subjects, including those not dosed, will be assigned sequential subject numbers. The subject number may not be used for any other subject. If a potential subject is rescreened, they will be given a new identification number.

CRS and the PRA medical monitor will confirm subject eligibility based on criteria in Section 5. Eligible subjects will be centrally randomized using IRT to receive oral treatment with BMS-986165 12 mg QD, 6 mg BID, 3 mg BID, or placebo BID according to a computer-generated block randomization scheme and in accordance with stratification criteria. Randomization numbers will be assigned prior to dosing.

Before the study is initiated, each user (at investigative sites) will receive log-in information and directions on how to access the IRT. Study treatment will be dispensed at study visits as shown in Section 1.3 (Schedules of Activities).

6.3 Blinding

6.3.1 Maintaining the Blind

Blinded treatment assignments will be managed using IRT. All capsules (BMS-986165 3 mg and placebo) are identical in appearance, and they will be supplied in blister packs with each daily dose made up of the appropriate combination of active and/or placebo capsules to provide the correct

treatment (as shown in Table 6). Investigative site staff, Sponsor and designee personnel, the [redacted] (Section 4.1.1), and subjects and their families will remain blinded to treatment assignments.

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 IP 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 IP, 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 [redacted] medical monitor, but the investigator 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 information on how to unblind in an emergency, consult the IRT manual.

In case of an emergency, the investigator has unrestricted access to randomization information via IRT and is capable of breaking the blind through the IRT system without prior approval from the Sponsor. After the unblinding, the investigator shall notify the [redacted] medical monitor and/or study director. The method of unblinding for emergency purposes is described in the IRT manual. Subject information and the reason for the blind being broken must be recorded on the appropriate study status page of the electronic case report form (eCRF). After unblinding via IRT, the investigator shall notify the [redacted] medical monitor.In cases of accidental unblinding, contact the [redacted] medical monitor and ensure every attempt is made to preserve the blind. Any request to unblind a subject for nonemergency purposes must be discussed with the [redacted] medical monitor prior to unblinding.

Designated staff of Bristol-Myers Squibb Research & Development (or designee) may be unblinded (obtain the randomization codes) prior to database lock to facilitate the bioanalytical analysis of pharmacokinetic samples. A bioanalytical scientist in the Bioanalytical Sciences department of Bristol-Myers Squibb Research & Development (or a designee in the external central bioanalytical laboratory) will be unblinded to (may obtain) the randomized treatment assignments in order to minimize bioanalytical analysis of samples.

6.4 Dosage Modification

There is no provision for dose modification of study treatment. Titration of CS and its use as rescue therapy are discussed in Section 6.7.3 [redacted]. Modification of other background SLE therapies or dose regimens is not permitted during study participation. Subjects should continue to take their assigned treatment even if they experience flares and/or are unable to taper their CS dose, unless any of the criteria in Section 7.1 are met.

If a subject interrupts treatment due to an AE, study treatment can be restarted in consultation with the [redacted] medical monitor.

6.5 Preparation/Handling/Storage/Accountability

The IP should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that IP is only dispensed to study subjects. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

The study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) required by BMS. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed and BMS should be contacted immediately.

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).

Further guidance and information for final disposition of unused study treatment are provided in APPENDIX 1.

6.5.1 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

6.6 Treatment Compliance

Study treatment compliance will be periodically monitored using standard drug accountability procedures (comparing the number of capsules returned to number dispensed, considering the expected regimen and any reported missed doses). Drug accountability will be reviewed by the investigative site staff at each visit to confirm treatment compliance. Site staff will discuss any discrepancies with the subject and remind the subject of the importance of compliance with the assigned regimen. A real-time monitoring platform may be used.

6.7 Concomitant Therapy

All medications ever taken for SLE including topical, discontinued, and investigational therapies must be recorded; medications with dose changes may record the overall dates with last dose used. All medications taken from within 4 weeks before screening until 30 days after the last dose of study treatment (inclusive) must be recorded on the eCRF. Other than existing treatment for SLE (with restrictions as described in the eligibility criteria [Section 5.1]), concomitant medications (prescription, over-the-counter [OTC], or herbal) should only be administered during the study if they are prescribed for treatment of specific clinical events.

6.7.1 Prohibited and/or Restricted Treatments

Restrictions and prohibitions on prior and concomitant medications are as follows:

1. Prior exposure to BMS-986165 or other TYK2 inhibitors is prohibited.
2. Rescue therapy other than prednisone or equivalent is prohibited.

3. Use of intramuscular, intra-articular, intrabursal, and IV CS is prohibited (Inclusion Criterion 3)b); Section 5.1). Initiation during the study of short-term treatment with inhaled CS for a nonlupus medical condition must be discussed with the [redacted] medical monitor. Topical CS use may not be initiated during treatment. Modified-release CS formulations are prohibited.
4. Topical NSAID use may not be initiated during treatment. No more than 1 oral NSAID may be used during the study. Aspirin is allowed (in addition to a single NSAID and topical NSAIDs) at stable doses no higher than 325 mg/day throughout the study. NSAIDs may not be used on an as-needed basis. Although regimens are required to be stable throughout the study, NSAID dosing may be decreased or discontinued if due to NSAID toxicity. Adjustments in NSAID regimens must be discussed with the [redacted] medical monitor.
5. Use of opioid analgesics is prohibited unless criteria outlined in Exclusion Criterion 3)e); Section 5.2, are met.
6. Use of cyclophosphamide (including ophthalmic) or any IV, intrabursal, intratendinous sheath, intramuscular, subcutaneous, intra-articular, or biologic agent is prohibited. Required discontinuation periods for immunomodulatory and biologic drugs before the signing of informed consent are provided in APPENDIX 7. For similar agents not listed, the discontinuation period is 4 weeks or 5 half-lives, whichever is longer, and must be discussed with the [redacted] medical monitor.
7. Live vaccines are prohibited during the TP or within the 2 months after the last dose. Heat-killed or otherwise inactivated or protein vaccines such as influenza and pneumococcal vaccines may be received at any time on study. Any other inactivated vaccines (eg, tetanus, etc) should be used according to local guidelines during the TP (Exclusion Criterion 4)g); Section 5.2).
8. Exposure to any investigational drug or placebo within 12 weeks or 5 half-lives (whichever is longer) before screening is prohibited (Exclusion Criterion 3)f); Section 5.2)
9. Use of any other drugs, including OTC medications and herbal preparations, within 1 week before the first dose of study treatment is prohibited, except medications cleared by the [redacted] medical monitor

6.7.2 Existing Therapies for Systemic Lupus Erythematosus

All subjects will continue their existing SLE treatment(s) during the study (if the treatment complies with the eligibility criteria; Section 5). The dose and regimen of background SLE treatments must not change during study participation. Details of permissible therapies are as follows:

- At least 1 background agent as specified in Inclusion Criterion 3)a) (Section 5.1); use of more than 1 immunosuppressant in combination is NOT permitted.
- CS therapy with prednisone or equivalent as specified in Inclusion Criterion 3)b) (Section 5.1); see restrictions in Section 6.7.1. CS tapering [redacted] are described in Sections 6.7.3 [redacted]
- Chronic NSAID therapy as specified in Inclusion Criterion 3)c) (Section 5.1)
- Stable preexisting topical CS therapy as specified in Inclusion 3)b) (Section 5.1)

6.7.3 Corticosteroid Tapering

For subjects receiving prednisone or equivalent, the dose of CS must be stable for 2 weeks before the screening visit (signing of informed consent) and throughout the SP until randomization. Up to 30 mg/day prednisone or equivalent is permitted during the SP (and for the preceding 2 weeks). Rules for CS tapering are as follows:

- Tapering of CS may begin at any time after the first dose of IP on Day 1.
- For subjects receiving > 7.5 mg/day prednisone or equivalent, tapering must start by Week 8.
- For all subjects, the CS dose must be ≤ 7.5 mg prednisone or equivalent by Week 20 (if this is not possible, the subject will remain on treatment, but will be a nonresponder for analysis purposes).
- Investigators must assess the subject's suitability for CS taper at each visit (taper is not required to start until Week 8), and the last day for CS taper is the Week 20 visit.
- The CS dose must be tapered (beginning by Week 8 and continuing until the Week 20 visit) unless any of the following are observed:
    - New or worse BILAG or SLEDAI-2K activity for any of the following parameters: central nervous system, vasculitis, myositis, cardiorespiratory, gastrointestinal, ophthalmologic, renal, or thrombocytopenia
    - New or worsening hemolytic anemia
    - CLASI activity score ≥ 10
    - Active joint count of 8 or more joints with both tenderness AND swelling
- Tapering is required if disease activity has not worsened. The investigator must justify any decision not to taper. Criteria met or not met for taper will be documented on the eCRF at each appropriate visit.
- The CS dose must remain stable from Week 20 until Week 32. Tapering may be resumed at the Week 32 visit according to the same parameters as earlier in the study. The last day for CS taper is the Week 40 visit, and the CS dose must remain stable from Week 40 until Week 48.

[redacted]

[redacted]

6.8 Treatment After the End of the Study

At the end of the study, the investigator should ensure that subjects continue to receive appropriate standard of care to treat the condition under study. In addition, for subjects who continue to demonstrate clinical benefit and who elect to enroll, BMS will continue to provide study treatment via Protocol IM011074, which is an LTE of the current study. Participation in IM011074 is not required for participation in this study, however.

BMS reserves the right to terminate access to BMS-supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of BMS-986165 is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the subject can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulations

7 DISCONTINUATION CRITERIA

7.1 Discontinuation from Study Treatment

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

- A subject requests to stop study treatment. Subjects who request to discontinue study treatment 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
- Any clinical AE, laboratory abnormality, or intercurrent illness that, 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 or a specific dose group (for subjects receiving that dose) by BMS
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Unblinding of a subject's treatment assignment for any reason (emergency or nonemergency)
- Pregnancy
- Abnormal liver tests suggestive of drug-induced liver injury (DILI) as defined in Section 8.3.8 or if the investigator believes that it is in the best interest of the subject.

Refer to the Schedules of Activities (Section 1.3) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

In the case of pregnancy, the investigator must immediately notify the [redacted] medical monitor or designee of this event. In the event a normal healthy female subject becomes pregnant during a clinical trial, the study treatment must be discontinued immediately. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the [redacted] medical monitor within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the [redacted] medical monitor must occur.

All subjects who discontinue study treatment should comply with protocol-specified follow-up procedures as outlined in Section 1.3. 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). Subject replacement is not permitted.

If study treatment 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 eCRF page.

Subjects who discontinue study treatment will remain in the study for continued follow-up.

7.2 Discontinuation from the Study

Subjects who request to discontinue study treatment (possible circumstances are listed in Section 7.1) 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 and entered on the appropriate eCRF 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.
- If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3 Post Study Treatment Follow-Up

In this study, the proportion of subjects who achieve BICLA response at Week 32 after treatment with BMS-986165 or placebo 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 treatment must continue to be followed for collection of [redacted] survival follow-up data as required and in line with Section 3 until death or the conclusion of the study.

7.4 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.
- Lost to follow-up is defined by the inability to reach the subject after a minimum of 3 documented phone calls, faxes, or emails as well as lack of response by subject to 1 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 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, 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.

7.5 Replacement of Subjects

Subject replacement is not permitted.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and timing are summarized in the Schedules of Activities (Section 1.3). Waivers or exemptions from protocol-required evaluations are not allowed.

8.1 Efficacy Assessments

Protocol-specific training and assessments must be successfully completed so that investigators or designees can be qualified to perform assessments using the BILAG, CLASI, SLEDAI-2K, and 40-joint count tools. Every effort must be made to ensure that the same evaluator(s) complete the assessment for each subject. If the evaluator(s) is unable to complete the evaluation, then a qualified individual with overlapping experience may perform the evaluation. Documentation of who performed the evaluation is to be recorded in source documents. Assessments are to be performed at approximately the same time of day throughout the duration of the study.

Baseline assessments must be performed per protocol (standard of care assessments may not be used for baseline). Procedures not specified in the protocol that are part of standard care may be performed if they do not interfere with study procedures; any data arising from such procedures are not to be reported in the eCRF.

Note: NSAIDs must be withheld for at least 12 hours before visits at which BILAG, SLEDAI-2K, joint counts, CLASI, or Physician's Global Assessment of Disease Activity are assessed (ie, all scheduled visits). Study treatment must not be taken on visit days until after efficacy assessments.

The following procedures or tools will be used to assess subjects' SLE disease activity during the study (see schedule in Section 1.3):

- BILAG-2004[10, 11, 12, 13] (APPENDIX 10): The BILAG-2004 rating is based on organ systems (constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal, and hematological). Each is scored by a number of assessments, from which an overall grade is derived for each organ system. The overall grades are represented as 5 different levels from A to E (A = very active, B = moderate disease activity, C = mild stable disease, D = no disease activity but suggests the system had previously been affected, and E = no current or previous disease activity).
- SLEDAI-2K [14,15] (APPENDIX 11): The SLEDAI-2K is a global index based on weighted scores for each of 24 clinical findings rated as present or absent at the time of the visit or in the last 30 days. The SLEDAI-2K assigns relative weights to each parameter.
- CLASI [16,17] (APPENDIX 12): The CLASI assesses cutaneous disease activity by body surface area; points are given for presence of erythema, scale, hypertrophy, mucous membrane lesions, recent hair loss, and physician-observed alopecia. For the damage assessments, points are given for dyspigmentation, scarring, and scarring alopecia.
- 40-joint count: A 40-joint count is used. This includes bilateral wrists, elbows, ankles, knees, interphalangeal joints of the thumb, individual proximal interphalangeal joints of the hand, second through fifth metacarpophalangeal joints of the hand, and individual metatarsophalangeal joints of the feet (which make up the 36-joint count).[18, 19, 20] To allow the 28-joint count evaluation, bilateral first metacarpophalangeal joints and shoulders are also included, bringing the total joint count to 40. Each joint is evaluated based upon the presence or absence of tenderness, the presence or absence of swelling, and the presence or absence of both tenderness and swelling.
- Physician's Global Assessment of Disease Activity assessed using a 3-point visual analog scale (VAS).

[redacted]

The following composite measures will be determined based on some of the assessments described above:

- BICLA response[21] as defined in Section 9.3.1.1

- SLE Responder Index[22] (SRI): The SRI is a composite endpoint that defines a responder as a patient whose disease course fulfills all of the following:
  - A predefined reduction (number of points) from baseline in SLEDAI-2K score[14,15] (APPENDIX 11). The SRI can be calculated based on the number of points of reduction in the SLEDAI-2K (SRI[4], SRI[5], SRI[6], and SRI[7]).
  - No new BILAG A (severe disease activity) or not more than 1 new BILAG B (moderate disease activity) organ domain grade
  - No worsening from baseline in the Physician's Global Assessment of Disease Activity scale by more than 0.3 points
- Lupus Low Disease Activity State (LLDAS):[23,24] LLDAS is defined as follows: (1) SLEDAI-2K ≤ 4, with no activity in major organ systems (renal, central nervous system, cardiopulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity (measured as maintaining a D or E score in the BILAG Gastrointestinal Body System); (2) no new lupus disease activity compared with the previous assessment measured as no new or worsening individual BILAG parameters; (3) Physician's Global Assessment of Disease Activity ≤ 1; (4) a current prednisolone (or equivalent) dose ≤ 7.5 mg daily; and (5) well-tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents.

[redacted]

8.2 Laboratory Assessments Related to SLE Disease Activity

The following laboratory tests will be performed according to the schedule in Section 1.3 to gather more information about SLE disease activity: Coomb's test (direct); serum complement (C3, C4); quantitative immunoglobulins (IgG, IgA, IgM); anti-dsDNA; anti-Sm; ANA; anti-Ro (SSA); anti- La (SSB); anti-ribonucleoprotein (RNP); T cells, B cells, and natural killer cells (TBNK); and high-sensitivity C-reactive protein. Laboratory assessments that are used in some efficacy assessments (eg, BILAG and SLEDAI-2K), such as complete blood count and renal function tests, are also used for safety assessments and are described in Section 8.5.3. Samples for confirmation of hemolysis (using haptoglobin and reticulocyte count) for the BILAG will be drawn at assessment visits and stored at the central laboratory; the samples will only be analyzed if there is clinical suspicion on the part of the investigator.

8.3 Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or serious adverse event (SAE) and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the subject to discontinue before completing the study.

The definitions of an AE or SAE can be found in APPENDIX 3.

Contacts for SAE reporting are specified in Appendix 3.

The event (term), along with its start and stop dates, maximum intensity (mild, moderate, or severe), seriousness (yes/no), relationship to the IP (yes/no), action taken with regard to the IP, and outcome will be recorded in the eCRF.

8.3.1 Adverse Events of Interest

Adverse events of interest (AEIs) are AEs for a particular product or class of products that a Sponsor may wish to monitor carefully. Adverse events of interest may be serious or nonserious. Such events may require further investigation to better characterize and understand them. In the BMS-986165 clinical development program, certain skin-related AEs (eg, acne) and infection AEs have been identified as potential AEIs; however, there has been no definitive assessment on the causal relationship between these events and treatment with BMS-986165. Therefore, additional information about certain AEs may be collected on the eCRF in order to better characterize and understand them.

8.3.2 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment and continue until the last follow-up visit, at the timepoints specified in the Schedules of Activities (Section 1.3).

The Reference Safety Information in Sections 5.6.1 and 5.6.2 of the IB should be used to determine the expectedness of SAEs for expedited reporting. Following the subject's written consent to

participate in the study, all SAEs, whether related or not related to study treatment, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs that occur from the time the informed consent form (ICF) is signed through 30 days after the final dose of the study treatment must be reported to [redacted] Drug Safety. After that time, only SAEs deemed by the investigator to be related to the study treatment or a study procedure should be reported.

- The investigator must report any SAE that occurs after these time periods and that is believed to be related to study treatment or protocol-specified procedure. Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in APPENDIX 3.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of this being available.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in APPENDIX 3.

8.3.3 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. To prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs. Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative). Nonserious SLE-related AEs will be collected only on the disease assessment instruments and not reported as AEs.

All AEs and SAEs that arise in the study will be reported and investigated. However, because of the characteristics of the disease under study and of BMS-986165 itself, subjects will be more closely monitored for signs of infection and for treatment-emergent rash (Section 8.3.9).

8.3.4 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see APPENDIX 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment 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. Completion of supplemental CRFs may be requested for certain AEs, such as

skin reactions and infections, and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 7.4).

Further information on follow-up procedures is given in APPENDIX 3.

8.3.5 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the institutional review board (IRB)/independent ethics committee (IEC), if appropriate according to local requirements.

The Sponsor or designee will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and Food and Drug Administration Code of Federal Regulations 21 CFR Parts 312 and 320. Suspected, unexpected serious adverse reactions are a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

8.3.6 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a 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 [redacted] Drug Safety of this event and complete and forward a Pregnancy Surveillance Form to [redacted] Drug Safety within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in APPENDIX 3.

In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

Any pregnancy that occurs in a female partner of a male study subject should be reported to [redacted] Drug Safety. For the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

Protocol-required procedures for study discontinuation and follow-up must be performed on subjects who become pregnant.

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.

8.3.7 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or electronic SAE Report Form, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- 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 treatment discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy

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

8.3.8 Potential Drug-Induced Liver Injury

Wherever 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 APPENDIX 3 for reporting details).

Potential DILI is defined by presence of all of the following characteristics:

- ALT or AST elevation > 3× ULN
- total bilirubin > 2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
- no other immediately apparent possible causes of AST or AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, preexisting chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

8.3.9 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, ECG, 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.

8.4 Overdose

For this study, any dose of blinded study treatment that is more than 2-days' worth of study treatment within a 24-hour time period will be considered an overdose.

In the event of an overdose the investigator should:

1. Contact the [redacted] medical monitor immediately.
2. Closely monitor the subject for AEs/SAEs and laboratory abnormalities until BMS-986165 can no longer be detected systemically (at least 3 days).
3. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the [redacted] medical monitor based on the clinical evaluation of the subject.

8.5 Safety

Planned timepoints for all safety assessments are listed in the Schedules of Activities (Section 1.3). All urgent safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue treatment.

Safety evaluations that will be performed in addition to AE monitoring are physical examinations (PE; Section 8.5.1), TB screening (Section 8.5.2), vital signs, ECGs, concomitant medication use, and laboratory tests (Section 8.5.3).

8.5.1 Physical Examinations

Schedules for PEs are provided in Section 1.3. Complete and/or targeted PEs 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 targeted examination may not be as comprehensive as the initial full examination, key aspects 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. A targeted 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 other body systems as clinically indicated. Every effort should be made to ensure the same evaluator will complete the examination for each subject at all visits throughout the study. Documentation of who performed the examination is to be recorded in source notes.

8.5.2 Tuberculosis Screening and Chest X-ray

A chest X-ray and PE are part of the process to assess a subject's eligibility as defined in Section 5.2, Exclusion Criterion 4a, and outlined in Section 1.3. A chest X-ray at the screening visit is required if not already performed within 6 months of obtaining written informed consent.

In addition to a complete PE and medical history to evaluate exposure to TB, all subjects will have a screening test, an IGRA (eg, T-spot® or QuantiFERON®), preferably performed centrally. If unable to obtain central laboratory results (eg, repeated test due to indeterminate result), an IGRA test could be obtained locally, after consultation with the [redacted] medical monitor.

8.5.3 Clinical Safety Laboratory Assessments

A central laboratory will perform assessments of safety laboratory assessments (except pregnancy tests) and provide reference ranges and laboratory reports. Investigators must document their review of each laboratory safety report. Any laboratory test result that the investigator considers clinically relevant is to be recorded on the appropriate AE page of the eCRF (Section 8.3.7). Results of clinical laboratory tests performed during screening must be available prior to randomization. Additional safety assessments may be performed at local laboratories at the investigator's discretion. The laboratory parameters to be assessed are as follows:

- Hematology: hemoglobin, hematocrit, total leukocyte count (including differential), platelet count, RBC count, and manual differential (separate smear)

- Chemistry: AST, ALT, gamma glutamyltransferase, total bilirubin, direct bilirubin, alkaline phosphatase, lactate dehydrogenase, creatinine, blood urea nitrogen, uric acid, fasting glucose, total protein, albumin, sodium, potassium, chloride, calcium, phosphorus, magnesium, creatine kinase, creatinine clearance (screening only)
- Coagulation: prothrombin time, INR, and either partial thromboplastin time or activated partial thromboplastin time
- TSH (screening only)
- Tests performed after a ≥ 10-hour fast: lipid panel (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides), plasma glucose
- Urinalysis: protein, glucose, blood, leukocyte esterase, specific gravity, pH; microscopic examination of the sediment if blood, protein, or leukocyte esterase are positive on dipstick; spot urine will be assessed for urine protein and urine creatinine
- Serology to be performed at screening: hepatitis C antibody, HBsAg, anti-HBc, HIV-1 and HIV-2 antibody, TB (screening only)

In addition, urine pregnancy testing will be performed for WOCBP, and follicle-stimulating hormone will be measured to confirm postmenopausal status (as applicable; at screening only).

8.5.4 Imaging Safety Assessment

Not applicable.

8.6 Pharmacokinetics

The PK of BMS-986165 and metabolites (if applicable) will be derived from plasma concentration versus time.

Plasma samples will be analyzed for BMS-986165 and BMT-153261 by a validated assay. Pharmacokinetic samples collected from subjects who receive placebo will not be analyzed. Individual subject PK parameter values will be derived by noncompartmental methods by a validated PK analysis program. Actual times will be used for the analyses. In addition, plasma samples will be archived for potential metabolites analysis, if the need arises and to the extent possible. Detailed instructions for PK blood collection, labeling, processing, storage, and shipping will be provided to the site in the Study Reference Manual.

The PK parameters to be assessed include:

Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
Ctrough	Trough observed plasma concentration

The area under the concentration-time curve in one dosing interval (AUC[TAU]) will be calculated if possible.

8.6.1 Sampling Schedule

The sampling schedule for the assessment of PK and PD is provided in Table 7. Predose samples must be drawn before the dose on all visit days, and after a fast (for Day 1 and Day 85 visits) of at least 10 hours. As described in Section 1.3, the timing of other procedures at a given visit can be adjusted so that PK sampling can be performed at the scheduled time. If possible, PK samples should be collected for subjects who discontinue treatment due to an AE. Further details of blood collection and processing are provided to sites in the Study Reference Manual.

Table 7: PK and PD Sampling Schedule for BMS-986165 and BMT-153261

Study Day of Sample Collection	Event	Time (Relative To Dose) Hour: Min	Blood Sample for PK	Blood Sample for IRG	Notes
1	predose	00:00	X	X	Samples will be collected after the subject has been fasted for ≥ 10 hours (fasting is required for other assessments at this visit as well). However, subjects may eat after the Hour 2 sample has been collected.
1		00:30	X		
1		02:00	X		
15	predose	00:00	X	X	
29	predose	00:00	X	X	
57	predose	00:00	X	X	
85	predose	00:00	X	X	Samples will be collected after the subject has been fasted for ≥ 10 hours (fasting is required for other assessments at this visit as well). However, subjects may eat after the Hour 4 sample has been collected.
85		00:30	X		
85		02:00	X	X	
85		04:00	X	X	
85		06:00	X	X	
113	predose	00:00		X	
141	predose	00:00		X	
169	predose	00:00	X	X	
197	predose	00:00		X	
225	predose	00:00	X	X	An aliquot of collected blood sample will be included for potential measurement of concomitant medication.
253	predose	00:00		X	
281	predose	00:00		X	
309	predose	00:00		X	
337	predose	00:00	X	X	

IRG = interferon-regulated gene; PD = pharmacodynamic(s); PK = pharmacokinetic(s)
Note: Predose samples must be drawn before the morning dose of study treatment on the visit day, ie, study treatment will be taken at the site on those days.

8.6.2 Sampling Windows

It is expected that every effort is made to collect PK samples at the times indicated. However, for flexibility in PK sampling, the following windows serve as a guideline for PK sample collection:

- Predose samples must be drawn before the morning dose on the visit day.
- The following windows apply to other samples:
  - ±0.25 hour for the 0.5-hour sample
  - ±0.5 hour for the 2-hour sample
  - ± 1 hour for the 4- and 6-hour samples

All samples should be collected using the timepoint labels provided even if they are outside of the suggested window. Actual sample times must be recorded. If samples cannot be taken within the specified time window every effort should be made to take a sample as soon as possible. Deviations from the sampling windows must be noted in the source documents.

Pharmacodynamic sampling will follow the same time window as PK and will be collected at matched PK timepoints.

8.7 Supplemental Assessments: Photography

Sites will be equipped with clinical photography supplies. [redacted] will use the photographs to assist in establishing appropriate use of the CLASI instrument for selected visits. Additionally, the photographs will be used to help distinguish a rash related to SLE from a rash arising as a side effect of the study treatment. Any photographs may be used as supplemental documentation for publications and to increase understanding of cutaneous manifestations of interest. Appropriate measures will be applied to ensure subject privacy. Details of study photography are provided in the Central Photography Manual. Only subjects who consented to photography will be photographed.

8.8 Pharmacogenomics

Not applicable

8.9 Biomarkers

Details of blood and urine collection and processing will be provided to the site in the Study Reference Manual. Biomarker samples will generally be collected from all study subjects (with the exception of Day 2 or 3 samples). Blood and urine will be collected at the timepoints shown in Section 1.3 and in Table 7.

The biomarkers to be assessed currently have no utility for clinical decision making, thus, the results for individual subjects will not be shared with either the investigator or the subject; however, the aggregated results may be shared. The aggregated results may be published to further the understanding of BMS-986165 or lupus; however, individually identifiable patient data will not. The end of the study for biomarker samples is defined as up to the maximum allowed in the individual ICF documents. Although the analysis of some biomarkers will be performed immediately, additional biomarker analysis may be delayed while the initial analysis of the study results are interpreted and integrated.

8.9.1 Predictors of Response

Blood will be collected at the screening visit to assess the level of activity of the Type I IFN pathway by measuring the expression of IRGs. In addition, steroid-regulated genes and other gene signatures may be assessed. These biomarkers will be used to test for potential differences in subjects' response to BMS-986165 and CS treatment.

8.9.2 Pharmacodynamics and Mechanism of Action

The PD effects of BMS-986165 will be assessed based on markers in blood and urine, which will be collected at the timepoints shown in Section 1.3 and in Table 7. Serum and plasma samples will be collected and analyzed for markers of tissue damage and regeneration, such as markers of inflammatory damage to collagen. Samples will be collected predose except for the FP visit. Samples can also be collected at any time for the Day 2 or 3 sample, which will be collected for a subset of subjects for blood ribonucleic acid (RNA) and inflammatory markers (this will be performed in a home visit or other means to avoid requiring subjects to return to the site). [redacted]

Lupus is an inflammatory/autoimmune disorder that results in damage to many different tissues. It is characterized by elevated expression of the Type I IFN pathway. To assess the effect of BMS-986165 on the IFN pathway, blood samples for RNA will be collected to assess the expression of IRGs and other genes. [redacted]

Patients with lupus typically have decreases in complement proteins, C3 and C4, and circulating lymphocytes. These will be assessed for evidence of PD activity. Anti-dsDNA will also be assessed for PD changes in serum and plasma.

BMS-986165 is expected to inhibit the actions of IL-12 and IL-23. This should result in alterations to T-helper cell phenotypes. In addition, B-cell populations are dysregulated in lupus, with increases in activated phenotypes. Blood will be collected for lymphocyte profiling including assessments of T-helper subpopulations, activated and memory T-cell subpopulations, B-cell populations, and dendritic cell populations. These populations will be enumerated in samples from a subset of subjects in the USA. In addition, the effects of BMS-986165 on IL-12- and IL-23-regulated genes and proteins will also be assessed.

Corticosteroid treatment is common in lupus; however, the effectiveness of this treatment varies in different patients. Thus, a broad range of doses are used across patient populations and even over time within individual patients. This treatment can confound the interpretation of investigational clinical trials. To address this issue, the biological effect of CS use will be assessed by measuring a gene signature of CS exposure.

Lupus patients have characteristic alterations in blood cell populations and activation status. Blood samples will be collected to assess the numbers and activation status of lymphocyte and leucocyte cell subsets.

[redacted]

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

Approximately 360 subjects will be randomized into 1 of 4 treatment arms in a 1:1:1:1 ratio, resulting in around 90 subjects per arm. [redacted]

[redacted] With a sample size of 90 subjects per arm, there will be at least 84% power to detect a treatment difference of 20% in SRI(4) response rates between the BID BMS-986165 treatment arms and placebo [redacted]

9.2 Populations for Analyses

The following populations are defined for analysis purposes:

Population	Description
Enrolled	All subjects who sign informed consent.
Randomized	All subjects who are randomized to a treatment. Subjects will be grouped according to the treatment to which they are randomized according to IRT at the start of the TP.
Modified intent-to-treat (mITT)	All subjects who are randomized and have received at least 1 dose of study treatment. Subjects will be grouped according to the treatment to which they are randomized within the IRT at the start of the TP. The mITT population will be the same as the Randomized population if all randomized subjects receive at least 1 dose of study treatment.
Biomarker	All subjects who receive at least 1 dose of study treatment and have at least 1 posttreatment biomarker measurement.
Pharmacokinetic	All subjects who receive at least 1 dose of BMS-986165 and have any available concentration-time data.
As-treated	All subjects who receive at least 1 dose of double-blind study treatment, analyzed according to the treatment actually received, regardless of assigned treatment.
Per Protocol Set (PPS)	All subjects who are compliant with study treatment (compliance criteria will be defined in the SAP) and who do not have any relevant protocol deviations that may impact the primary efficacy endpoint assessments. The PPS will be a supportive efficacy analysis population.

9.3 Statistical Analyses

The SAP will be developed and finalized before database lock for the primary efficacy analysis and will provide detailed specifications of the analysis of all efficacy endpoints and safety, and it will also describe the selection of subjects to be included in the analyses and procedures for

accounting for missing data. This section provides a summary of planned statistical analyses of the primary and secondary endpoints.

9.3.1 Efficacy Analysis

9.3.1.1 Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint is:

- Proportion of subjects who meet SRI(4) response at Week 32 (SRI response is defined in Section 8.1)

Secondary Efficacy Endpoints

Secondary efficacy endpoints are as follows:

- Proportion of subjects who meet SRI(4) response at Week 48
- Proportion of subjects who achieve BICLA response at Week 48, where BICLA response is defined as follows:
    - Improvement in all organ systems with activity graded as BILAG-2004 A or B at baseline
    - No new organ system with activity graded as BILAG A; no more than 1 new organ system with activity graded as BILAG B
    - No increase from baseline in SLEDAI-2K (≤ 0 points for change from baseline score)
    - No increase ≥ 10% in the Physician's Global Assessment of Disease Activity on a 3-point VAS
    - No discontinuation of IP or use of restricted medications beyond the protocol allowed threshold before assessment
- Proportion of subjects who achieve LLDAS at Week 48
- Proportion of subjects with a CLASI activity score ≥ 10 at baseline who achieve a CLASI response, defined as a decrease of ≥ 50% from baseline CLASI activity score at Week 48
- Change from baseline in the 40-joint count for tender, swollen, and tender + swollen joints at Week 48

[redacted]

9.3.1.2 Nonresponders

Subjects will be considered nonresponders in the TP for the responder-type efficacy endpoints (ie, BICLA and SRI) in the primary and secondary analyses at weeks 32 and 48, respectively, if they meet any of the following criteria:

- Requires CS dose > 7.5 mg/day prednisone or equivalent after Week 20
- Requires CS rescue therapy beginning after the Week 8 visit
- Requires more than 1 burst of CS rescue therapy
- Requires dose increase in background immunosuppressant or antimalarial medication
- Requires treatment with medications prohibited by the protocol (Section 6.7.1 and APPENDIX 7)
- Discontinues treatment before the assessment timepoint or has a missing value for the particular endpoint

Nonresponder definitions for other time points will be provided in the SAP.

9.3.1.3 Analysis Methodology

General Summaries

Summaries will be provided for the following efficacy variables by each visit for which the variable is collected, in addition to the above endpoints:

- Proportion of subjects who:

- Meet SRI(4) response criteria
- Meet BICLA response criteria
- Meet LLDAS response criteria
- Have a CLASI activity score ≥ 10 at baseline who achieve a CLASI response, defined as a decrease of ≥ 50% from baseline CLASI activity score
- Are receiving a daily CS dose ≤ 7.5 mg/day prednisone (or equivalent) in those receiving CS at baseline

- Change from baseline in:
  - BILAG-2004 score
  - SLEDAI-2K score
  - Joint counts for tender, swollen, and tender + swollen joints
  - Physician's Global Assessment of Disease Activity

  - CLASI activity score in subjects with a CLASI activity score ≥ 10 at baseline

Statistical Methodology

Efficacy analyses will be performed using the population of randomized subjects.

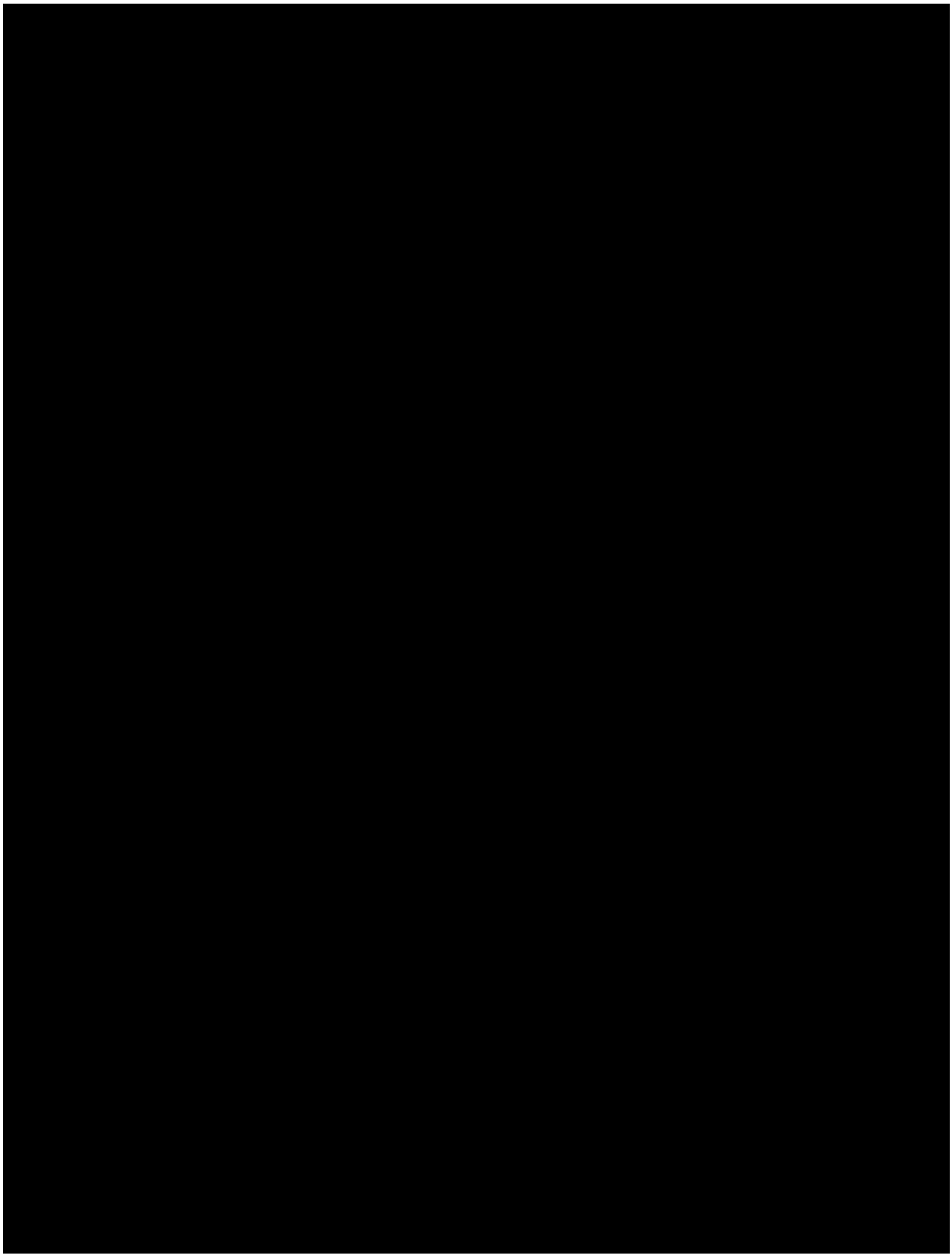
Endpoint	Statistical Analysis Methods
Primary	The primary endpoint, the proportion of subjects who meet the response criteria for SRI(4) at Week 32, will be analyzed using logistic regression with covariate for the randomization stratum to compare the response rates between each treatment group and placebo. The odds ratio (odds for active treatment /odds for placebo) and the corresponding 2-sided 95% confidence interval (CI) will be provided from the logistic regression model. Additionally, a sensitivity analysis will be conducted using a Cochran-Mantel-Haenszel (CMH) chi-square test stratified by randomization stratum; or alternatively a chi-square test if a CMH test cannot be performed. Differences in response rates and corresponding 2-sided 95% CI will be provided along with the point estimates and corresponding 95% CI for each group using a binomial model. The above analyses will be conducted for the mITT population. The primary efficacy analysis will be performed after all subjects have completed Week 48 efficacy assessments (or discontinued).

Endpoint	Statistical Analysis Methods
Secondar [redacted]	Similar analyses will be performed as for the primary efficacy analyses for the proportion-type secondary [redacted] efficacy endpoints to compare differences between the active treatment groups and placebo. The response rates over time will be analyzed using a repeated measure model when applicable. Repeated continuous measures will be analyzed using a mixed effect model with treatment, visit, treatment-by-visit interaction, and randomization stratum as the fixed effects and changes from baseline within each subject as the repeated measurements. The baseline value will be added into the model as a covariate. Based on the mixed effect model, the point estimate, and 95% CI will be calculated for the difference between each active treatment group and the placebo group at each specified visit. All analyses will be conducted for the mITT population. The handling of missing values will be described in the SAP.

[redacted]

Additionally, subgroup analyses to be performed will be described in the SAP.

[redacted]



9.3.2 Safety Analyses

Safety analyses will be performed using the As-treated population. The primary safety endpoint is a secondary endpoint of the study. For analysis, all recorded AEs 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. ECG readings will be evaluated by the investigator and abnormalities, if present, will be summarized and listed.

9.3.3 Other Analyses

[redacted]

9.3.3.1 Pharmacokinetics

PK evaluation is a secondary endpoint. Plasma concentration values will be summarized by dose and study day using descriptive statistics. If warranted, analysis of PK and exposure-response relationships of BMS-986165 will be conducted using a population approach as appropriate and reported separately from the clinical study report.

9.3.3.2 Pharmacodynamics

Pharmacodynamic evaluation is a secondary endpoint. Selected PD endpoints such as IRG expression, C3, C4, and anti-dsDNA will be summarized by treatment and timepoint, and their corresponding changes and percent change from baseline will be calculated and summarized. Change from baseline in lymphocyte count, serum or plasma proteins, genome-wide RNA expression, lymphocyte subsets and activation status, etc, will be summarized by time. Baseline values will be defined as the last measurement before the first dose.

9.3.4 Interim Analyses

One interim analysis may be performed after at least 50% of subjects have achieved the Week 32 primary endpoint to aid in planning for subsequent clinical development. Details and timing of the interim analysis will be described in the SAP. Results will be reviewed by an unblinded Sponsor team independent from the blinded study team. The unblinded team will provide recommendations to the blinded study team as appropriate. The study team responsible for managing the study, including medical monitors, will remain blinded. The SAP will further describe any potential interim analyses.

9.3.5 Analysis and Reporting

The final database lock will occur once all randomized subjects have completed 48 weeks of double-blind treatment (or have discontinued) and the 4-week safety follow-up for those who have not enrolled into the LTE study IM011074. Details of these efficacy and safety analyses will be described in the SAP.

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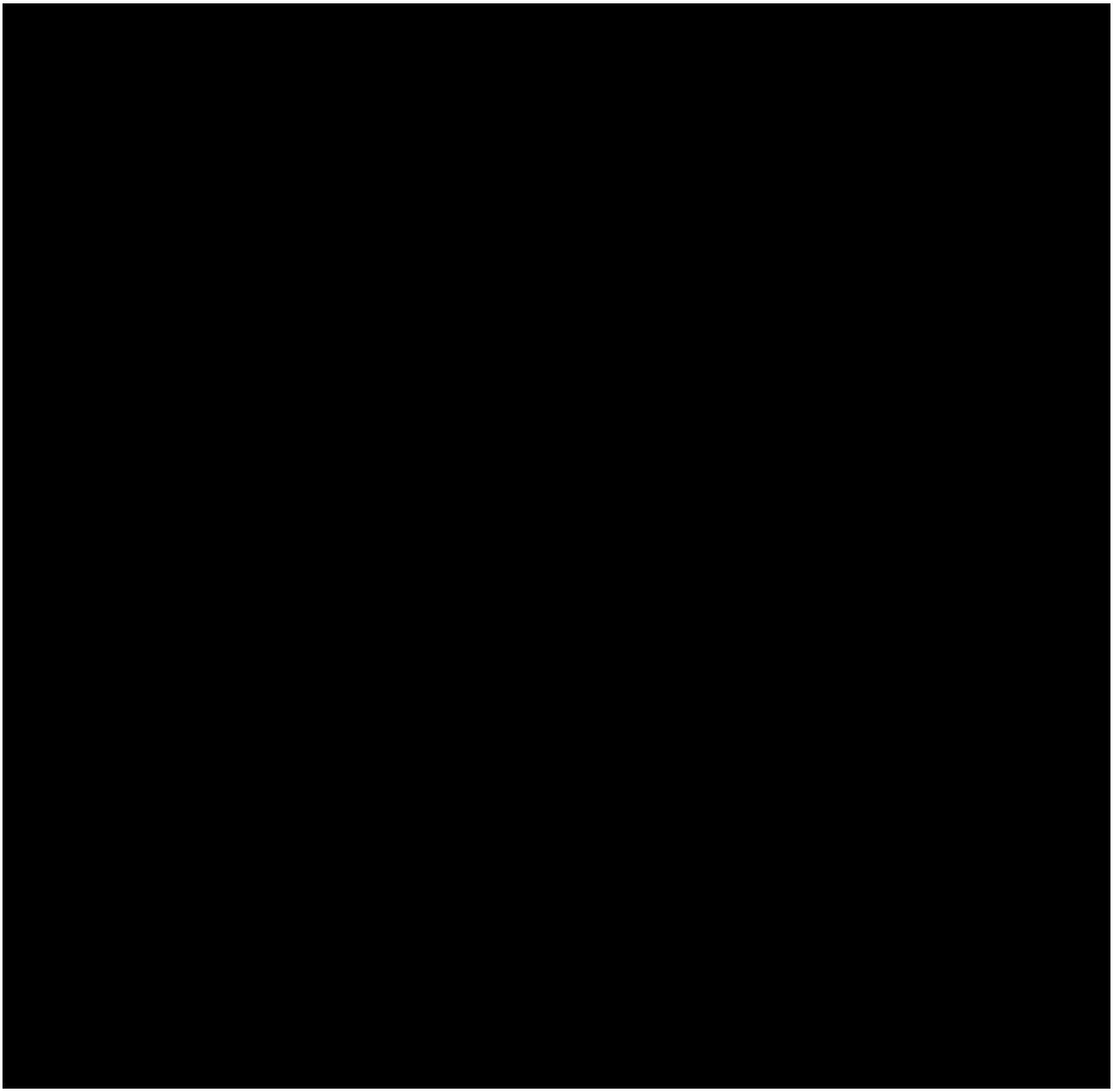

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11 APPENDICES

APPENDIX 1 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the eCRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Good Clinical Practice (GCP)
- as defined by the International Council for Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States (US) Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to Sponsor or designee 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).

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, participant 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, Sponsor or designee 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.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if

applicable, also by local health authority) 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 relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (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.

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

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

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 participant volunteers to participate.

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

Investigators must:

- Provide a copy of the ICF and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.

- Obtain an ICF signed and personally dated by the participant or the participant'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 ICF 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 participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the ICF whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant'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 participants' signed ICF and, in the US, the participants' signed Health Insurance Portability and Accountability Act (HIPAA) Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to participant records.

Subjects unable to give their written consent (eg, those with stroke or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant 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 participants are the most important considerations and should prevail over interests of science and society.

SOURCE DOCUMENTS

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.

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	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 participant, including unique participant 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.
Sourced by site, and not supplied by BMS or its vendors (examples include investigational product sourced from the site stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the standard operating procedures of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

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 adverse events (AEs) and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture (EDC) tool, electronic CRFs will be prepared for all data collection fields except for fields specific to serious adverse events (SAEs) and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If an electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

The confidentiality of records that could identify participants 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 and SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the BMS EDC 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 Sponsor or designee training requirements and must only access the BMS EDC tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

MONITORING

Sponsor or designee 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. Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by Sponsor or designee 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 Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) 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 or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) 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, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS, a vendor, or sourced by the investigator) such as partially used study treatment containers, vials, and syringes may be destroyed on site (as applicable; some sites will return unused study treatments depending on circumstances).

If	Then
Study treatments supplied by BMS (including its vendors)	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (eg, study treatments sourced from the site's stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, 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. The following minimal standards must be 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, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, 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.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of nonstudy treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

For sites that will not destroy study treatment on-site, it is the investigator's or designee's responsibility to arrange for disposal of all empty study treatment 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. The return of full or partially used study treatments supplied by BMS or its vendors will be arranged by the responsible Study Monitor.

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 one or more of the following criteria:

- External principal investigator designated at protocol development
- National Coordinating investigator
- Study Steering Committee chair or their designee
- Participant 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 Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing study site or investigator participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

APPENDIX 2 ABBREVIATIONS AND TRADEMARKS

Term	Definition
6-MP	6-mercaptopurine
ACR	American College of Rheumatology
ADL	activity of daily living
AE	adverse event
AEI	adverse event of interest
ALT	alanine aminotransferase
ANA	antinuclear antibody
anti-Sm	anti-Smith
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(0-24)	area under the concentration-time curve from 0 to 24 hours
AUC(INF)	area under the concentration-time curve extrapolated to infinity
AUC(TAU)	area under the concentration-time curve in one dosing interval
AZA	azathioprine
β-HCG	beta-human chorionic gonadotropin
BCRP	breast cancer resistance protein
BICLA	BILAG-based Composite Lupus Assessment
BID	bis in die (twice daily)
BILAG	British Isles Lupus Assessment Group
BMS	Bristol-Myers Squibb
Cavg	average concentration during a dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
Cmax	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CRS	Central Review Services
CS	corticosteroid(s)

Term	Definition
CTA	clinical trial agreement
Ctrough	trough observed plasma concentration
CYP450	cytochrome p-450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
[redacted]	
dsDNA	double-stranded deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
Emax	direct effect
FIH	first-in-human
FP	follow-up period
GCP	Good Clinical Practice
HBc	hepatitis B core
HBs	hepatitis B surface
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
hsCRP	high-sensitivity C-reactive protein
IB	Investigator Brochure
IBD	inflammatory bowel disease
IC50	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	interferon

Term	Definition
Ig	immunoglobulin
IGRA	interferon gamma release assay
IL	interleukin
IMP	investigational medicinal product
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRG	interferon-regulated gene
IRT	interactive response technology
IV	intravenous
JAK	Janus kinase
KLH	keyhole limpet hemocyanin
LLDAS	Lupus Low Disease Activity State
LTE	long-term extension
[redacted]	
mITT	modified intent-to-treat
MMF	mycophenolate mofetil/mycophenolic acid
MTX	methotrexate
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OTC	over-the-counter
PD	pharmacodynamic(s)
PE	physical examination
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PPS	Per Protocol Set
[redacted]	
QD	quaque die (once daily)

Term	Definition
RBC	red blood cell
RNA	ribonucleic acid
RNP	ribonuclear protein
SAE	serious adverse event
SAP	statistical analysis plan
[redacted]	
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
[redacted]	
SLICC	Systemic Lupus International Collaborating Clinics
SP	screening period
SRI	Systemic Lupus Erythematosus Responder Index
STAT	signal transducer and activator of transcription
T4	thyroxine
TB	tuberculosis
TBNK	T cell, B cell, natural killer cell
TDAR	T cell-dependent antibody response
Tmax	time to maximum plasma concentration
TP	treatment period
TSH	thyroid-stimulating hormone
TYK2	tyrosine kinase 2
UK	United Kingdom
ULN	upper limit of normal
UPCR	urine protein/creatinine ratio
US/USA	United States of America
VAS	visual analog scale
WOCBP	women of childbearing potential

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:

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.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

SERIOUS ADVERSE EVENTS

Serious Adverse Event Definition: 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) 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)
Results in persistent or significant disability or permanent damage
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 8.3.8 for the definition of potential DILI).

Pregnancy and potential DILI must follow the same transmission timing and processes to BMS as used for SAEs (see Section 8.3.6 for reporting pregnancies).

EVALUATING AES AND SAES

Assessment of Intensity

The intensity of AEs is determined by a physician and will use the following levels:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. A "reasonable possibility of a relationship" conveys that there are facts, evidences, and/or arguments to suggest a causal relationship rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. Note: Follow-up SAE reports must 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, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

SAEs, whether related or not related to study drug, and pregnancies must be reported to [redacted] Drug Safety within 24 hours of awareness of the event.

SAEs must be recorded on the SAE Report Form. For studies capturing SAEs through electronic data capture, electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: [redacted]

SAE Fax Number:

Americas: [redacted]

Europe/East Asia-Pacific: [redacted]

SAE Telephone Contact - For questions on SAE/pregnancy reporting, please call:

Americas: [redacted]

Europe/East Asia-Pacific: [redacted]

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

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

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman older than 45 years in the absence of other biological or physiological causes. In addition, women younger than 55 years must have a serum follicle-stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

Note: Women 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 periods below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels.

- 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. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

CONTRACEPTION GUIDANCE FOR FEMALE SUBJECTS OF CHILDBEARING POTENTIAL

One of the highly effective methods or less than highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 3 days after the end of study treatment, plus 30 days.

Local laws and regulations may require use of alternative and/or additional contraception methods (eg, one highly effective method plus another method).

Highly Effective Contraceptive Methods That Are User-Dependent *Failure rate of < 1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation o oral o intravaginal o transdermal • Combined (estrogen- and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy
• Progestogen-only hormonal contraception associated with inhibition of ovulation o oral o injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy
Highly Effective Methods That Are User-Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device[b] • Intrauterine hormone-releasing system[b] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 1.3. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

b Intrauterine devices and intrauterine hormone-releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness.
Less Than Highly Effective Contraceptive Methods That Are User-Dependent *Failure rate of > 1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method

CONTRACEPTION GUIDANCE FOR MALE SUBJECTS WITH FEMALE PARTNER(S) OF CHILDBEARING POTENTIAL

Male subjects with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment:

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Condom use is not required.
- Female partners of men participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as the duration of the study treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 8.3.6.

APPENDIX 5 SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS CLASSIFICATION CRITERIA FOR SYSTEMIC LUPUS ERYTHEMATOSUS

***Notes:**

CLINICAL CRITERIA

1) Acute Cutaneous Lupus OR Subacute Cutaneous Lupus

- Acute cutaneous lupus: lupus malar rash (do not count if malar discoid), bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash (in the absence of dermatomyositis)
- Subacute cutaneous lupus: nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)

2) Chronic Cutaneous Lupus

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

3) Oral Ulcers OR Nasal Ulcers

- Oral: palate, buccal, tongue
- Nasal ulcers
- In the absence of other causes, such as vasculitis, Behçet's disease, infection (herpes virus), inflammatory bowel disease, reactive arthritis, and acidic foods

4) Nonscarring Alopecia

Diffuse thinning or hair fragility with visible broken hairs, in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia

5) Synovitis Involving 2 Or More Joints

- Characterized by swelling or effusion
- OR tenderness in 2 or more joints and at least 30 minutes of morning stiffness

6) Serositis

- Typical pleurisy for more than 1 day OR pleural effusions OR pleural rub
- Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day OR pericardial effusion OR pericardial rub OR pericarditis by electrocardiography
- In the absence of other causes, such as infection, uremia, and Dressler's pericarditis

7) Renal

Urine protein–to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein per 24 hours OR red blood cell casts

8) Neurologic

Seizures, psychosis, mononeuritis multiplex (in the absence of other known causes such as primary vasculitis), myelitis, peripheral or cranial neuropathy (in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus), acute confusional state (in the absence of other causes, including toxic/metabolic, uremia, drugs)

9) Hemolytic Anemia

10) Leukopenia (< 4000/mm^3) OR Lymphopenia (< 1000/mm^3)

Leukopenia at least once: In the absence of other known causes such as Felty's syndrome, drugs, and portal hypertension.

Lymphopenia at least once: in the absence of other known causes such as corticosteroids, drugs, and infection

11) Thrombocytopenia (< 100,000/mm^3)

At least once in the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura

IMMUNOLOGIC CRITERIA

1) **ANA** level above laboratory reference range
2) **Anti-dsDNA** antibody level above laboratory reference range (or 2-fold the reference range if tested by enzyme-linked immunosorbent assay [ELISA]); indeterminate results are considered positive
3) **Anti-Sm**: presence of antibody to Sm nuclear antigen
4) **Antiphospholipid antibody** positivity, as determined by
   - Positive test for lupus anticoagulant
   - False-positive test result for rapid plasma reagin (RPR)
   - Medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM)
   - Positive test result for anti–2-glycoprotein I (IgA, IgG, or IgM)
5) **Low complement** (C3, C4, or CH50)
6) **Direct Coombs test** (in the absence of hemolytic anemia)

Source:

Petri M, Orbai AM, Alarcon GS, et al. Derivation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012 Aug;64(8):2677-86.

APPENDIX 6 COMMONLY USED CORTICOSTEROID EQUIVALENTS

Medication	Dose Equivalence
Prednisone	20 mg
Cortisone	100 mg
Hydrocortisone	80 mg
Prednisolone	20 mg
Methylprednisolone	16 mg
Triamcinolone	16 mg
Budesonide	4 mg
Dexamethasone	3 mg
Betamethasone	2.4 mg
Deflazacort	26 mg

APPENDIX 7 REQUIRED RECOVERY (WASHOUT) TIMES FOR SPECIFIC MEDICATIONS PRIOR TO SCREENING

Medications	Discontinuation Prior to Signing Consent
Abatacept (CTLA4Ig)	12 weeks
Acthar® gel (repository corticotropin injection)	6 weeks
Adalimumab	12 weeks
Alefacept	8 weeks
AMG 623	12 weeks
Anakinra	12 weeks
Apremilast	4 weeks
Atacicept (TACI-Ig)	48 weeks
Belimumab	24 weeks
BIIB059	15 weeks
Certolizumab pegol	24 weeks
Cyclophosphamide	24 weeks
Cyclosporine	4 weeks for systemic use (oral, IV, etc)
Danazol	4 weeks
Dapsone	4 weeks
Eculizumab	12 weeks
Efalizumab	8 weeks
Epratuzumab	18 weeks
Etanercept	4 weeks
Infliximab	12 weeks
Intravenous globulin	4 weeks
Leflunomide	36 weeks
Lenalidomide with cholestyramine	24 weeks
Lulizumab	6 weeks
Lupuzor (IPP-201101)	12 weeks
Memantine	4 weeks
Natalizumab	12 weeks
Obinutuzumab	26 weeks
Ocrelizumab	24 weeks
Ofatumumab	26 weeks
Plasmapheresis	24 weeks

Medications	Discontinuation Prior to Signing Consent
Retinoids (oral isotretinoin, and acitretin; topical retinoids are allowed)	4 weeks
Rituximab	24 weeks
Sifalimumab	26 weeks
Sirolimus	4 weeks
Sulfasalazine	4 weeks
Tabalumab	14 weeks
Tacrolimus	4 weeks for systemic use (oral, IV, etc)
Thalidomide	4 weeks
Tocilizumab	12 weeks
Tofacitinib	4 weeks

APPENDIX 8 DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS IV

Alcohol abuse:

In the past year, have you:

- Found that drinking – or being sick from drinking – often interfered with taking care of your home or family? Or caused job troubles? Or school problems?
- More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?
- More than once gotten arrested, been held at a police station, or had other legal problems because of your drinking?
- Continued to drink even though it was causing trouble with your family or friends?

The presence of any 1 of the above is considered indicative of alcohol abuse.

Alcohol dependence:

In the past year, have you:

- Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?
- Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart, or a seizure? Or sensed things that were not there?
- Had times when you ended up drinking more, or longer, than you intended?
- More than once wanted to cut down or stop drinking, or tried to, but couldn't?
- Spent a lot of time drinking? Or being sick or getting over other aftereffects?
- Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?
- Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?

The presence of any 3 of the above is considered indicative of alcohol dependence.

National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism. Alcohol use disorder: a comparison between DSM-IV and DSM-5. NIH Publication No. 13-7999. Reviewed July 2016.

APPENDIX 9 INTERPRETATION OF HEPATITIS B SEROLOGIC TEST RESULTS

Because BMS-986165 is expected to demonstrate immunosuppressive effects, it is imperative to carefully evaluate and exclude participants with potentially active hepatitis B infection. For this reason, to fully evaluate a participant's eligibility for enrollment, the exclusion criterion (see Section 5.2) requires interpretation of data from 3 standard tests for hepatitis B, ie, measurement of hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs).

The participant's eligibility for enrollment should be assessed as described below:

- Hepatitis B serological test negative (neg) for all results may be included in the study
- HBsAg (neg), anti-HBc (neg), and anti-HBs positive (POS) may be included in the study (immunized due to hepatitis B vaccination)
- HBsAg (neg), anti-HBc (POS), and anti-HBs (POS) are to be excluded from the study (immune due to natural infection exposure)
- Participants that are HBsAg (POS) are excluded from the study (acute or chronic infection)
- Participants that are anti-HBc (POS) are excluded from the study (acute or chronic infection)
- Participants that are HBsAg (neg), anti-HBc (POS), and anti-HBs (neg) are to be excluded from the study (interpretation unclear)

Please refer to the schematic "Interpretation of Hepatitis B Serologic Test Results" (below) provided by the Department of Health and Human Services, Centers for Disease Control and Prevention.

Interpretation of Hepatitis B Serologic Test Results

Hepatitis B serologic testing involves measurement of several hepatitis B virus (HBV)-specific antigens and antibodies. Different serologic "markers" or combinations of markers are used to identify different phases of HBV infection and to determine whether a patient has acute or chronic HBV infection, is immune to HBV as a result of prior infection or vaccination, or is susceptible to infection.

HBsAg **anti-HBc** **anti-HBs**	negative negative negative	Susceptible
HBsAg **anti-HBc** **anti-HBs**	negative positive positive	Immune due to natural infection
HBsAg **anti-HBc** **anti-HBs**	negative negative positive	Immune due to hepatitis B vaccination
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive positive negative	Acutely infected
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive negative negative	Chronically infected
HBsAg **anti-HBc** **anti-HBs**	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection

Adapted from: A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. Part I: Immunization of Infants, Children, and Adolescents. MMWR 2005;54(No. RR-16).

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention
Division of Viral Hepatitis

www.cdc.gov/hepatitis

- **Hepatitis B surface antigen (HBsAg):** A protein on the surface of hepatitis B virus; it can be detected in high levels in serum during acute or chronic hepatitis B virus infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is the antigen used to make hepatitis B vaccine.
- **Hepatitis B surface antibody (anti-HBs):** The presence of anti-HBs is generally interpreted as indicating recovery and immunity from hepatitis B virus infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.
- **Total hepatitis B core antibody (anti-HBc):** Appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus in an undefined time frame.
- **IgM antibody to hepatitis B core antigen (IgM anti-HBc):** Positivity indicates recent infection with hepatitis B virus (≤6 mos). Its presence indicates acute infection.

APPENDIX 10 BRITISH ISLES LUPUS ASSESSMENT GROUP INDEX – 2004

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

CONSTITUTIONAL

1. Pyrexia – documented > 37.5°C	( )
2. Weight loss – unintentional >5%	( )
3. Lymphadenopathy/splenomegaly	( )
4. Anorexia	( )

MUCOCUTANEOUS

5. Skin eruption – severe	( )
6. Skin eruption – mild	( )
7. Angio-oedema – severe	( )
8. Angio-oedema – mild	( )
9. Mucosal ulceration – severe	( )
10. Mucosal ulceration – mild	( )
11. Panniculitis/Bullous lupus – severe	( )
12. Panniculitis/Bullous lupus – mild	( )
13. Major cutaneous vasculitis/thrombosis	( )
14. Digital infarcts or nodular vasculitis	( )
15. Alopecia – severe	( )
16. Alopecia – mild	( )
17. Peri-ungual erythema/chilblains	( )
18. Splinter haemorrhages	( )

NEUROPSYCHIATRIC

19. Aseptic meningitis	( )
20. Cerebral vasculitis	( )
21. Demyelinating syndrome	( )
22. Myelopathy	( )
23. Acute confusional state	( )
24. Psychosis	( )
25. Acute inflammatory demyelinating polyradiculoneuropathy	( )
26. Mononeuropathy (single/multiplex)	( )
27. Cranial neuropathy	( )
28. Plexopathy	( )
29. Polyneuropathy	( )
30. Seizure disorder	( )
31. Status epilepticus	( )
32. Cerebrovascular disease (not due to vasculitis)	( )
33. Cognitive dysfunction	( )
34. Movement disorder	( )
35. Autonomic disorder	( )
36. Cerebellar ataxia (isolated)	( )
37. Lupus headache – severe unremitting	( )
38. Headache from IC hypertension	( )

MUSCULOSKELETAL

39. Myositis – severe	( )
40. Myositis – mild	( )
41. Arthritis (severe)	( )
42. Arthritis (moderate)/Tendonitis/Tenosynovitis	( )
43. Arthritis (mild)/Arthralgia/Myalgia	( )

Weight (kg):	Serum Urea (mmol/l)c
African ancestry: Yes/No	Serum Albumin (g/l):

VAS(Patient) 0----------10cm

BLOOD RESULTS: ESR DNA C3 C4 CR-P

CARDIORESPIRATORY

44. Myocarditis – mild	( )
45. Myocarditis/Endocarditis + Cardiac failure	( )
46. Arrhythmia	( )
47. New valvular dysfunction	( )
48. Pleurisy/Pericarditis	( )
49. Cardiac tamponade	( )
50. Pleural effusion with dyspnoea	( )
51. Pulmonary haemorrhage/vasculitis	( )
52. Interstitial alveolitis/pneumonitis	( )
53. Shrinking lung syndrome	( )
54. Aortitis	( )
55. Coronary vasculitis	( )

GASTROINTESTINAL

56. Lupus peritonitis	( )
57. Abdomial serositis or ascites	( )
58. Lupus enteritis/colitis	( )
59. Malabsorption	( )
60. Protein losing enteropathy	( )
61. Intestinal pseudo-obstruction	( )
62. Lupus hepatitis	( )
63. Acute lupus cholecystitis	( )
64. Acute lupus pancreatitis	( )

OPHTHALMIC

65.Orbital inflammation/myositis/proptosis	( )
66. Keratitis – severe	( )
67. Keratitis – mild	( )
68. Anterior uveitis	( )
69. Posterior uveitis/retinal vasculitis – severe	( )
70. Posterior uveitis/retinal vasculitis – mild	( )
71. Episcleritis	( )
72. Scleritis – severe	( )
73. Scleritis – mild	( )
74. Retinal/choroidal vaso-occlusive disease	( )
75. Isolated cotton-wool spots (cytoid bodies)	( )
76. Optic neuritis	( )
77. Anterior ischaemic optic neuropathy	( )

RENAL

78. Systolic blood pressure (mmHg)	value	( )
79. Diastolic blood pressure (mmHg)	value	( )
80. Accelerated hypertion	Yes/No	( )
81. Urine dipstick protein	(+=1, ++=2, +++=3)	( )
82. Urine albumin-creatinine ratio	mg/mmol	( )
83. Urine protein-creatinine ratio	mg/mmol	( )
84. 24 hour urine protein (g)	value	( )
85. Nephrotic syndrome	Yes/No	( )
86. Creatinine (plasma/serum)	µmol/l	( )
87. GFR (calculated)	ml/min/1.73 m²	( )
88. Active urinary sediment	Yes/No	( )
89. Active nephritis	Yes/No	( )

HAEMATOLOGICAL

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

VAS(Dr)0----------10cm

SCORING OF DISEASE ACTIVITY OF THE BILAG-2004 BASED ON THE PRINCIPLE OF PHYSICIAN'S INTENTION TO TREAT			
Scoring by grade	**Disease severity**	**Numerical scores**	**Assumption about the treatment for each grade**
A = Active	Severe	12	Severe disease activity requiring any of the following treatment: 1. systemic high-dose oral glucocorticoids (equivalent to prednisolone >20 mg/day) 2. intravenous pulse glucocorticoids (equivalent to pulse methylprednisolone ≥500 mg) 3. systemic immunomodulators (include biologicals, immunoglobulins and plasmapheresis) 4. therapeutic high-dose anticoagulation in the presence of high-dose steroids or immunomodulators; e.g., warfarin with target INR 3–4
B = Beware	Moderate	8	Moderate disease activity requiring any of the following treatment: 1. systemic low dose oral glucocorticoids (equivalent to prednisolone ≤20 mg/day) 2. intramuscular or intra-articular or soft tissue glucocorticoids injection (equivalent to methylprednisolone <500 mg) 3. topical glucocorticoids 4. topical immunomodulators 5. antimalarials or thalidomide or prasterone or acitretin 6. symptomatic therapy; e.g., NSAIDs for inflammatory arthritis
C = Contentment	Mild	1	Patient requires symptomatic treatment (e.g., analgesics or NSAIDs)
D = Discount	Inactive but previously affected	0	Not applicable
E = No Evidence	Inactive with no previous involvement	0	Not applicable

Sources:

Isenberg, DA, Rahman A, Allen E, et al. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. Rheumatology (Oxford) 2005;44(7):902-6.

Yee CS, Farewell V, Isenberg DA, et al. Revised British Isles Lupus Assessment Group 2004 Index - A Reliable Tool for Assessment of Systemic Lupus Erythematosus Activity. Arthritis Rheum 2006;54:3300–05.

Yee CS, Farewell V, Isenberg DA, et al. British Isles Lupus Assessment Group 2004 index is valid for assessment of disease activity in systemic lupus erythematosus. Arthritis Rheum 2007;56(12):4113-19.

Yee CS, Cresswell L, Farewell V, et al: Numerical scoring for the BILAG-2004 index. Rheumatology (Oxford) 2010 Sep;49(9):1665-9.

APPENDIX 11 SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX 2000 DISEASE ACTIVITY QUESTIONNAIRE

Note: Detailed definitions of the individual items are included in a quick reference guide for sites.

For an item to be scored the indicated weight, the manifestation must have been present in the past 30 days.

The glossary of the terms is adjacent on the form itself.

Enter weight in SLEDAI-2K Score column if descriptor is present at the time of the visit or in the preceding 30 days.

Sources:

Gladman, DD., Ibañez, D., Urowitz, MB. Systemic Lupus Erythematosus Disease Activity Index 2000. J Rheumatol 2002;29:288-91.

Touma Z, Urowitz MB, Gladman DD. SLEDAI-2K for a 30-day window. Lupus 2010;19:49-51.

SLEDAI 2K Weight	SCORE	Descriptor	Definition
8	_____	Seizure	Recent onset, exclude metabolic, infectious or drug causes.
8	_____	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes
8	_____	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	_____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	_____	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	_____	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	_____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	_____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	_____	Arthritis	≥ 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	_____	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	_____	Urinary casts	Heme-granular or red blood cell casts.
4	_____	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____	Proteinuria	>0.5 gram/24 hours
4	_____	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	_____	Rash	Inflammatory type rash.
2	_____	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	_____	Mucosal ulcers	Oral or nasal ulcerations.
2	_____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory
2	_____	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____	Fever	>38° C. Exclude infectious cause.
1	_____	Thrombocytopenia	<100,000 platelets / $x10^9$/L, exclude drug causes.
1	_____	Leukopenia	< 3,000 white blood cells / $x10^9$/L, exclude drug causes.

TOTAL SCORE: _____

APPENDIX 12 CUTANEOUS LUPUS ERYTHEMATOSUS DISEASE AREA AND SEVERITY INDEX (CLASI)

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

activity ⟷ damage

Extent

Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
	0-absent 1-pink; faint erythema 2- red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentaton	0 … absent 1 … scarring 2 … severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
Back, buttocks					Back, buttocks
Arms					Arms
Hands					Hands
Legs					Legs
Feet					Feet

Mucous membrane

Mucous membrane lesions (examine if patient confirms involvement)	
0-absent; 1-lesion or ulceration	

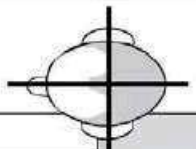
Dyspigmentation

Report duration of dyspigmentation after active lesions have resolved (verbal report by patient … tick appropriate box)

☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)

☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia



Recent Hair loss (within the last 30 days/as reported by patient)	
1-Yes 0-No	

NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score (For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)		Total Damage Score (For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)	

Sources:

Albrecht J, Taylor L, Berlin JA, et al. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): An outcome instrument for cutaneous lupus erythematosus. J Invest Dermatol 2005;125:889 -94.

Bonilla-Martinez ZL, Albrecht J, Troxel AB, et al. The Cutaneous Lupus Erythematosus Disease Area and Severity Index - A responsive instrument to measure activity and damage in patients with cutaneous lupus erythematosus. Arch Dermatol 2008;144(2):173-80.

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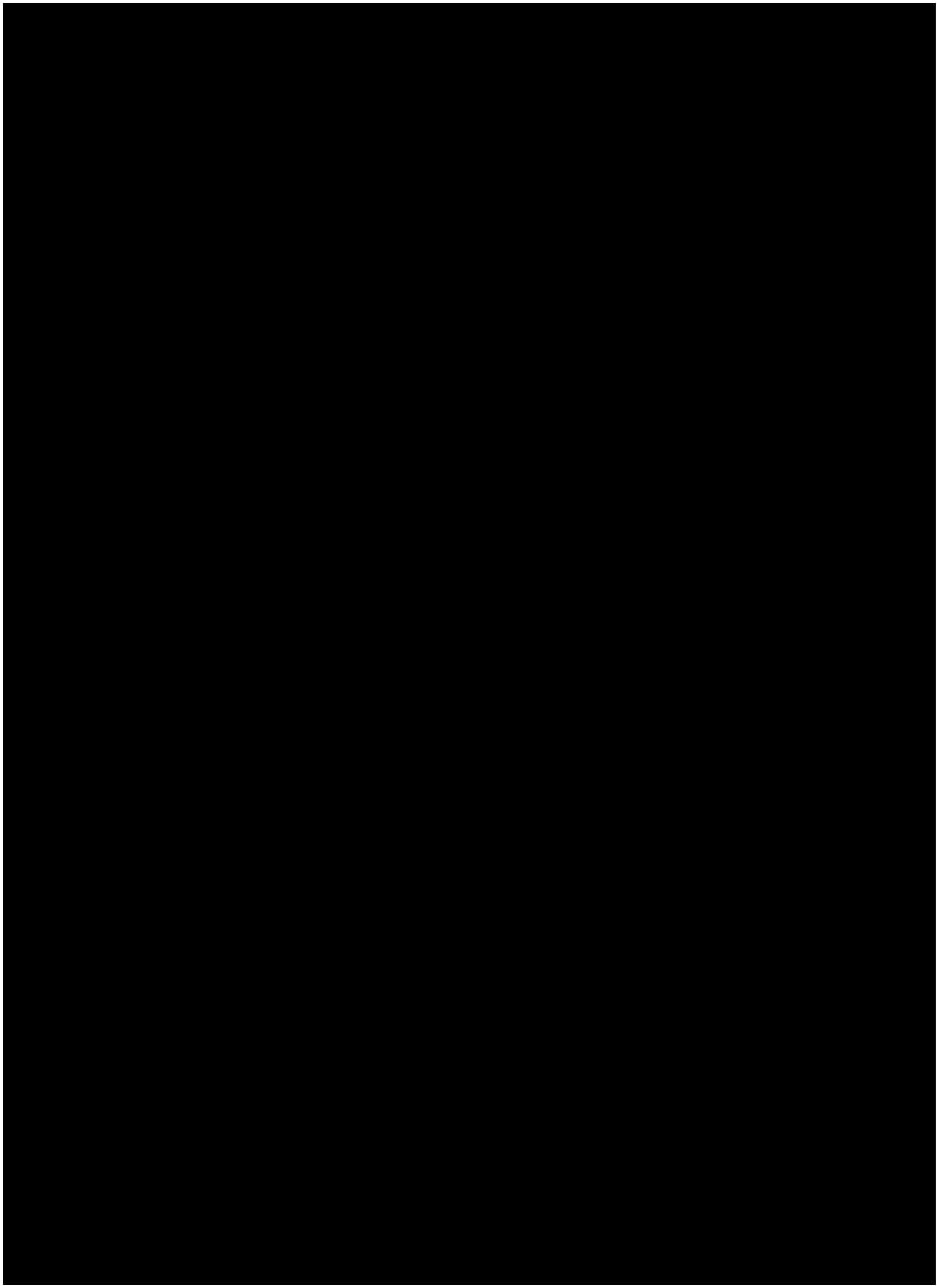

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APPENDIX 17 OTHER ASSESSMENTS

Physician's Global Assessment of Disease Activity

How do you assess your patient's (the subject's) current disease activity as compared to the last visit? Please mark the line below.

Patient's Global Assessment of Disease Activity

Considering all the ways in which your lupus has affected you in the PAST WEEK, please make a mark on the line below to show how you are doing.

Very Poorly Very Well

Patient-Reported Pain Assessment

On a scale of 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable, how would you rate your pain in the PAST WEEK?

Please circle the number below that represents your pain.

APPENDIX 18 MORPHINE MILLIGRAM EQUIVALENTS FOR OPIOIDS

The following table shows daily morphine milligram equivalents for some opioids. This list is not exhaustive, and the 30 mg morphine equivalence limit applies to all opioid analgesics even if they are not listed here.

Opioid	30 mg morphine equivalent
butorphanol	4.3 mg/day
codeine	200 mg/day
dihydrocodeine	120 mg/day
fentanyl transdermal	12.5 mcg/hr
hydrocodone	30 mg/day
hydromorphone	7.5 mg/day
levorphanol tartrate	2.7 mg/day
meperidine HCl	300 mg/day
oxycodone	20 mg/day
oxymorphone	10 mg/day
pentazocine	81.1 mg/day
tapentadol	75 mg/day
tramadol	300 mg/day

Reference:

Centers for Medicare and Medicaid Services. Opioid Oral Morphine Milligram Equivalent Conversion Factors.

https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-Aug-2017.pdf. Accessed 04-Jun-2019.