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A Multi-Center Study to Characterize the Long-Term Safety and Efficacy of BMS-986165 in Subjects with Systemic Lupus Erythematosus

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CLINICAL PROTOCOL IM011074

A Multi-Center Study to Characterize the Long-Term Safety and Efficacy of BMS-986165 in Subjects with Systemic Lupus Erythematosus

Short Title: Long-Term Safety and Efficacy of BMS-986165 in Subjects with Systemic Lupus Erythematosus

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DOCUMENT HISTORY

Document	Date of Issue	Approver(s)	Summary of Change
Revised Protocol 3 (Revision 3, Version 4.0[a]) (im011074-revprot03)	15-Jan-2021	[redacted]	-Included a safety follow-up visit at the end of the study -Changed the on-treatment portion of the study from 108 weeks to 174 weeks -Allowed subjects who experience a disruption in treatment due to exceptional circumstances after completion of the parent study, IM011021, to enter the IM011074 long-term extension (LTE)
Revision 2, Version 3.0 (im011074-revprot02)	12-Feb-2019		Clarified additional blood samples to be collected for BILAG scoring
Revision 1, Version 2.0 (im011074-revprot01)	14-Dec-2018		Included LLDAS response as an additional endpoint, allowed a larger window for selected visits, described treatment assignment details [redacted]
Original Protocol (im011074-prot)	26-Oct-2018		Not applicable

[a] Document naming conventions have been updated. Legacy PRA numbering is provided for consistency.

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 03:

The primary purpose of this revised protocol is to include the following updates:

- To include a safety follow-up visit at the end of the study
- To change the on-treatment portion of the study from 108 weeks to 174 weeks
- To allow subjects who experience a disruption in treatment due to exceptional circumstances after completion of the parent study, IM011021, to enter the IM011074 long-term extension (LTE)

This revised protocol will be implemented after the Investigator receives all appropriate agency and IRB/EC approvals.

Generally, only major additions and deletions are provided in this summary of changes document, and all minor grammatical, formatting, rephrasing, stylistic changes, or clarifications, as well as reorganizational changes are not included. All changes applied to the protocol body were applied to the protocol synopsis, as necessary; synopsis changes are not included in the summary of key changes table.

The rationale for the change to this Revised Protocol is provided in the summary of key changes table, as shown below:

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Study Acknowledgment /Disclosure	This page was removed.	To align with BMS protocol standards, this page is now provided as a standalone component.
Section 1.3, Schedule of Activities (SOA) Section 4, Study Design Figure 1, IM011074 Study Design Section 7.1, Discontinuation from Study Treatment Section 8.5.1, Sampling Schedule	The last treatment visit for nondiscontinuing subjects was changed from Week 108 to Week 174. A follow-up (end-of-study) visit was added at Week 178. Timing of assessments was adapted to the increased number of weeks and visits where applicable.	To provide an additional 66 weeks of therapy and to add a follow-up (end-of-study) visit for subject safety
Section 4.1.2.1, Data Monitoring Committee	The timing of the data monitoring committee's planned meetings was removed.	To remove potential incongruity as these details are listed in the data monitoring committee's charter.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1, Inclusion Criteria	Inclusion criterion 2)a was updated to allow subjects experiencing exceptional circumstances to participate in the LTE with sponsor approval. Several reproductive status–related inclusion criteria were updated.	To allow inclusion of subjects (with approval from the BMS Clinical Trial Physician) who are willing to participate in the study but cannot meet some original requirements. To align reproductive status–related criteria with those in the parent study, IM011021, and the sponsor-approved guidelines specific to the BMS-986165 program.
Section 5.3, Lifestyle Restrictions	Fasting requirements were removed; and the suggestion that caffeine, alcohol, tobacco, and activity should be limited was removed.	To reduce unnecessary inconvenience to subjects based on updated sponsor-approved guidelines specific to the BMS-986165 program and to align with Section 8.4.4.
Section 6.3.2, Circumstances for Unblinding	The clarification that certain members of the BMS study team would be partially unblinded after database lock of the parent study was added.	To clarify IM011074 remains blinded to investigators, site personnel, and subjects if and when the parent study, IM011021, is unblinded to some members of the BMS study team.
Section 6.7.1, Prohibited and/or Restricted Treatments	The restriction on initiating topical corticosteroid use was removed. NSAID dosing restrictions are reduced during the study.	To reduce the restriction on topical corticosteroids and the need for continuation of NSAIDs in IM011074 if indicated medically.
Section 7.1.2, Post-study Treatment Follow-up	Definitions of the end-of-treatment visit and end-of-study visit for subjects who do not complete the study were clarified.	To clarify, for data analysis purposes, which visits should be considered end-of-treatment and end-of-study for subjects who discontinue early.
Section 8.1.1.5, SLE Responder Index (SRI[4])	The fourth requirement to fulfill the SRI(4) composite endpoint was removed.	To align with the parent protocol and original publication for SRI.
Section 8.2.1 (new), Adverse Events of Interest	A section outlining potential adverse events of interest (AEIs) was added.	To allow for additional information collection throughout the study regarding potential AEIs, which are collected across the BMS-986165 program.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.4.3, Tuberculosis Assessment	Procedures for subjects who are at increased risk for tuberculosis were clarified.	To clarify that subjects who are at increased risk for tuberculosis can potentially roll over into the study from the parent study but must have an interferon gamma release assay (IGRA) at Week 0.
Section 8.4.4, Clinical Safety Laboratory Assessments	The fasting glucose assessment was replaced with nonfasting glucose, and the fasting lipid panel was removed.	To reduce unnecessary inconvenience related to fasting glucose assessment and fasting lipid panel, which are no longer necessary assessments.
Section 9.1, Sample Size Determination	Additional details related to the sample size determination were added.	To add 95% CI information.
Section 9.2, Populations for Analyses	The definition of the 'As-treated' population was clarified to include subjects who took study treatment other than the treatment he or she was assigned.	To clarify data analysis procedures for subjects who did not take the same dose they were assigned.
Appendix 4, Women of Childbearing Potential Definitions and Methods of Contraception	Contraception guidance for female and male subjects was updated.	To align contraception guidance with guidance in the parent study, IM011021, and the sponsor-approved guidelines specific to the BMS-986165 program.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Multi-Center Study to Characterize the Long-Term Safety and Efficacy of BMS-986165 in Subjects with Systemic Lupus Erythematosus

Short Title: Long-Term Safety and Efficacy 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 autoimmune diseases. TYK2 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). 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. 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.

Inhibition of TYK2 is expected to provide therapeutic benefit for subjects with SLE for multiple reasons: 1) The major pathways in the TYK2 signaling cascade (Type 1 IFN and IL-12/23 and the downstream mediators IFNγ and IL-17) have been implicated in SLE disease pathogenesis; 2) It is conceivable that TYK2 inhibition may show improved benefits over existing anti-IFN monoclonal antibody therapies currently in development because of combined blocking effects on both the IL-12/23 and Type 1 IFN pathways.

A Phase 2 study (IM011021) of BMS-986165 in the treatment of SLE is ongoing. This long-term extension (LTE) study will provide additional safety, efficacy, and patient-reported outcome (PRO) data of BMS-986165 in subjects who complete IM011021.

Study Population:

Subjects with SLE who have completed the protocol-required treatment period in BMS-986165 protocol IM011021 will be eligible to participate.

Objectives and Outcome Measures:	
Objective	**Outcome Measure**
Primary	
Safety	
• To characterize the long-term safety and tolerability of BMS-986165 in subjects with SLE	• Adverse events and serious adverse events, vital sign measurements, and laboratory parameters

Objectives and Outcome Measures:	
Objective	**Outcome Measure**
Additional	
Efficacy	

• To characterize the long-term maintenance of response of BMS-986165 in the treatment of subjects with SLE	• CLASI response
	• 40-joint count for tender, swollen, and tender + swollen joints
	• SRI(4) response
	• BICLA response
	• PGA
	• Corticosteroid use (yes/no)
	• Corticosteroid dose ≤ 7.5 mg/day (yes/no)
	• Flare Analysis
	  o Time to first flare
	  o Number and frequency of flares
	  o Flares leading to hospitalization
	• SDI total score
	• BILAG response
	• SLEDAI-2K score
	• LLDAS response

• To characterize patient-reported outcomes in subjects with SLE on long-term BMS-986165 therapy	• PROMIS Fatigue Short Form 7a score
Pharmacokinetic	
• To explore long-term pharmacokinetics of BMS-986165	• Plasma concentrations of BMS-986165
Pharmacodynamic	
• To explore long-term pharmacodynamics of BMS-986165	• dsDNA, CRP, Complement levels, UPCR

BICLA = BILAG-based Composite Lupus Assessment; BILAG = British Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CRP = C-reactive protein; dsDNA = double stranded deoxyribonucleic acid; LLDAS = Lupus Low Disease Activity State; PGA = Physician's Global Assessment; PROMIS = Patient-Reported Outcomes Measurement Information System; SDI = Systemic Lupus Erythematosus International Collaborating Clinics / American College of Rheumatology Damage Index; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLE = systemic lupus erythematosus; SRI(4) = Systemic Lupus Erythematosus Responder Index; UPCR = urine protein/creatinine ratio

Overall Design:

This will be a multi-year, multi-center study to evaluate the long-term safety and tolerability of BMS-986165 in subjects who have completed the Phase 2 SLE study IM011021. Subjects who complete IM011021 through Week 48 will be offered the opportunity to continue to IM011074.

The final treatment visit for IM011021 and the relevant procedures performed, will serve as the Week 0 visit and assessments, respectively, for IM011074. Procedures will not be duplicated between the IM011021 Week 48 treatment visit and the Week 0 visit of this protocol.

In this longitudinal study, qualified subjects from the Phase 2 study IM011021 will receive blinded BMS-986165 at the same oral dose (12 mg once daily [QD], 6 mg twice daily [BID], or 3 mg BID) as the subjects received at the time of completion of IM011021. Those receiving placebo in IM011021 will be randomized 1:1:1 to one of the active blinded treatment doses.

All subjects will return to the clinic for assessments every 4 weeks for the first 12 weeks, with subsequent visits occurring every 12 to 14 weeks through the end of treatment (EOT; Week 174 or early discontinuation). An additional visit will occur at Week 44 to ensure an appropriate comparator visit for the Week 48 efficacy assessments. Investigator- and subject-administered endpoint assessments will be performed at each scheduled clinic visit through the EOT visit (Week 174 or early discontinuation); subjects will return to the clinic 28 days after the EOT visit for a safety follow-up visit. Unscheduled visits will be allowed throughout the study period as needed for additional safety monitoring. Adjustments to subjects' background SLE therapy will be considered after consultation by the investigator with the Medical Monitor(s).

Number of Subjects:

The total number of subjects will be based on the number that complete IM011021 and continue into IM011074.

Treatment Arms and Duration:

Study treatment: Subjects in all treatment groups of the parent study IM011021 that enroll in IM011074 will take oral doses of the investigational product (IP) for the duration of the study as follows: BMS-986165 12 mg QD, BMS-986165 6 mg BID, or BMS-986165 3 mg BID. Those receiving placebo in IM011021 will be randomized 1:1:1 to one of the aforementioned active blinded treatment doses.

Study Treatments for IM011074		
Medication	**Potency**	**IP/Non-IP**
BMS-986165 tablet	3 mg	IP
BMS-986165 tablet	6 mg	IP
BMS-986165 tablet	12 mg	IP
Placebo	n/a	IP

IP = investigational product; n/a = not applicable

Statistical Considerations

Sample Size and Power Determination:

As the primary purpose of this study is to understand the longer term safety of BMS-986165 in patients with SLE who have completed the parent study (IM011021), no formal calculations of sample size and power determination were made. All qualified subjects who complete the final treatment visit from the parent SLE study IM011021 will be eligible to participate.

General Methodology:

The 'as-treated' population will be used to summarize subject data. The 'as-treated' population will include all subjects enrolled in the LTE study who took at least one dose of study treatment during the LTE study.

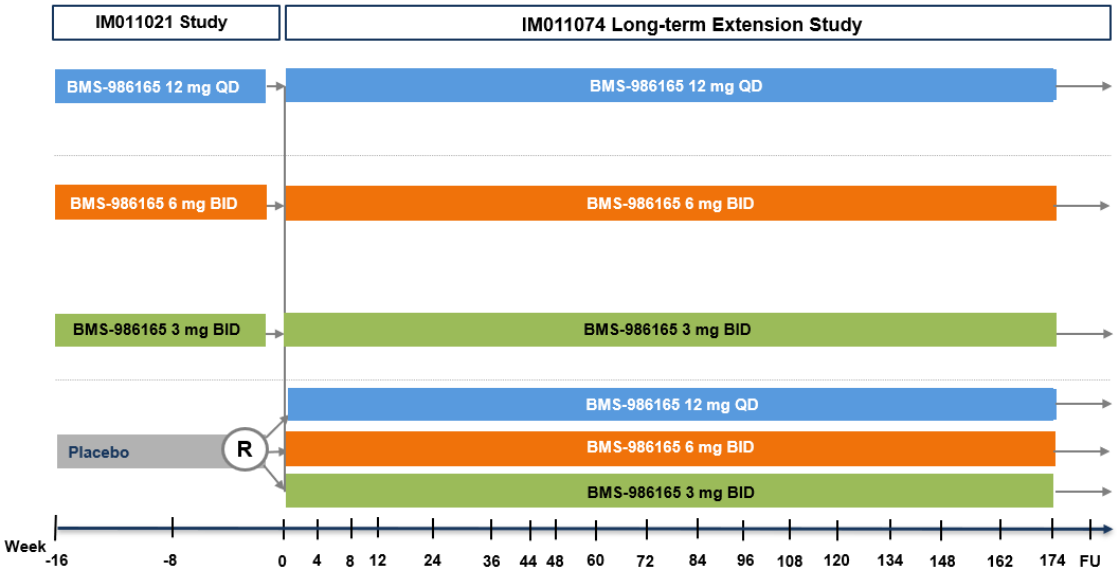
The treatment group 'as-treated' will be the same as the treatment group the subjects were assigned to in this study, except in the following cases:

- If a subject took the same incorrect treatment throughout this study, then the subject will be analyzed based on the treatment received.
- If a subject took study drug from more than one treatment group, and none of the administrations were consistent with the assigned treatment group, then the subject will be analyzed based on the first treatment taken.

Data will be summarized descriptively at each timepoint and by treatment group. Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified.

1.2 Schema

IM011074 Study Design



Abbreviations: BID = twice daily; FU = follow-up; QD = once daily; R = randomize
Note: For illustrative purposes only. Due to the long treatment period, the number of weeks represented and the distances between hashmarks are not to scale.

1.3 Schedule of Activities (SOA)

The schedules of assessments and procedures for Weeks 0 through 96 and Weeks 108 through 174 are documented in Table 1 and Table 2, respectively.

Table 1: On-Treatment Procedural Outline (IM011074): Week 0 through Week 96

Procedure	Wk 0 D1[a]	Wk 4 D29 ±3d	Wk 8 D57 ±3d	Wk 12 D85 ±3d	Wk 24 D169 ±7d	Wk 36 D253 ±7d	Wk 44 D309 ±3d	Wk 48 D337 ±3d	Wk 60 D421 ±7d	Wk 72 D505 ±7d	Wk 84 D589 ±7d	EOT 1[b] Wk 96 D673 or ET ±7d	Notes
Eligibility	X												
Safety Assessments													
Complete Physical Examination	X							X				X	General, head, eyes, ears, nose, throat, neck, CV, lungs, abdominal, extremities, neurologic, psychiatric, skin, musculoskeletal
Targeted Physical Examination		X	X	X	X	X	X		X	X	X		General, eyes, throat, CV, lungs, abdominal, extremities, skin, musculoskeletal, and others as clinically indicated
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	
AE Assessment	X[c]	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication Use	X	X	X	X	X	X	X	X	X	X	X	X	
History of Tobacco Use	X												Include description of current tobacco use
Corticosteroid Use Assessment	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1: On-Treatment Procedural Outline (IM011074): Week 0 through Week 96

Procedure	Wk 0 D1[a]	Wk 4 D29 ±3d	Wk 8 D57 ±3d	Wk 12 D85 ±3d	Wk 24 D169 ±7d	Wk 36 D253 ±7d	Wk 44 D309 ±3d	Wk 48 D337 ±3d	Wk 60 D421 ±7d	Wk 72 D505 ±7d	Wk 84 D589 ±7d	EOT 1[b] Wk 96 D673 or ET ±7d	Notes
Laboratory Tests													
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry Panel	X	X	X	X	X	X	X	X	X	X	X	X	Include CK
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	
UPCR	X	X	X	X	X	X	X	X	X	X	X	X	
Coombs Test (direct)	X	X	X	X	X	X	X	X	X	X	X	X	
Blood samples for hemolysis confirmation	X	X	X	X	X	X	X	X	X	X	X	X	Haptoglobin and reticulocyte count
hs-CRP	X			X	X	X	X	X	X	X	X	X	
TB Questionnaire	X							X				X	IGRA for increased-risk subjects
Pregnancy Test (Urine)	X	X	X	X	X	X	X	X	X	X	X	X	WOCBP only
Biomarker Assessments													
Serum Complement	X	X	X	X	X	X	X	X	X	X	X	X	
Anti-dsDNA autoantibodies	X	X	X	X	X	X	X	X	X	X	X	X	

[redacted]

Table 1: On-Treatment Procedural Outline (IM011074): Week 0 through Week 96

Procedure	Wk 0 D1[a]	Wk 4 D29 ±3d	Wk 8 D57 ±3d	Wk 12 D85 ±3d	Wk 24 D169 ±7d	Wk 36 D253 ±7d	Wk 44 D309 ±3d	Wk 48 D337 ±3d	Wk 60 D421 ±7d	Wk 72 D505 ±7d	Wk 84 D589 ±7d	EOT 1[b] Wk 96 D673 or ET ±7d	Notes
Pharmacokinetic Assessments													See Section 8.5
Blood samples for PK assessments	X	X	X		X			X				X	
Clinical Efficacy/Health Outcomes													
CLASI	X	X	X	X	X	X	X	X	X	X	X	X	
40-joint count	X	X	X	X	X	X	X	X	X	X	X	X	
PGA	X	X	X	X	X	X	X	X	X	X	X	X	
SDI	X				X			X		X		X	
BILAG	X	X	X	X	X	X	X	X	X	X	X	X	
SLEDAI-2K	X	X	X	X	X	X	X	X	X	X	X	X	
PROMIS Fatigue Short Form 7a	X	X	X	X	X	X		X	X	X	X	X	
Study Treatment													
Randomize using IRT	X												Only subjects on placebo in IM011021 will be rerandomized
Dispense Blinded Study Treatment	X	X	X	X	X	X	X	X	X	X	X	X	
Study Treatment Compliance		X	X	X	X	X	X	X	X	X	X	X	

AE = adverse event; BILAG = British Isles Lupus Assessment Group; CK = creatine kinase; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CV = cardiovascular; D = Day; d = days; DNA = deoxyribonucleic acid; dsDNA = double stranded deoxyribonucleic acid; EOS = end of study; EOT = end of treatment; ET = early termination; hs-CRP = high-sensitivity C-reactive protein; IGRA = interferon gamma release assay; IRT = interactive response technology; PGA = Physician's Global Assessment; PK = pharmacokinetic; PROMIS = Patient-Reported Outcomes Measurement Information System; [redacted]

[redacted]; SDI = Systemic Lupus Erythematosus Damage Index; SLEDAI 2K = Systemic Lupus Erythematosus Disease Activity Index 2000; TB = tuberculosis; UPCR = urine protein/creatinine ratio; Wk = week; WOCBP = women of childbearing potential

[a] This is the same visit as the EOT visit in IM011021. Any assessments that overlap between IM011074 and IM011021 will not be repeated.

[b] Unless they withdraw consent for follow-up, subjects who discontinue treatment prior to Week 96 should attend the EOT 1 visit, and then the EOS/follow-up visit shown in Table 2 28 days (±3 days) later.

[c] Events that are ongoing at the time subject signs the informed consent will be reported as AEs. Events reported during IM011021 that have resolved will be considered medical history in IM011074.

Table 2: On-Treatment Procedural Outline (IM011074): Week 108 through Week 174

Procedure	Wk 108 D757 ±7d	Wk 120 D841 ±7d	Wk 134 D939 ±7d	Wk 148 D1037 ±7d	Wk 162 D1135 ±7d	Wk 174 D1219 EOT 2[a] or ET ±7d	FU/EOS Wk 178 D1247 (28d ±3d after EOT)	Notes
Safety Assessments								
Complete Physical Examination	X					X	X	General, head, eyes, ears, nose, throat, neck, CV, lungs, abdominal, extremities, neurologic, psychiatric, skin, musculoskeletal
Targeted Physical Examination		X	X	X	X			General, eyes, throat, CV, 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	
AE Assessment	X	X	X	X	X	X	X	
Concomitant Medication Use	X	X	X	X	X	X	X	
Corticosteroid Use Assessment	X	X	X	X	X	X	X	
Laboratory Tests								
Hematology	X	X	X	X	X	X	X	
Chemistry Panel	X	X	X	X	X	X	X	Include CK
Urinalysis	X	X	X	X	X	X	X	
UPCR	X	X	X	X	X	X		
Coombs Test (direct)	X	X	X	X	X	X		
Blood samples for hemolysis confirmation	X	X	X	X	X	X	X	Haptoglobin and reticulocyte count

Table 2: On-Treatment Procedural Outline (IM011074): Week 108 through Week 174

Procedure	Wk 108 D757 ±7d	Wk 120 D841 ±7d	Wk 134 D939 ±7d	Wk 148 D1037 ±7d	Wk 162 D1135 ±7d	Wk 174 D1219 EOT 2[a] or ET ±7d	FU/EOS Wk 178 D1247 (28d ±3d after EOT)	Notes
hs-CRP	X	X	X	X	X	X		
TB Questionnaire			X			X		IGRA for increased-risk subjects
Pregnancy Test (Urine)	X	X	X	X	X	X	X	WOCBP only
Biomarker Assessments								
Serum Complement	X	X	X	X	X	X	X	
Anti-dsDNA autoantibodies	X	X	X	X	X	X	X	
Clinical Efficacy/Health Outcomes								
CLASI	X	X	X	X	X	X		
40-joint count	X	X	X	X	X	X		
PGA	X	X	X	X	X	X		
SDI		X		X		X		
BILAG	X	X	X	X	X	X		
SLEDAI-2K	X	X	X	X	X	X		
PROMIS Fatigue Short Form 7a	X	X	X	X	X	X		
Study Treatment								
Dispense Blinded Study Treatment	X	X	X	X	X			
Study Treatment Compliance	X	X	X	X	X	X		

AE = adverse event; BILAG = British Isles Lupus Assessment Group; CK = creatine kinase; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CV = cardiovascular; D = Day; d = days; dsDNA = double-stranded deoxyribonucleic acid; EOS = end of study; EOT = end of treatment; ET = early termination; FU = follow-up; hs-CRP = high-sensitivity C-reactive protein; IGRA = interferon gamma release assay; PGA = Physician's Global Assessment;

PROMIS = Patient-Reported Outcomes Measurement Information System; SDI = Systemic Lupus Erythematosus Damage Index; SLEDAI 2K = Systemic Lupus Erythematosus Disease Activity Index 2000; TB = tuberculosis; UPCR = urine protein/creatinine ratio; Wk = week; WOCBP = women of childbearing potential

[a] Unless they withdraw consent for follow-up, subjects who discontinue treatment prior to Week 174 but after Week 96 should attend the EOT 2 visit and the EOS/follow-up visit.

2 INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic progressive autoimmune disease characterized by pleiotropic organ/tissue involvement and clinical manifestations which 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. Current therapies are unsatisfactory and include immunosuppressive drugs and corticosteroids, 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. Tyrosine kinase 2 (TYK2) inhibitors would be expected to demonstrate good efficacy in SLE by blocking multiple pathways involved in its pathogenesis and fill an unmet need for novel, well-tolerated orally administered therapies.

2.1 Study 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 autoimmune diseases. TYK2 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, 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 SLE) and in healthy humans.[5, 6]

Inhibition of TYK2 is expected to provide therapeutic benefit for subjects with SLE for multiple reasons: 1) The major pathways in the TYK2 signaling cascade (Type 1 IFN and IL-12/23 and the downstream mediators IFNγ and IL-17) have been implicated in SLE disease pathogenesis[7]; 2) It is conceivable that TYK2 inhibition may show improved benefits over existing anti-IFN monoclonal antibody therapies currently in development because of combined blocking effects on both the IL-12/23 and Type 1 IFN pathways.[8]

A Phase 2 study of BMS-986165 (IM011021) in the treatment of SLE is ongoing. This long-term extension (LTE) study will provide additional safety, efficacy, and patient-reported outcome (PRO) data of BMS-986165 in subjects participating in IM011021.

2.2 Background

TYK2 is a nonreceptor tyrosine kinase associated with receptors for the p40 containing cytokines IL-12 and IL-23, as well as the Type I IFN receptor, and is required for the activation of their downstream signaling pathways. TYK2 catalyzes the phosphorylation of the intracellular receptor domains and STAT proteins resulting in the activation of STAT-dependent transcription and functional responses specific for these cytokines.[1, 2, 3] Because TYK2-dependent cytokines (eg,

Type I IFNs, IL-12, IL-23) are distinct from those dependent on closely related Janus kinase (JAK) family members JAK1/JAK3 (eg, IL-2, IL-15, IL-7) or JAK2 (eg, erythropoietin, thrombopoietin, GM-CSF), a TYK2 inhibitor would be expected to have a highly differentiated profile from inhibitors of other JAK family kinases. TYK2-dependent pathways and the cytokine networks they modulate (eg, IL-23/IL-17, IFNα) have been implicated in the pathophysiology of multiple immune-mediated diseases, including psoriasis, SLE, spondyloarthritides, and Crohn's disease.

2.2.1 Early Clinical Development

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

Overall, BMS-986165 has been generally well-tolerated across all studies, and no safety issues have been identified to limit the investigation of BMS-986165 in further clinical studies. 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

The dose selection of BMS-986165 for this study is based on the doses used in the Phase 2 study IM011021. At this 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, the Phase 2 study in patients with moderate-to-severe plaque psoriasis (IM011011)[9], and within exposure margins based on comparisons of systemic exposure and body surface area (BSA).

In a Phase 2 study of subjects with moderate-to-severe plaque psoriasis (Study IM011011), BMS-986165 was generally safe and well-tolerated. The most common adverse events (AEs) reported by subjects were nasopharyngitis, upper respiratory tract infection, headache, diarrhea, and nausea. Most of the AEs reported in the study were mild or moderate in intensity. There were 8 reversible events of mild to moderate nature of acne that were dose-related (4 at 12 mg once daily [QD], 2 at 6 mg twice daily [BID], 1 at 3 mg BID, and 1 at 3 mg every other day). There were 7 events of localized oral or nasal herpes simplex lesions that appeared to be dose-related (4 at 12 mg QD, 2 at 6 mg BID, and 1 at 3 mg BID). No reports of herpes zoster were noted in this study. A total of 6 subjects had creatine kinase (CK) elevations of Grade 3 or higher with no clear dose dependence and the CK elevations were temporally associated with increased physical activity by the subjects, and thus unlikely to be drug related. No drug-related changes were observed in lymphocyte subsets, neutrophils, red blood cells, or cholesterol, which are markers of off-target activity on JAK family members JAK1-3, thus supporting the selectivity of BMS-986165.

At the maximum concentrations expected in this study (in portal vein or systemic circulation, as appropriate), the potential for drug-drug interactions (DDIs) involving cytochrome P450 (CYP450) enzymes and most transporters is low. BMS-986165 has low turnover in in vitro

metabolism studies, and a number of enzymes are involved in the metabolism of the fraction metabolized. Additionally, BMS-986165 is not an inhibitor or inducer of CYP450 enzymes at the expected clinical concentrations. Therefore, the potential for DDIs resulting from CYP450 inhibition or induction is low. BMS-986165 is a breast cancer resistance protein (BCRP) inhibitor with an in vitro half-maximal inhibitory concentration (IC50) = 0.31 μM. However, due to overlapping substrate specificity between BCRP and other transporters not affected by BMS-986165 at the expected concentrations, the impact of BMS-986165 on the exposures of potential comedications that are BCRP substrates, such as rosuvastatin, was also expected to be low. This was confirmed in the IM011015 DDI study where co-administration of BMS-986165 12 mg QD and rosuvastatin 10 mg had no impact on the exposure of rosuvastatin, a BCRP, and organic-anion-transporting polypeptide substrate.

Nonclinical data and clinical experience in both healthy subjects, and those with psoriasis in combination with the design and doses selected for the current LTE 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 OUTCOME MEASURES

Table 3: Objectives and Outcome Measures

Objective	Outcome Measure
Primary	
Safety	
• To characterize the long-term safety and tolerability of BMS-986165 in subjects with SLE	• Adverse events and serious adverse events, vital sign measurements, and laboratory parameters
Additional	
Efficacy	
• To characterize the long-term maintenance of response of BMS-986165 in the treatment of subjects with SLE	• CLASI response • 40-joint count for tender, swollen, and tender + swollen joints • SRI(4) response • BICLA response • PGA • Corticosteroid use (yes/no) • Corticosteroid dose ≤ 7.5 mg/day (yes/no) • Flare Analysis ○ Time to first flare

Table 3: Objectives and Outcome Measures

Objective	Outcome Measure
	○ Number and frequency of flares ○ Flares leading to hospitalization • SDI total score • BILAG response • SLEDAI-2K score • LLDAS response
• To characterize patient-reported outcomes in subjects with SLE on long-term BMS-986165 therapy	• PROMIS Fatigue Short Form 7a score
Pharmacokinetic	
• To explore long-term pharmacokinetics of BMS-986165	• Plasma concentrations of BMS-986165
Pharmacodynamic	
• To explore long-term pharmacodynamics of BMS-986165	• dsDNA, CRP, Complement levels, UPCR

BICLA = BILAG-based Composite Lupus Assessment; BILAG = British Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CRP = C-reactive protein; dsDNA = double stranded deoxyribonucleic acid; LLDAS = Lupus Low Disease Activity State; PGA = Physician's Global Assessment; PROMIS = Patient-Reported Outcomes Measurement Information System; SDI = Systemic Lupus Erythematosus International Collaborating Clinics / American College of Rheumatology Damage Index; SLE = Systemic Lupus Erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SRI(4) = Systemic Lupus Erythematosus Responder Index; UPCR = urine protein/creatinine ratio

4 STUDY DESIGN

4.1 Overall Design

This will be a double-blind, multi-year, multi-center study to evaluate the long-term safety and tolerability of BMS-986165 in subjects who have completed the double-blind treatment period of the Phase 2 SLE study IM011021. The blinding to study treatment employed in Study IM011021 will be maintained in this study. Physical exams, clinical laboratory evaluations, and other assessments will be done at select visits during the study. Subjects will be monitored for AEs, and blood samples will be collected for biomarker and PK analysis.

Investigator- and subject-administered endpoint assessments will be performed at each scheduled clinic visit (Table 1 and Table 2) through the end-of-treatment (EOT) visit (Week 174 or early discontinuation); subjects will return to the clinic 28 days after the EOT visit for a safety follow-up visit. Unscheduled visits will be allowed throughout the study period as needed for additional safety monitoring. Adjustments to subjects' background SLE therapy will be considered after consultation by the investigator with the Medical Monitor(s).

The study design schematic is presented in Figure 1.

4.1.1 Qualification

At the final treatment visit (Week 48) for the parent SLE study IM011021, the end of study procedures will be performed per protocol. Subjects who successfully complete the protocol-required treatment period will be offered the opportunity to continue to the LTE study. The final treatment visit for IM011021 (Week 48) will be the Week 0 visit in IM011074. Refer to Table 1 in the Schedule of Activities (SOA). Prior to enrollment into IM011074, the investigator will ensure the following:

1) subjects remain qualified for continued long-term participation based on the inclusion and exclusion criteria from Sections 5.1 and 5.2
2) subjects in IM011021 remain blinded to current treatment prior to enrollment into the LTE

Relevant laboratory data, along with clinical and PRO assessments from the final treatment visit (Week 48) in IM011021 will not be repeated at the Week 0 visit.

Any assessments specific to IM011074 will be performed prior to assignment of IM011074 study drug.

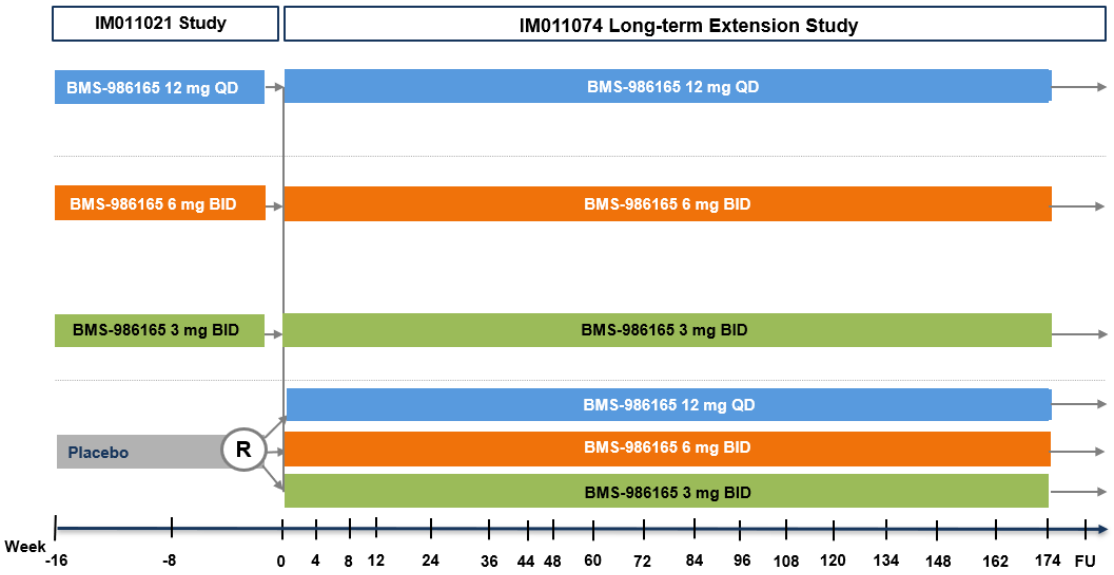
4.1.1.1 Treatment Allocation

Qualified subjects from IM011021 will receive blinded BMS-986165 at the same dose as they received at the time of study completion. Qualified subjects receiving placebo in IM011021 will be randomized 1:1:1 to one of the following active blinded treatment doses:

- BMS-986165 12 mg orally (po) QD
- BMS-986165 6 mg po BID
- BMS-986165 3 mg po BID

Subjects will return to the clinic for assessments every 4 weeks for the first 12 weeks to characterize safety and tolerability and efficacy response. Clinic visits will be reduced to every 12 to 14 weeks thereafter through EOT (Week 174 or early discontinuation). An additional visit will occur at Week 44 to ensure an appropriate comparator visit for the Week 48 efficacy assessments. Subjects and investigators will remain blinded to the treatment in both the IM011021 parent study and IM011074. The study design schematic is presented in Figure 1.

Figure 1: IM011074 Study Design



BID = twice daily; FU = follow-up; QD = once daily; R = randomize

Note: For illustrative purposes only. Due to the long treatment period, the number of weeks represented and the distances between hashmarks are not to scale.

4.1.2 Data Monitoring Committee [redacted]

4.1.2.1 Data Monitoring Committee

An external data monitoring committee (DMC) with multi-disciplinary representation will be used during the study to evaluate AEs, laboratory measurements, and safety assessments to ensure the ongoing safety of study subjects. An independent reporting statistician not involved in the conduct of the study will be designated by PRA to provide the DMC with essential safety data during the study.

The DMC responsibilities, authorities, and procedures will be documented and followed according to the DMC charter.

[redacted]

4.2 Number of Subjects

The total number of subjects will be based on the number that complete IM011021 and continue into IM011074.

4.3 End of Study Definition

The maximal duration of study participation for individual subjects is expected to be approximately 178 weeks.

The start of the study is defined as first visit for first subject completing their parent SLE study and enrolling into the IM011074 study. The end of the study is defined as the last visit or scheduled procedure shown in the SOA (Section 1.3) for the last subject. Study completion is defined as the final date on which data were or are expected to be collected (plus 4 additional weeks for collection of potential serious AEs [SAEs]).

4.4 Scientific Rationale for Study Design

The primary purpose of the study is to observe the long-term safety and tolerability of BMS-986165 in the treatment of subjects with SLE. All subjects will be permitted to continue their background therapies for SLE used in IM011021, 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.

4.5 Justification for Dose

Subjects will receive the same dose as in IM011021. Those who were receiving placebo in IM011021 will be randomized to one of the 3 active treatments. See Section 4.1.1.1.

5 STUDY POPULATION

Eligibility criteria for this study have been carefully considered to ensure: 1) safety of the study subjects and 2) potential benefit to subjects. It is imperative that subjects fully meet all eligibility criteria.

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) Subjects must be willing to participate in the LTE study and must have the ability to sign the informed consent form (ICF).
2) **Type of Subject and Target Disease Characteristics**
   a) Completion of Study IM011021 through the protocol-required treatment period, and currently receiving blinded study drug. Note: If a subject is not receiving blinded study drug due to exceptional circumstances (eg, missed investigational product [IP] due to COVID-19 pandemic, delays in study approval, etc), the subject may be allowed to enroll with approval from the BMS Clinical Trial Physician or designee.
3) **Reproductive Status**
   a) Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) within 24 hours prior to the start of study drug.

b) Women must not be pregnant, lactating, breastfeeding, or planning pregnancy during the study period.

c) WOCBP must agree to use correctly a highly effective or less than highly effective method(s) of contraception for the duration of treatment with study drug(s) BMS-986165 plus 5 half-lives of study drug (3 days) plus 30 days (duration of ovulatory cycle) for a total of 33 days post-treatment completion (total of 33 days after last dose of study drug). WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements, but must still undergo pregnancy testing as described in this protocol Appendix 4.

d) Male subjects 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.

e) Azoospermic males are exempt from contraceptive requirements.

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

5.2 Exclusion Criteria

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

1) Medical History and Concurrent Diseases

a) Any disease or medical condition that, in the opinion of the investigator, would make the subject unsuitable for this study, would interfere with the interpretation of subject safety or study results, or considered unsuitable by the investigator for any other reason.

2) Findings Related to Possible Tuberculosis (TB) Infection

a) Evidence of active TB

5.3 Lifestyle Restrictions

No restrictions are required. However, general skin care measures that are standard for patients with SLE are recommended 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.

5.3.1 Meals and Dietary Restrictions

Study treatment may be taken without regard to meals.

5.3.2 Caffeine, Alcohol and Tobacco

No restrictions are required.

5.3.3 Activity

No restrictions are required.

6 TREATMENT

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

Study treatment includes Investigational [Medicinal] Product (IP/IMP) and can consist of the following: BMS-986165 and placebo.

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 preventive, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-IP. Table 4 shows the study treatments for Protocol IM011074.

Table 4: Study Treatments for IM011074

Product Description / Class and Dosage Form	Active Treatment Potency	IP/ Non-IMP	Blinded or Open-Label	Packaging / Appearance	Storage Conditions (per label)
BMS-986165 tablet Placebo tablet to match BMS-986165 6 mg and 12 mg	3 mg	IP	Blinded	Blister card containing 45 tablets (Active 3 mg BMS-986165) and placebo tablets to match 6 mg and 12 mg (5 tablets per day)	Store at 15 to 25°C; Protect from light
BMS-986165 tablet Placebo tablet to match BMS-986165 3 mg and 12 mg	6 mg	IP	Blinded	Blister card containing 45 tablets (Active 6 mg BMS-986165) and placebo tablets to match 3 mg and 12 mg (5 tablets per day)	Store at 15 to 25°C; Protect from light
BMS-986165 tablet Placebo tablet to match BMS-986165 3 mg and 6 mg	12 mg	IP	Blinded	Blister card containing 45 tablets (Active 12 mg BMS-986165) and placebo tablets to match 3 mg and 6 mg (5 tablets per day)	Store at 15 to 25°C; Protect from light

IMP = investigational medicinal product; IP = investigational product

6.1 Treatments Administered

Study treatment will be supplied in blister card kits. Each blister card will contain a nine-day supply of 45 tablets arranged into sets where 3 tablets are taken in the morning and 2 tablets are taken in the evening, approximately 12 hours apart. For example, a subject in the 12-mg arm would take an active 12-mg tablet and 2 placebo tablets (to match 3 mg and 6 mg) in the morning, and 2 placebo tablets (to match 3 mg and 6 mg) in the evening. Complete dosing information for each treatment group is provided in Table 5.

Table 5: 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	12 mg	1 active tablet and 2 placebo tablets in the morning, and 2 placebo in the evening	Oral
6 mg BID BMS-986165	6 mg	1 active tablet and 2 placebo tablets in the morning, and 1 active tablet and 1 placebo tablet in the evening	Oral
3 mg BID BMS-986165	3 mg	1 active tablet and 2 placebo tablets in the morning, and 1 active tablet and 1 placebo tablet in the evening	Oral

BID = twice daily; QD = once daily

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.

6.2 Method of Treatment Assignment

Before the study is initiated, each user (at investigative sites) will receive log-in information and directions on how to access the interactive response technology (IRT) system. At the time of the first visit in IM011074, immediately after informed consent is obtained and before any study-related procedures are performed, the investigative site will access the enrollment option of the IRT system for assignment of a subject number for all subjects. The subject number is assigned sequentially by the system and will be unique across all sites. All enrolled subjects will be assigned sequential subject numbers. The subject number will not be used for any other subject. For continuity purposes, the subject number from the parent study will be recorded for each subject enrolled in IM011074.

All subjects who were receiving placebo in the parent study will be centrally randomized in a 1:1:1 ratio to BMS-986165 12 mg QD, 6 mg BID or 3 mg BID as determined by a computer-generated randomization schedule using IRT. All subjects who were on active treatment in the parent study will be reallocated to the same treatment regimen in a blinded fashion. A treatment group will be assigned by IRT based on the above-described randomization schedule and each subject will be assigned a unique randomization number regardless of treatment group in the parent study.

In addition, a kit number will be assigned to the subject corresponding to the treatment assignment. The kit will be comprised of blister cards as described in Section 6.1. At subsequent visits, when new

treatment kits need to be provided, the investigative site will access IRT to obtain the kit number to assign to the subject.

The investigator will confirm subject eligibility based on criteria in Section 5.

6.3 Blinding

6.3.1 Maintaining the Blind

Blinded treatment assignments will be managed using IRT. IP supply will be controlled by IRT at each visit.

Tablets of each potency of BMS-986165 and its matching placebo are identical in appearance and will be supplied in blister cards with each daily dose made up of the appropriate combination of active and/or placebo capsules/tablets to provide the correct treatment, as shown in Table 5. Investigative site staff, Sponsor and designee personnel, and subjects and their families will remain blinded to treatment assignments.

6.3.2 Circumstances for Unblinding

Blinding of treatment assignment is critical to the integrity of this clinical study and the parent study (IM011021). 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 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.

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 Medical Monitor and/or Clinical Trial Physician. The method of unblinding for emergency purposes is described in the IRT manual. Subject and unblinded treatment 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 Medical Monitor.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind for subject, all other site personnel and the Sponsor/PRA personnel. Any request to unblind a subject for nonemergency purposes must be discussed with the Medical Monitor prior to unblinding.

After database lock of the parent study, certain members of the BMS study team will be partially unblinded to treatment assignments of some subjects in the current study (ie, those subjects who were receiving BMS-986165 in the parent study). An unblinding plan will be created prior to database lock of the parent study. Investigators, site personnel, and subjects in both studies will remain blinded to treatment assignment.

Designated staff of Bristol-Myers Squibb Company may be unblinded (obtain the randomization codes) prior to database lock to facilitate the bioanalytical analysis of pharmacokinetic samples and immunogenicity. 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.

If a subject is unblinded for any reason, the subject will be discontinued from treatment.

6.4 Dosage Modification

There is no provision for dose-modification of study treatment. If a subject interrupts treatment due to an AE, study treatment can be restarted in consultation with the 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 the 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 product storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by Bristol-Myers Squibb (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.

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

IP 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).

- Guidance and information for final disposition of unused study treatment are provided in Appendix 2.

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 tablets 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

6.7.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications during the study are described below.

1) Exposure to any investigational drug or placebo outside of the current study is prohibited.
2) Rescue therapy other than prednisone or equivalent is prohibited.
3) Use of intramuscular, intra-articular, intrabursal, and intravenous corticosteroids is prohibited. Modified-release corticosteroid formulations are prohibited.
4) Extended-release formulations of nonsteroidal anti-inflammatory drugs (NSAIDs) are prohibited. No more than any one type of oral NSAID may be used during the study. NSAID dosing may be decreased or discontinued.
5) Use of cyclophosphamide (including ophthalmic) or any biologic agent is prohibited.
6) Live vaccines are prohibited during the study or within 2 months after the last dose. Heat killed, or otherwise inactivated or protein vaccines such as influenza, COVID-19, 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.

The investigator should contact and confirm agreement with the Medical Monitor prior to the administration of any concomitant medications.

6.7.2 Permitted Concomitant Medications

Stable doses of concomitant medication for chronic medical conditions are permitted as long as neither the medication nor the medical condition meet exclusion criteria as detailed in Section 5.2. Dose adjustments of these medications should be avoided during the study unless clinically indicated. If a dose adjustment of these medications should occur, they must be recorded on the Concomitant Medications eCRF or the Diagnostic and Medical Procedures eCRF. The investigator should instruct the subject to notify the study site about any new treatments he/she takes after the start of the study treatment. All medications and significant nondrug therapies (including physical therapy and blood transfusions) administered after the subject starts study treatment must be listed on the Concomitant Medications eCRF or the Diagnostic and Medical Procedures eCRF.

6.7.3 Existing Therapies for Systemic Lupus Erythematosus

All subjects will continue their existing concomitant SLE treatment(s) from IM011021 during the IM011074 study. The dose and regimen of background SLE treatments should not change during study participation unless approved by the Medical Monitor.

6.7.4 Corticosteroid Treatment

Subjects may continue on existing corticosteroids from the parent study. (Note restrictions in Section 6.7.1.) Corticosteroids may be tapered during the study. For increased SLE disease activity per investigator judgment, subjects may receive 1 burst of oral corticosteroids within the first 8 weeks

of IM011074. Subsequently, 1 burst every 6 months is allowed. If additional bursts are needed, the Medical Monitor should be contacted. The burst must not exceed 40 mg/day prednisone or equivalent and must return within 7 days to the previous corticosteroids dose used before the burst.

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.

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment. Study treatment will be provided via an extension of the study, another rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS supplied study 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 IP (and non-IP at the discretion of the investigator) for any of the following reasons:

- 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 clinically significant AE, laboratory abnormality, or intercurrent illness, which in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject. If treatment is discontinued due to an AE, the AE eCRF must be completed to show that the AE caused discontinuation.
- Abnormal liver tests suggestive of drug-induced liver injury (DILI), as defined in Section 8.2.8 or if the investigator believes that it is in the best interest of the subject
- The subject develops a malignancy, with the exception of a subject who develops nonmelanoma skin cancer who may continue in the study at the discretion of the investigator
- Pregnancy, positive pregnancy test, or subject expresses an interest in becoming pregnant (refer to Section 8.2.6)
- Subject develops active TB during the study or prematurely discontinues treatment for latent tuberculosis infection (LTBI), or subject is noncompliant with LTBI therapy (refer to Section 8.4.3)
- Termination of the study or program by BMS
- Unblinding of a subject's treatment assignment for any reason (emergency or nonemergency)

- Inability or failure to comply with protocol requirements in the opinion of the investigator
- Loss of ability to provide consent without undue influence through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness

Refer to the SOA (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.

All subjects who discontinue BMS-986165 prior to Week 96 should complete the EOT 1 visit (Table 1); all subjects who discontinue BMS-986165 after Week 96 but prior to Week 174 should complete the EOT 2 visit (Table 2); 28 days (±3 days) after the appropriate EOT visit, all subjects should proceed to the 28-day safety follow-up visit with protocol-specified follow-up procedures as outlined in Table 2. 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). Replacement of subjects 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.

7.1.1 Temporary Discontinuation of Study Medication

Temporary study treatment discontinuation is only allowed if the subject develops an AE which, in the opinion of the investigator, indicates that it is in the subject's best interest that the study treatment be placed on hold. Study treatment in this situation should be stopped for no longer than 30 days until the AE is medically treated and has resolved per principal investigator's judgment.

Any temporary study treatment discontinuation as well as restart must be documented on the corresponding eCRF.

7.1.2 Post-study Treatment Follow-up

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 outcomes and/or survival follow-up data as required and in line with Section 4 until death or the conclusion of the study.

Subjects who discontinue study treatment should be encouraged to complete the appropriate EOT visit (EOT 1 or EOT 2; see Section 7.1) and proceed to the 28-day safety follow-up visit.

If the subject completes the EOT visit, the date of the EOT visit is the subject's EOT date, and the 28-day follow-up visit is the subject's end-of-study (EOS) date. If a subject discontinues treatment early, the EOT date is the date of the subject's last dose, and the EOS date is the date of the 28-day safety follow-up EOS visit. If a discontinued subject withdraws consent for further visits or follow-up, both the EOT and EOS date are the date of the subject's last dose.

7.2 Discontinuation from the Study

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures as specified in Section 1.3. 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 case report form (CRF) page.
- In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- 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 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 **three** documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records.
- If it is determined that the subject has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the SOA (Section 1.3) and described in Section 4.1.
- Protocol waivers or exemptions are not allowed.
- All significant safety concerns must be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue treatment.

- Adherence to the study design requirements, including those specified in the SOA (Section 1.3), is essential and required for study conduct.
- Procedures conducted as part of the subject's EOT visit from the parent study and obtained before signing of informed consent may be utilized for Week 0 purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the SOA (Section 1.3).
- The term "baseline" refers to the baseline visit of the parent study, IM011021.
- For several assessments, appropriate training will be provided to investigators at sites. Only those individuals trained and certified to perform these assessments will be performing them during the study.

8.1 Efficacy Assessments

For new investigators and site staff added since the parent study, 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.

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.

8.1.1 Investigator-Administered Assessments

8.1.1.1 British Isles Lupus Assessment Group (BILAG)-2004

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 for SLE disease activity, 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). An example is provided in Appendix 5.

8.1.1.2 Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)

The SLEDAI-2K is a global index based on weighted scores for each of 24 clinical findings rated as present or absent due to SLE disease activity at the time of the visit or in the last 30 days.[10, 11] The SLEDAI-2K assigns relative weights to each parameter (see Appendix 6).

8.1.1.3 Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)

The CLASI assesses cutaneous disease activity by BSA; 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 (see Appendix 7).

8.1.1.4 40-joint Count

A 40-joint count 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).[12, 13, 14] 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 related to SLE disease activity.

8.1.1.5 SLE Responder Index (SRI[4])

The SRI(4) is a composite endpoint that defines a responder as a patient whose disease course fulfills all of the following[15]:

- A ≥4-point reduction from baseline in SLEDAI-2K score[10, 11] (Appendix 6)
- No new BILAG A (severe disease activity) and 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

8.1.1.6 BILAG-based Composite Lupus Assessment (BICLA)

BICLA response is defined as follows[16]:

- Improvement in all organ systems with BILAG-2004 activity defined as all A scores at baseline improved to B, C, or D; and all B scores at baseline improved to C or D
- 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 visual analog scale (VAS)
- No discontinuation of IP or use of restricted medications beyond the protocol allowed threshold before assessment

8.1.1.7 Physician's Global Assessment (PGA) of Disease Activity

The PGA represents the physician's overall assessment of average SLE disease severity over the last 4 weeks assessed using a 3-point VAS (see Appendix 8).

8.1.1.8 SLE Flares

SLE flares are compared with the previous visit and defined as follows:

- Severe flare: Any new or recurrent BILAG-2004 A grade in any body system due to items that are scored new or worse
- Moderate flare: ≥ 2 new or recurrent B grades that are due to items scored new or worse
- Mild flare: 1 new or recurrent B grade due to items that are scored new or worse; or ≥ 3 new or recurrent C grades due to items that are scored new or worse
- No flare: Meeting none of the criteria for mild, moderate, or severe

8.1.1.9 Systemic Lupus Erythematosus International Collaborating Clinics / American College of Rheumatology Damage Index (SDI)

The SDI[17] assesses damage based on a weighted scoring system for assessments in the following areas: ocular, neuropsychiatric, renal, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, skin, gonadal, endocrine, and malignancy. Damage is defined as nonreversible change, not related to active inflammation, occurring since the onset of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes must occur at least 6 months apart to score 2. The same lesions cannot be scored twice. An example is provided in Appendix 9.

8.1.1.10 Lupus Low Disease Activity State (LLDAS)

LLDAS[18, 19] 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.

8.1.2 Subject-Reported Assessments

8.1.2.1 Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue

The Patient-Reported Outcomes Measurement Information System (PROMIS™) provides item banks that offer the potential for PRO measurement that is efficient (minimizes item number without compromising reliability), flexible (enables optional use of interchangeable items), and precise (has minimal error in estimate) measurement of commonly-studied PROs.[20, 21, 22, 23, 24]

In the health outcomes measurement perspective, fatigue is defined as an overwhelming, debilitating, and sustained sense of exhaustion that decreases one's ability to carry out daily activities, including the ability to work effectively and to function at one's usual level in family or social roles. Similar subjective feelings, yet fewer behavioral impacts, are associated with lower levels of fatigue. Fatigue is divided conceptually into the experience of fatigue (such as its intensity, frequency, and duration), and the impact of fatigue upon physical, mental, and social activities.

The fatigue item bank consists of 95 items assessing the intensity, frequency, and impact of fatigue. Most PROMIS items employ response scales with 5 options. A 7-item short form showed strong correlation with the full bank, and used the following questions. A 7-day recall is applied because there is reasonably high correspondence between real-time symptom reports and 7-day recall of the same symptoms.

An example is provided in Appendix 10.

8.2 Adverse Events

The definitions of an AE and SAE can be found in Appendix 3.

All AEs 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 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.

Contacts for SAE reporting are specified in Appendix 3.

8.2.1 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. AEIs 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 will be collected on the eCRF in order to better characterize and understand them.

8.2.2 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until the follow-up visit at 28 days after EOT, at the timepoints specified in the SOA (Section 1.3).

Section 5.6 in the IB represents the Reference Safety Information to determine 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 drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs and AEs related to SARS-CoV-2 infection must be collected from the date of subject's written consent until 30 days after the final dose of the study drug or subject's participation in the study if the last scheduled visit occurs at a later time. Monitoring for SAEs will occur at every study visit.

- The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug 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 CRF.

- 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.

8.2.3 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs).

8.2.4 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 reactionsand 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 and AES related to COVID-19 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 7.3).

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

8.2.5 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 IRB/IEC, if appropriate according to local requirements.

The Sponsor or a 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 (FDA) Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

8.2.6 Pregnancy

In the event a subject becomes pregnant during the trial, the study treatment must be discontinued immediately. If the subject becomes pregnant while on treatment or within 3 days of discontinuing study treatment, the investigator must immediately notify the PRA Drug Safety department of this event and complete and forward a Pregnancy Surveillance Form to PRA Drug Safety within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3. The investigator must also notify the Medical Monitor or designee of this event within 24 hours of awareness of pregnancy.

The pregnant subject will need to be followed up until the conclusion of the pregnancy for pregnancy outcomes. The safety data of the subject will continue to be collected under the same rules as instructed in Section 7.1.

Any pregnancy that occurs in a female partner of a male study subject should be reported to PRA Drug Safety. In order 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.

8.2.7 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE electronic 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 vs low hemoglobin value).

8.2.8 Potential Drug-Induced Liver Injury (DILI)

All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 8.2 and Appendix 3 for reporting details). Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event.

Potential DILI is defined as:

1) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation >3 times upper limit of normal (ULN)

AND

2) Total bilirubin >2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3) No other immediately apparent possible causes of liver function test 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.

8.2.9 Other Safety Considerations

Any significant worsening of a preexisting medical condition noted during interim or final physical examination, x-ray filming, or 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.

8.3 Overdose

For this study, taking > 24 mg of study drug within a 24-hour time period will be considered an overdose. If a subject has frequent or longer durations of taking more than the specified doses, the investigator should discuss the situation with the Medical Monitor.

In the event of an overdose the investigator should:

1) Contact the Medical Monitor immediately
2) Closely monitor the subject for AEs/SAEs and laboratory abnormalities

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

8.4 Safety

Planned time points for all safety assessments are listed in the SOA (Section 1.3).

8.4.1 Physical Examinations

A complete physical examination will include general appearance, vital signs, eyes, ears, nose, mouth, throat, neck, respiratory, cardiovascular, respiratory, gastrointestinal/abdomen, lymphatic, musculoskeletal, skin, psychiatric, and neurologic exams. A targeted physical examination will include any organ system associated with an AE or a laboratory abnormality.

8.4.2 Vital Signs

Refer to SOA (Section 1.3).

8.4.3 Tuberculosis Assessment

A subject must not have active signs or symptoms of TB, as judged by the investigator, to be eligible for the study.

In addition to a complete PE and medical history to evaluate exposure to TB, all subjects will complete a TB questionnaire annually (refer to Appendix 11). If subjects are at increased risk for TB, they may still roll over into the study and begin study treatment and procedures at Week 0 (Section 1.3); however, they will have an Interferon Gamma Release Assay (IGRA) at the Week 0 visit, and the result should be obtained promptly. If IGRA results are:

a) Negative; no further action is needed

b) Positive; subject must initiate prophylaxis treatment per local guidelines. IP will be held until subject has been on prophylaxis treatment for 30 days.

c) Indeterminate; an IGRA retest will be allowed. Subject must initiate prophylaxis treatment per local guidelines. IP will be held until subject has been on prophylaxis treatment for 30 days.

8.4.4 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 8.2.7) unless lupus-related and recorded on the lupus assessments. 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, red blood cell count, and manual differential (separate smear)
- Chemistry: AST, ALT, gamma-glutamyltransferase, hs-CRP, total bilirubin, direct bilirubin, alkaline phosphatase, lactate dehydrogenase, creatinine, blood urea nitrogen, uric acid, glucose, total protein, albumin, sodium, potassium, chloride, calcium, phosphorus, magnesium, CK, creatinine clearance (Week 0 only)
- 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
- IGRA

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. In addition, urine pregnancy testing will be performed for WOCBP.

8.5 Pharmacokinetics

The PK of BMS-986165 and metabolites (if applicable) will be derived from plasma concentration vs time data. The PK parameter to be assessed will be trough observed plasma concentration (Ctrough).

Plasma samples will be analyzed for BMS-986165 by a validated assay. 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. Population PK modelling might be conducted and documented in a separate report.

In addition, plasma samples will be archived for potential metabolite 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.

8.5.1 Sampling Schedule

The sampling schedule for the assessment of PK is provided in Table 6. Predose samples must be drawn before the dose on visit days. 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.

Table 6: Pharmacokinetic Sampling Schedule for BMS-986165

Study Visit of Sample Collection	Event	Time (Relative to Dose) Hour: Min	Blood Sample for PK	Notes
Week 0	predose	00:00	X	
Week 4	predose	00:00	X	
Week 8	predose	00:00	X	
Week 24	predose	00:00	X	
Week 48	predose	00:00	X	
Week 96	predose	00:00	X	

min = minute; PK = pharmacokinetic

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.

8.5.2 Sampling Windows

It is expected that every effort is made to collect PK samples at the times indicated. Predose samples must be drawn before the morning dose on the visit day.

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. Any missed PK sample collections must be noted in the source documents.

8.6 Exploratory Biomarker Assessments

[redacted]

[redacted]

8.6.2 Additional Research Collection

This protocol will include residual sample storage for additional research.

For All US sites:

Additional research is required for all study subjects, except where prohibited by IRBs/ethics committees, or academic/institutional requirements. Where one or more of these exceptions occurs, participation in the additional research should be encouraged, but will not be a condition of overall study participation.

- If the IRB/ethics committees and site agree to the mandatory additional research retention and/or collection, then the study subject must agree to the mandatory additional research as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study subjects may opt out of the additional research retention and/or collection.

For non-US Sites

Additional research is optional for all study subjects, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

This collection for additional research is intended to expand the translational Research and Development (R&D) capability at BMS and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

Sample Collection and Storage

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study Sponsor's senior leaders in R&D (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

- Residual PK [redacted] (see Table 7) will be retained for additional research purposes.

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than 15 years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by research Sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion and no researcher will have access to the key. The key is securely held by the investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Table 7: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for which residual samples will be retained
PK	All
[redacted]	[redacted]

[redacted] PK = pharmacokinetic; [redacted]

8.7 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

As this LTE study is for observational purposes only, no formal calculations of sample size and power determination were made. All qualified subjects who complete the final treatment visit from the parent study will be eligible to participate. If a [redacted] response rate is observed in a treatment group with a sample size of [redacted], then one can be 95% confident that the interval [redacted] contains the true response rate. Assuming 360 subjects enrolling from IM011021, there will be approximately a [redacted] chance of observing an AE that occurs in at least [redacted] of the population.

9.2 Populations for Analyses

For purposes of analysis, the following analysis sets will be used in this trial:

Enrolled Population: All subjects who sign informed consent for entry into IM011074

As-treated Population: All subjects who took at least one dose of study treatment in IM011074. The treatment group 'as-treated' will be the same as the treatment group the subjects were assigned to in this study, except in the following cases:

- If a subject took the same incorrect treatment throughout this study, then the subject will be analyzed based on the treatment received.
- If a subject took study drug from more than one treatment group, and none of the administrations were consistent with the assigned treatment group, then the subject will be analyzed based on the first treatment taken.

Biomarker Population: All subjects who receive at least one dose of study treatment in IM011074 and have at least 1 post-treatment biomarker measurement

Pharmacokinetic (PK) Population: All subjects who receive at least one dose of study treatment in IM011074 and have any available concentration-time data

9.3 Endpoints

9.3.1 Safety Assessments – Primary Endpoint

The primary objective of this LTE study is to characterize the long-term safety and tolerability of BMS-986165 in subjects with SLE. The following assessments will be summarized for the evaluation of this objective:

- AEs, SAEs, AEs leading to study discontinuation
- Change from baseline in vital signs over time
- Change from baseline in laboratory measurements over time

9.3.2 Secondary Endpoints

Not applicable

9.3.3 Additional Endpoints

The following endpoints will be measured throughout the study:

- Proportion of subjects with a CLASI activity score ≥ 10 at baseline and who achieve a CLASI response, defined as a decrease of ≥ 50% from baseline CLASI activity score
- Proportion of subjects with a CLASI activity score at baseline < 10 who maintain a score of < 10 at each visit
- Change from baseline in CLASI activity score
- Change from baseline in the 40-joint count for tender, swollen and tender + swollen joints
- Proportion of subjects who meet SRI(4) response criteria. SRI(4) response is defined in Section 8.1.1.5.
- Proportion of subjects who achieve BICLA response. BICLA response is defined in Section 8.1.1.6.
- Change from baseline in PGA of Disease Activity
- Proportion of subjects using corticosteroids at each visit during the Blinded LTE Study Period
- Proportion of subjects receiving daily corticosteroid dose ≤7.5 mg/day assess at each visit during the Blinded LTE Study Period
- SLE Flare Analysis:
    - Time to subjects first flare
    - Proportion of subjects with flares and severity
    - Total number of flares per subject
    - Frequency of flares
    - Proportion of flares leading to hospitalization
- Changes in SDI Score
- Proportion of subjects with BILAG-2004 response
- Change from baseline in BILAG-2004 score
- Change from baseline in SLEDAI-2K score
- Proportion of subjects with LLDAS response
- PROs:
    - Change from baseline in PROMIS Fatigue Short Form 7a Score

9.3.4 PK Endpoints

Plasma concentration values

9.3.5 PD Endpoints

Exploratory Biomarkers

9.4 Efficacy Analyses

As this study is for observational purposes, no statistical tests for treatment comparisons will be conducted. Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using number of subjects (n), mean, standard deviation, median, minimum, and maximum unless otherwise specified. Efficacy variables will be summarized for all visits in which the variable is assessed. Complete details of the planned analyses will be documented in the statistical analysis plan and finalized before database lock. Summaries will be provided for the 'as-treated' population.

Summaries of outcome measures (or endpoints) will be presented for the following groups:

- BMS-986165 3 mg BID (treatment from previous study) → BMS-986165 3 mg BID
- BMS-986165 6 mg BID (treatment from previous study) → BMS-986165 6 mg BID
- BMS-986165 12 mg QD (treatment from previous study) → BMS-986165 12 mg QD
- Placebo BID (treatment from previous study) → BMS-986165 3 mg BID
- Placebo BID (treatment from previous study) → BMS-986165 6 mg BID
- Placebo BID (treatment from previous study) → BMS-986165 12 mg QD

9.5 Safety Analyses

Safety data will be analyzed for AEs, SAEs, laboratory analytes, and vital signs. Safety will be summarized using the 'as-treated' population. Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified.

Safety summaries will be presented according to the following groups:

- BMS-986165 3 mg BID (treatment from previous study) → BMS-986165 3 mg BID
- BMS-986165 6 mg BID (treatment from previous study) → BMS-986165 6 mg BID
- BMS-986165 12 mg QD (treatment from previous study) → BMS-986165 12 mg QD
- Placebo BID (treatment from previous study) → BMS-986165 3 mg BID
- Placebo BID (treatment from previous study) → BMS-986165 6 mg BID
- Placebo BID (treatment from previous study) → BMS-986165 12 mg QD

9.5.1 Adverse Events

Adverse events will be recorded at the time of the last study visit in the parent study. Events that are ongoing at the time subject signs the informed consent will be reported as AEs. Events reported during IM011021 that have resolved will be considered medical history in IM011074.

Treatment-emergent adverse events (TEAEs) are events that occur after the first dose of study drug is given in the LTE study. Events that were ongoing during the parent study and worsen once study drug is initiated in IM011074 will also be considered treatment-emergent. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and presented by system organ class and preferred term. Serious AEs and deaths, AEs leading to study treatment discontinuation, AEs by maximum severity, and AEs by relationship will also be summarized by the MedDRA system organ class and preferred term. All TEAEs will also be summarized by preferred term sorted by decreasing frequency.

9.5.2 Vital Signs, and Physical Examinations

Vital signs will be summarized as raw change from baseline, and change from maximum postbaseline value. Incidence of abnormal physical examination findings will also be summarized.

9.5.3 Clinical Laboratory Tests

Laboratory analytes will be summarized as raw change from baseline, and change from maximum postbaseline value. Incidence of abnormal, high, or low values will be summarized. Shift tables will also be provided.

9.6 Other Analyses

Other analysis summaries will be presented by treatment groups similar as defined in Section 9.5.

9.6.1 Demographics and Baseline Data

Demographics and baseline data obtained during the screening visit of study IM011021 will be summarized for subjects entering the LTE and will be summarized by randomized treatment for each applicable analysis population. Categorical data will be summarized as frequency counts and percentages. Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum unless otherwise specified.

9.6.2 Prior and Concomitant Medications

Prior and concomitant medications, categorized by medication group and subgroup according to the World Health Organization (WHO) Drug Dictionary, will be summarized by treatment for the 'as-treated' population. Medications with an end date prior to the first dose of LTE study drug will be considered prior medications.

9.6.3 Pharmacokinetics

Ctrough will be summarized by dose and timepoint for the PK population. 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 CSR.

9.6.4 Exploratory Biomarkers

Selected biomarkers will be summarized by treatment and time point for the biomarker population. Summaries will be provided for raw, change from baseline, and percent change from baseline.

9.7 Interim Analyses

No interim analysis is currently planned.

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11 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
[redacted]	[redacted]
AE	adverse event
AEI	adverse event of interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(TAU)	area under the concentration-time curve for 1 dosing interval
BCRP	breast cancer resistance protein
BICLA	BILAG-based Composite Lupus Assessment
BID	twice daily
BILAG	British Isles Lupus Assessment Group
BMS	Bristol-Myers Squibb
BSA	body surface area
Cavg, ss	average concentration at steady state
CFR	Code of Federal Regulations
CK	creatine kinase
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CRF	case report form
CRP	C-reactive protein
[redacted]	[redacted]
CSR	clinical study report
Ctrough	trough observed plasma concentration
CV	cardiovascular
CXR	chest x-ray
CYP450	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury

Term	Definition
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
dsDNA	double stranded DNA
eCRF	electronic case report form
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
hCG	human chorionic gonadotropin
hs-CRP	high-sensitivity C-reactive protein
IB	Investigator Brochure
IBD	inflammatory bowel disease
IC50	half-maximal inhibitory concentration
ICF	informed consent form
IEC	Independent Ethics Committee
IFN	interferon
IFNγ	interferon gamma
IGRA	interferon gamma release assay
IL	interleukin
IMP	investigational medicinal product
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
JAK	Janus kinase
LLDAS	Lupus Low Disease Activity State
LTBI	latent tuberculosis infection
LTE	long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamics
PGA	Physician Global Assessment

Term	Definition
PK	pharmacokinetics
po	orally
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
QD	once daily
R&D	Research and Development
[redacted]	[redacted]
SAE	serious adverse event
SDI	Systemic Lupus Erythematosus International Collaborating Clinics / American College of Rheumatology Damage Index
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SOA	Schedule of Activities
SRI(4)	SLE Responder Index
STAT	signal transducer and activator of transcription
SUSAR	Suspected, Unexpected Serious Adverse Reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
Tmax	time of maximum observed plasma concentration
TYK2	tyrosine kinase 2
ULN	upper limit of normal
UPCR	urine protein/creatinine ratio
VAS	visual analog scale
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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 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 subject 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, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator, 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 subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

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

Financial Disclosure

Investigators and Subinvestigators 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 subject 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 consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.

- Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written 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 subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.

Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

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

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

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the ICF approved for the study prior to clinical study participation. The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

Minors who are judged to be of an age of reason must also give their written assent.

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

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

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), AE 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 subject, including unique subject identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product

If	Then
	dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites 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 SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject 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 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 tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and paper Pregnancy Surveillance Form, respectively. If electronic SAE form is not available, a paper SAE form can be used.

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

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

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the electronic data capture 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.

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) (examples include study treatments sourced from the sites 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 of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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.

Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the CSR.

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

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to 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 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, electrocardiograms, 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 8.2.8 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 8.2.6 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 PRA 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: BMSSafety@prahs.com

SAE Fax Number:

Americas: 1-888-772-6919 (or 1-434- 951-3482)

Europe/East Asia-Pacific: +44-1792-525-720

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

Americas: 1-800 772 2215 (or 1-434-951-3489)

Europe/East Asia-Pacific: +49-621-878-2154.

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 over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle-stimulating hormone (FSH) level >40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout 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 CHILD BEARING POTENTIAL

One of the highly effective 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 – oral – intravaginal – transdermal • Combined (estrogen- and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of therapy
• Progestogen-only hormonal contraception associated with inhibition of ovulation – oral – 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 • Intrauterine device (IUD)[b] • Intrauterine hormone-releasing system (IUS)[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 subject.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP subjects 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 subjects 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 subjects 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 (LAM)

CONTRACEPTION GUIDANCE FOR MALE SUBJECTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male subjects with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- 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.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as the duration of study treatment.
- Condom use is not required.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 8.2.6 and APPENDIX 3.

APPENDIX 5 BRITISH ISLES LUPUS ASSESSMENT GROUP (BILAG)-2004

(For Reference Use Only)

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

CONSTITUTIONAL

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

MUCOCUTANEOUS

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

NEUROPSYCHIATRIC

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

MUSCULOSKELETAL

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

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

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. Malabsoeption ( )
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 hyptention Yes/No ( )
81. Urine dipstick protein (+=1. ++=2. +++=3) ( )
82. Urine albumin-creatinine ratio mg/mmol ( )
83. Urine protein-creatinine ratio mg/mmol ( )
84. 24 hour urine protein (g) value ( )
85. Nephrotic syndrome Yes/No ( )
86. Creatinine (plasma/serum) µmol/l ( )
87. GFR (calculated) ml/min/1.73 m^2 ( )
88. Active urinary sediment Yes/No ( )
89. Active nephritis Yes/No ( )

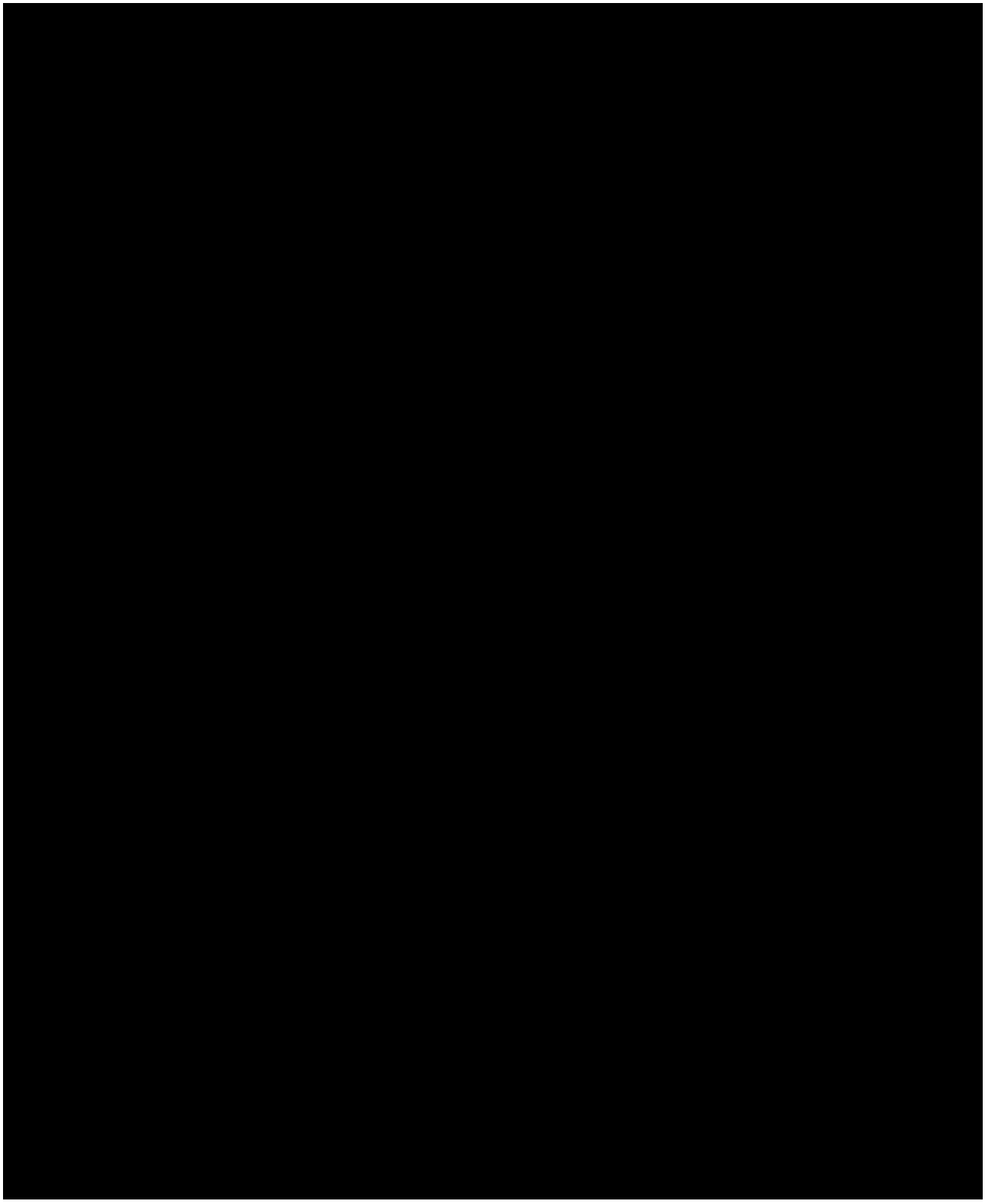
HAEMATOLOGICAL

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

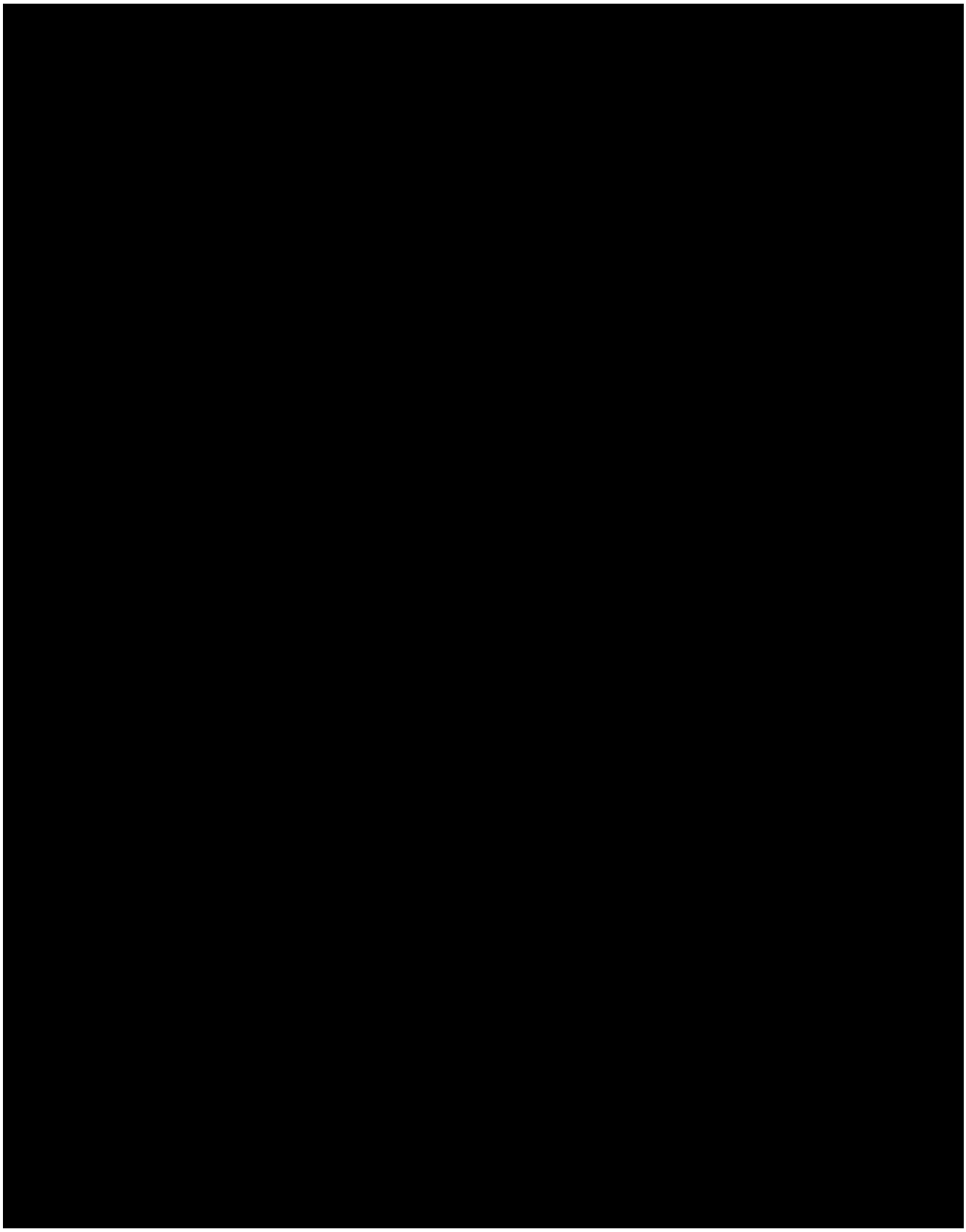
VAS(Dr)0----------10cm

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

APPENDIX 6 SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX 2000



APPENDIX 7 CUTANEOUS LUPUS ERYTHEMATOSUS DISEASE AREA AND SEVERITY INDEX (CLASI)

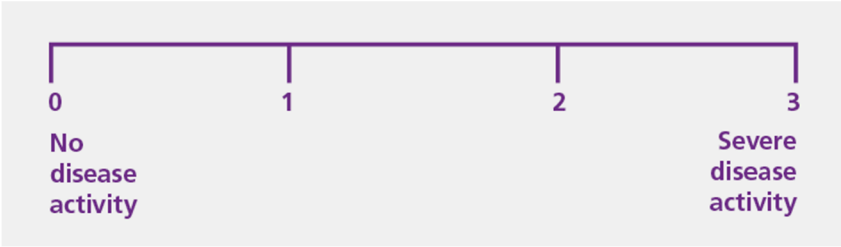


APPENDIX 8 VISUAL ANALOG SCALE FOR PHYSICIAN'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY

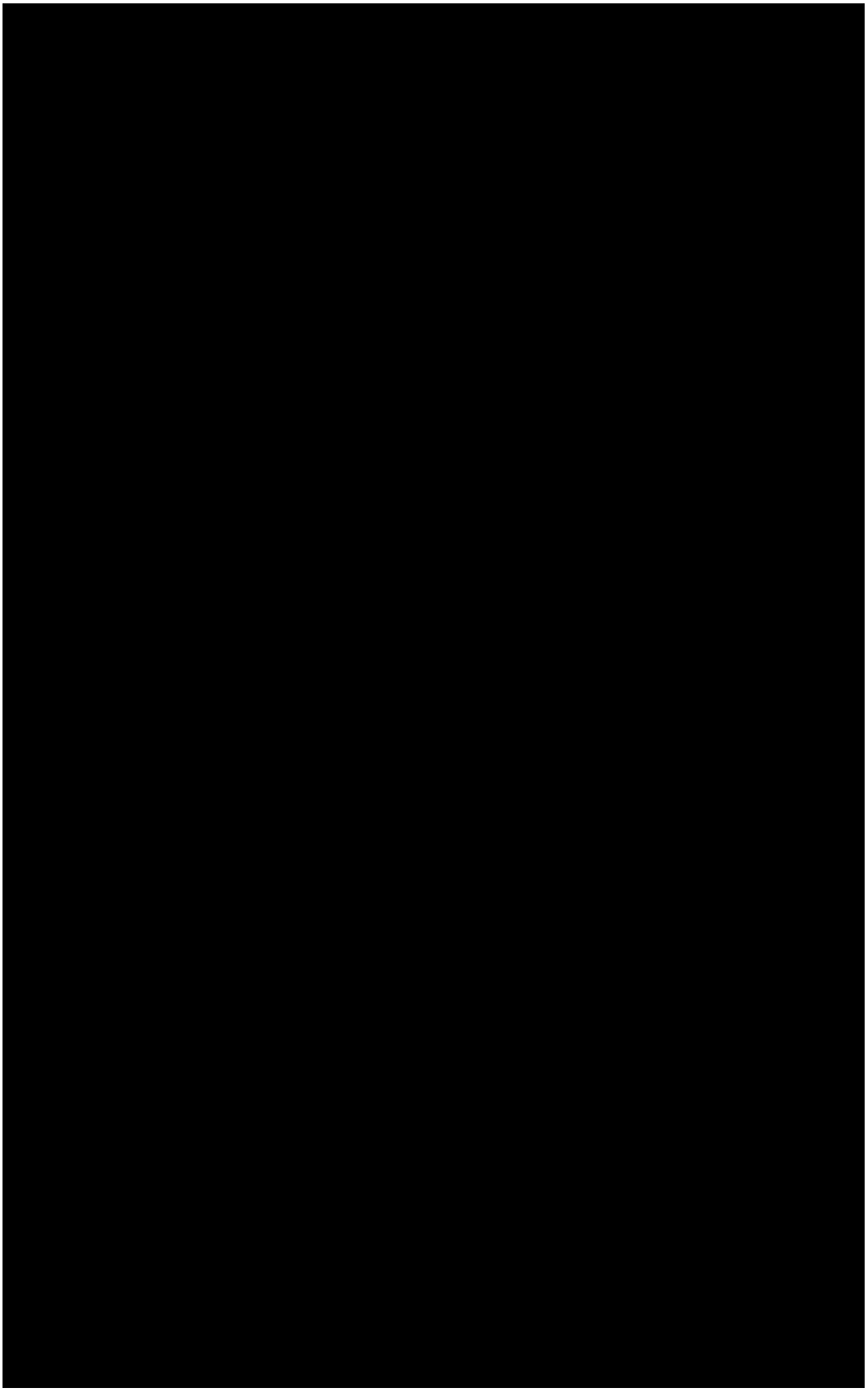
(For Reference Use Only)

The physician's global assessment of disease activity will be measured with a 4-point visual analog scale evaluating average SLE disease severity over the last 4 weeks.

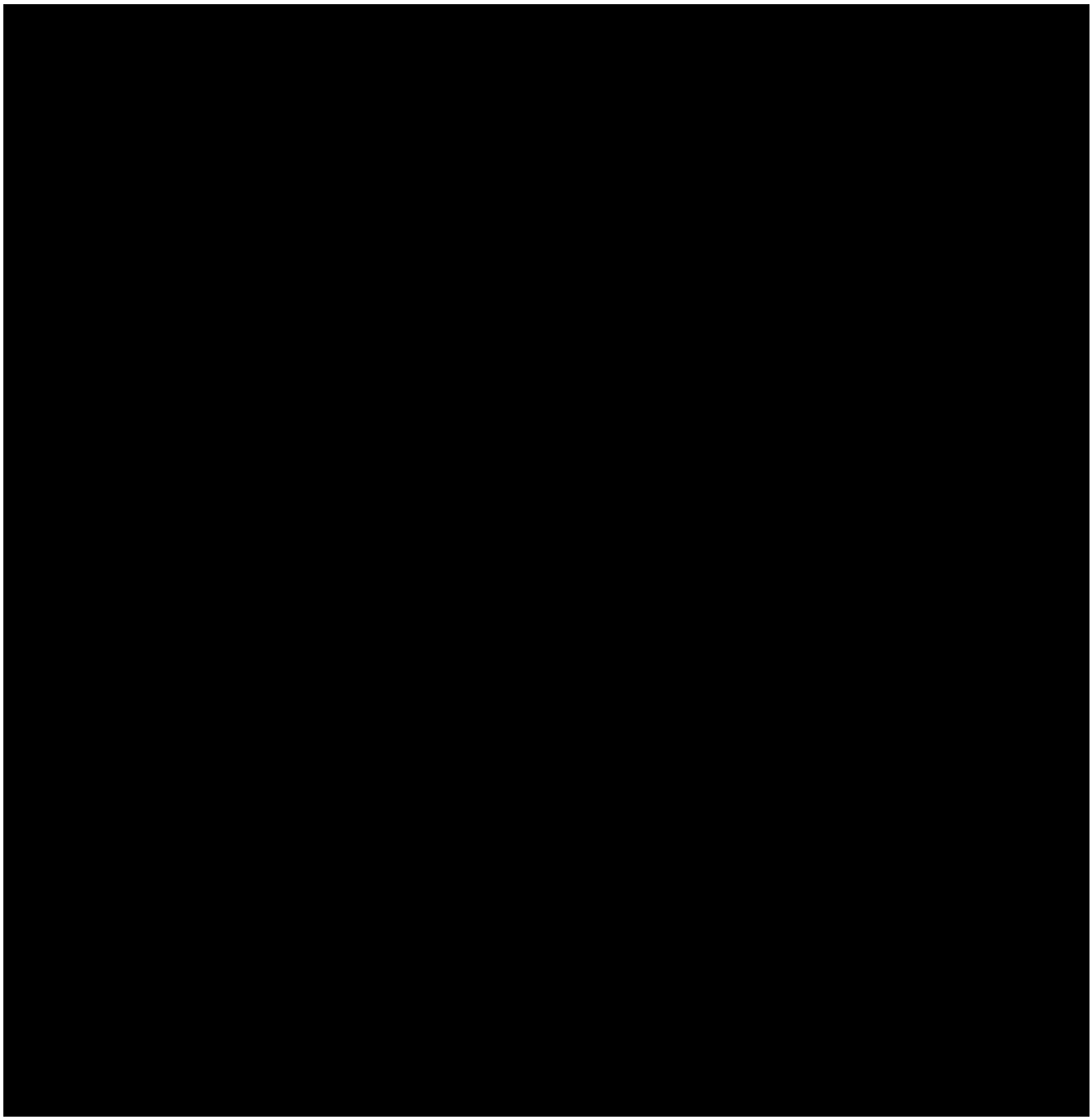
How do you assess your patient's (the subject's) current disease activity as compared to the last visit? Please mark the line below.



APPENDIX 9 SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS/ AMERICAN COLLEGE OF RHEUMATOLOGY DAMAGE INDEX



APPENDIX 10 PATIENT-REPORTED OUTCOMES MEASUREMENT INFORMATION SYSTEM (PROMIS) FATIGUE



APPENDIX 11 TUBERCULOSIS RISK ASSESSMENT TOOL

A subject with any of the 3 following high-risk factors will have an interferon gamma release assay (IGRA):

	Yes	No
1. Recent close or prolonged contact with someone with infectious TB disease		
2. High-risk profession or situations, like being patient-facing, eg, healthcare providers		
3. Recent travel to or from a high burden country for TB (please see country list from UN partner website [Stop TB]): http://www.stoptb.org/countries/tbdata.asp		