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PROTOCOL NUMBER: 230LE201 / NCT02847598

PHASE OF DEVELOPMENT: 2

PROTOCOL TITLE: A 2-Part Phase 2 Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of BIIB059 in Subjects with Systemic Lupus Erythematosus and Active Skin Manifestations and in Subjects with Active Cutaneous Lupus Erythematosus with or without Systemic Manifestations

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SPONSOR SIGNATURE PAGE

Protocol 230LE201 was approved by:

[redacted]

20 March 2019

[redacted] MD, PhD

Date

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For urgent medical issues in which the study's Medical Director should be contacted, please refer to the Study Reference Guide's Official Study Contact List for complete contact information.

Biogen may transfer any or all of its study-related responsibilities to a contract research organization (CRO) and other third parties; however, Biogen retains overall accountability for these activities.

2. LIST OF ABBREVIATIONS

ACLE	acute cutaneous lupus erythematosus
ACR	American College of Rheumatology
AE	adverse event
ANCOVA	analysis of covariance
AUC	area under the concentration-time curve
BDCA2	blood dendritic cell antigen-2
BILAG	British Isles Lupus Activity Group
CCLE	chronic cutaneous lupus erythematosus
CL	clearance
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLASI-A	CLASI–Activity
CLASI-D	CLASI– Damage
CLE	cutaneous lupus erythematosus
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CPK	creatine phosphokinase
CRO	contract research organization
DHA	Directions for Handling and Administration
DLE	discoid lupus erythematosus
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HRQoL	health-related quality of life
IA	interim analysis
IC_{90}	concentration resulting in 90% inhibition of response
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IFN	interferon
IFN-α	interferon-alpha
IgG1	immunogloblulin, class G, type 1
IHC	immunohistochemistry
IRT	interactive response technology
IM	intramuscular
ITT	intent-to-treat
IV	intravenous
LE	lupus erythematosus
LTBI	latent tuberculosis infection

[redacted]	[redacted]
MCP	metacarpophalangeal
MCP-Mod	Multiple Comparison Procedure - Modelling
MCS	Mental Component Summary
MMF	mycophenolate mofetil
MMRM	Mixed Effect Model Repeat Measurement
MPS	mycophenolate sodium
mRNA	messenger RNA
[redacted]	[redacted]
NSAID	nonsteroidal anti-inflammatory drug
PCS	Physical Component Summary
PD	pharmacodynamic
pDC	plasmacytoid dendritic cell
PGA	Physician's Global Assessment
PGI	Physician's Global Impression
PIP	proximal interphalangeal
PK	pharmacokinetics
PP	per-protocol
Q2W	every 2 weeks
Q4W	every 4 weeks
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCLE	subacute cutaneous lupus erythematosus
SELENA	Safety of Estrogen in Lupus: National Assessment
[redacted]	[redacted]
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SoC	standard of care
SRI	Systemic Lupus Erythematosus Responder Index
SRI-4	Systemic Lupus Erythematosus Responder Index Response of ≥4
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
TB	tuberculosis
TLG	tables, listings and graphs
TLR	toll-like receptor
VAS	visual analog scale
WOCF	worst observation carried forward

3. SYNOPSIS

Protocol Number:	230LE201
Protocol Title:	A 2-Part Phase 2 Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of BIIB059 in Subjects with Systemic Lupus Erythematosus and Active Skin Manifestations and in Subjects with Active Cutaneous Lupus Erythematosus with or without Systemic Manifestations
Version Number	5
Name of Study Treatment:	BIIB059
Study Indication:	Part A: Systemic lupus erythematosus with active joint and active skin manifestations Part B: Active cutaneous lupus erythematosus (subacute or chronic cutaneous lupus erythematosus including discoid lupus erythematosus) with or without systemic manifestations
Study Rationale	Most therapies used to treat systemic lupus erythematosus (SLE) are only partially effective and are associated with considerable toxicity. Furthermore, no medicines are specifically approved for the treatment of cutaneous lupus erythematosus (CLE). Blood dendritic cell antigen-2 (BDCA2) is a type II, C-type lectin receptor that is uniquely expressed on the cell surface of plasmacytoid dendritic cells (pDC) and was the first receptor described to negatively down-regulate the type I interferon (IFN) response in these cells. In both CLE and SLE, type I IFN expression correlates with disease activity and severity. By binding to BDCA2, BIIB059 treatment is expected to target pDC in affected tissues leading to decreased IFN production, as well as the reduction of other pDC-derived factors that contribute to SLE and CLE pathogenesis.
Phase of Development:	2
Study Objectives and Endpoints:	The primary objective of the study is to evaluate the efficacy of BIIB059 in reducing disease activity in subjects with SLE with active skin manifestations and joint involvement (Part A), and in subjects with active CLE (subacute CLE [SCLE] or chronic CLE [CCLE], including discoid lupus erythematosus [DLE]) with or without systemic manifestations (Part B). • Part A: The primary endpoint that relates to this objective is the change in active joint count (28-joint assessment) from Baseline to Week 24. The active joint count is defined as the sum of the tender joint count and the swollen joint count.

- Part B: The primary endpoint that relates to this objective is the percent change in Cutaneous Lupus Erythematosus Disease Area and Severity Index--Activity (CLASI-A) score from Baseline to Week 16.

Secondary Objectives and Endpoints

To evaluate additional efficacy parameters of BIIB059 in reducing SLE/CLE disease activity.

The endpoints that relate to this objective are:

Skin related

- CLASI-50, defined as a 50% improvement from baseline in CLASI-A score, at Week 24 (Part A) and at Weeks 12 and 16 (Part B).
- Percent change in CLASI-A score from Baseline to Week 12, Week 16, and Week 24 (Part A) and Week 12 (Part B).
- A ≥4-point reduction in CLASI-A score at Week 24 (Part A) and at Weeks 12 and 16 (Part B) compared with baseline.

SLE disease activity related (Part A Only)

- Proportion of subjects with a composite response, defined as:
  - SLE Responder Index (SRI) of ≥4 (SRI-4) at Week 24, where SRI-4 is defined as:
    - A reduction from baseline of ≥4 points in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), and
    - No new organ system affected, as defined by no new British Isles Lupus Activity Group (BILAG)-2004 A and no more than one new BILAG-2004 B, and
    - No worsening from baseline in subject's lupus disease activity defined by <0.3 point increase in the Physician's Global Assessment (PGA) [visual analog scale (VAS)]
  - No protocol-prohibited medication or treatment.
  - Concomitant corticosteroid dosage at Week 24 to be ≤10 mg/day.
  - Concomitant corticosteroid dosage at Week 24 to be ≤Day 1 corticosteroid dosage.
  - No increase in corticosteroid dose between Weeks 17 and 24.

- Change from baseline to Week 24 in SLEDAI-2K score
- Proportion of subjects with no new organ system affected, as defined by no new BILAG-2004 A and no more than one new BILAG-2004 B from baseline to Week 24
- Change from baseline to Week 24 in PGA (VAS) score

Pharmacokinetics Objectives and Endpoints (Parts A and B):

To evaluate the pharmacokinetic parameters of BIIB059, including:

- BIIB059 clearance, volume of distribution, and absorption rate.

Safety and Tolerability Objectives and Endpoints (Parts A and B)

To evaluate the safety and tolerability of BIIB059.

The endpoints that relate to this objective are as follows:

- Nature, severity, relationship to study treatment, and incidence of adverse events (AEs) and serious adverse events (SAEs)
- Change from baseline in standard laboratory parameters, vital signs and electrocardiogram (ECG) results
- Immunogenicity (antibodies to BIIB059)
- Absolute and percent change from baseline over time in immunoglobulin levels and vaccine-related immunoglobulin titers

Additional study objectives are listed in Section 6.

Study Design: 2-part, randomized, double-blind, parallel group, placebo-controlled study

Study Location: The study will be conducted at approximately 130 centers in the United States, Europe, Latin America, and Asia.

Number of Planned Subjects:

Part A:

The maximum number of subjects in Part A is approximately 190 subjects. Of these 190 subjects, approximately 100 subjects will be enrolled under protocol version 2 or subsequent versions. If the study is not stopped for futility at the interim analysis (IA 1), then up to 70 additional subjects may be added (up to a total of approximately 170 subjects under protocol version 2 or subsequent versions). Subjects enrolled under protocol version 1 will remain on their original treatment assignment (up to a total of approximately 20 subjects).

Part B:

The maximum number of subjects in Part B is approximately 130 subjects. Of these 130 subjects, approximately 100 subjects will be enrolled under protocol version 2 or subsequent versions. Subjects enrolled under protocol version 1 will remain on their original treatment assignment (up to a total of approximately 30 subjects).

An interim analysis (IA 1) for futility of Part B and possible expansion of Part A will be performed. IA 1 will be performed after approximately 45% of Part B subjects under protocol version 2 or subsequent versions have completed their Week 12 Treatment Period visit. At the time of this IA, it is estimated that over 50% of subjects in Part A will have completed their Week 12 Treatment Period visit. Following the IA, up to an additional 70 subjects may be enrolled in Part A and the BIIB059 dose may be adjusted. Details are provided in Section 16.7.1.

A second IA (IA 2) of efficacy and safety data will occur after the last subjects complete the Double-Blind Treatment Periods for Part A (at Week 24) and Part B (at Week 16). Details are provided in Section 16.7.2.

For both IAs (1 and 2), all Investigators, study site personnel, and subjects will remain blinded to treatment assignments until after the final database lock.

Study Population:

The study (Parts A and B) will be conducted in subjects 18 to 75 years of age, inclusive.

Part A:

All subjects must have a diagnosis of SLE according to the 1997 revised American College of Rheumatology (ACR) classification for SLE along with active skin manifestations and joint involvement (Appendix C) .

At Screening and randomization, all subjects must have at least 4 tender joints and at least 4 swollen joints, with at least 4 of the swollen joints in the proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints and/or wrist. A joint that is both tender and swollen will be included in both categories (counts as 1 tender and 1 swollen).

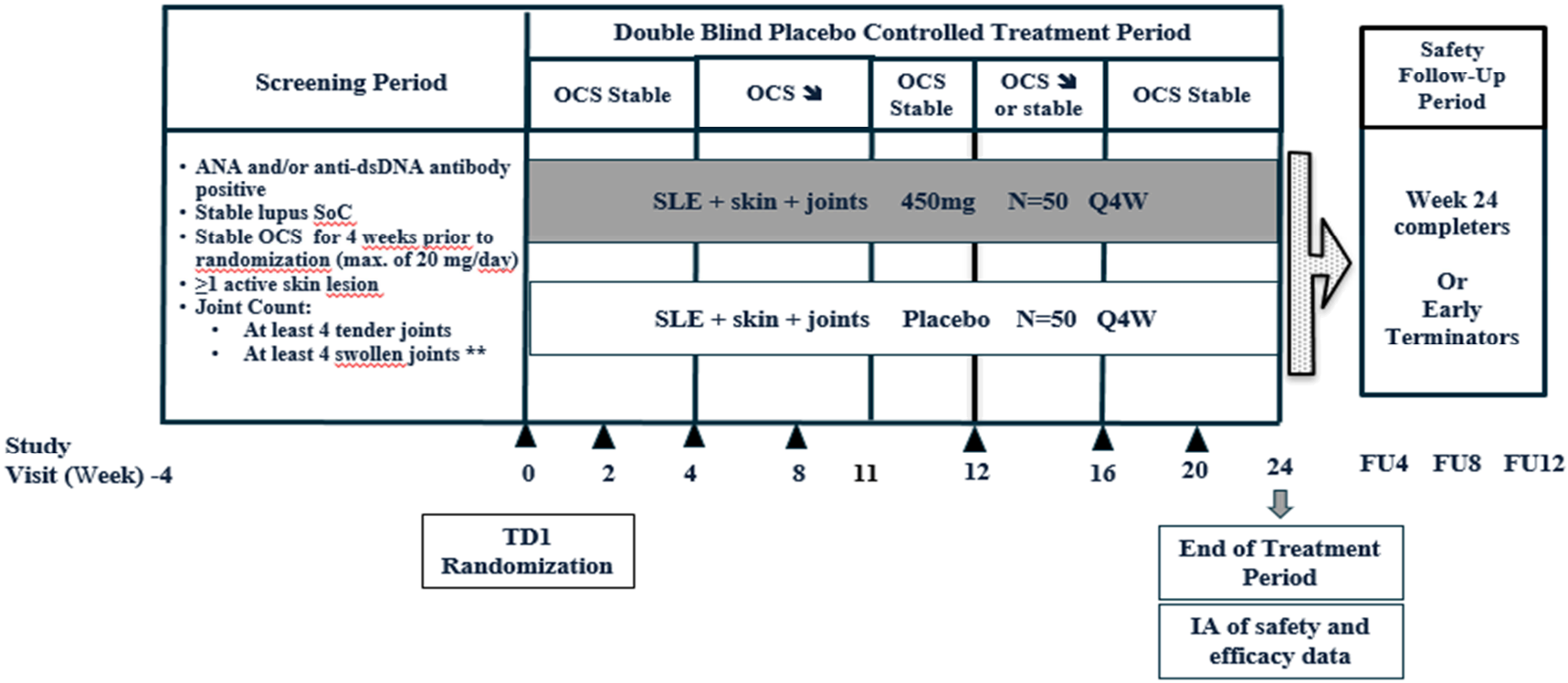
Subjects must also demonstrate at least one sign of active lupus skin disease, including ACLE, SCLE, and/or CCLE (e.g., DLE), with skin activity defined by SLEDAI-2K at the time of Screening and randomization.

	Part B: All subjects must have active skin manifestations (CLASI-A ≥8) and a diagnosis of CLE that has been histologically confirmed (in the past or at Screening), with or without SLE manifestations. Active CLE is defined as follows: • SCLE with a CLASI-A erythema score ≥2 and/or • CCLE, including DLE, with at least 1 active DLE lesion with a minimum CLASI-A erythema score ≥2, and a CLASI-D scarring score ≥1. Detailed criteria are described in Section 8.
Treatment Groups:	**Part A:** Subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups to receive subcutaneous BIIB059 (450 mg) or placebo every 4 weeks, with an additional dose at Week 2, for a total of 7 doses (Weeks 0, 2, 4, 8, 12, 16, and 20). This randomization scheme will apply to the approximately 100 subjects randomized under protocol version 2 or subsequent versions and to any additional subjects if a decision to expand is made following the IA. **Part B:** Subjects will be randomized in a 1:1:1:1 ratio to 1 of 4 treatment groups to receive subcutaneous BIIB059 (50 mg, 150 mg, or 450 mg) or placebo every 4 weeks, with an additional dose at Week 2, for a total of 5 doses (Weeks 0, 2, 4, 8, and 12). This randomization scheme will apply to the approximately 100 subjects randomized under protocol version 2 or subsequent versions.
Duration of Treatment and Follow-up:	**Part A:** Study duration for each subject may be up to 40 weeks: Screening Period: up to 4 weeks Treatment Period: 24 weeks Follow-up Period: 12 weeks **Part B:** Study duration for each subject may be up to 32 weeks: Screening Period: up to 4 weeks Treatment Period: 16 weeks Follow-up Period: 12 weeks

4. STUDY SCHEMATIC AND SCHEDULE OF ACTIVITIES FOR STUDY 230LE201

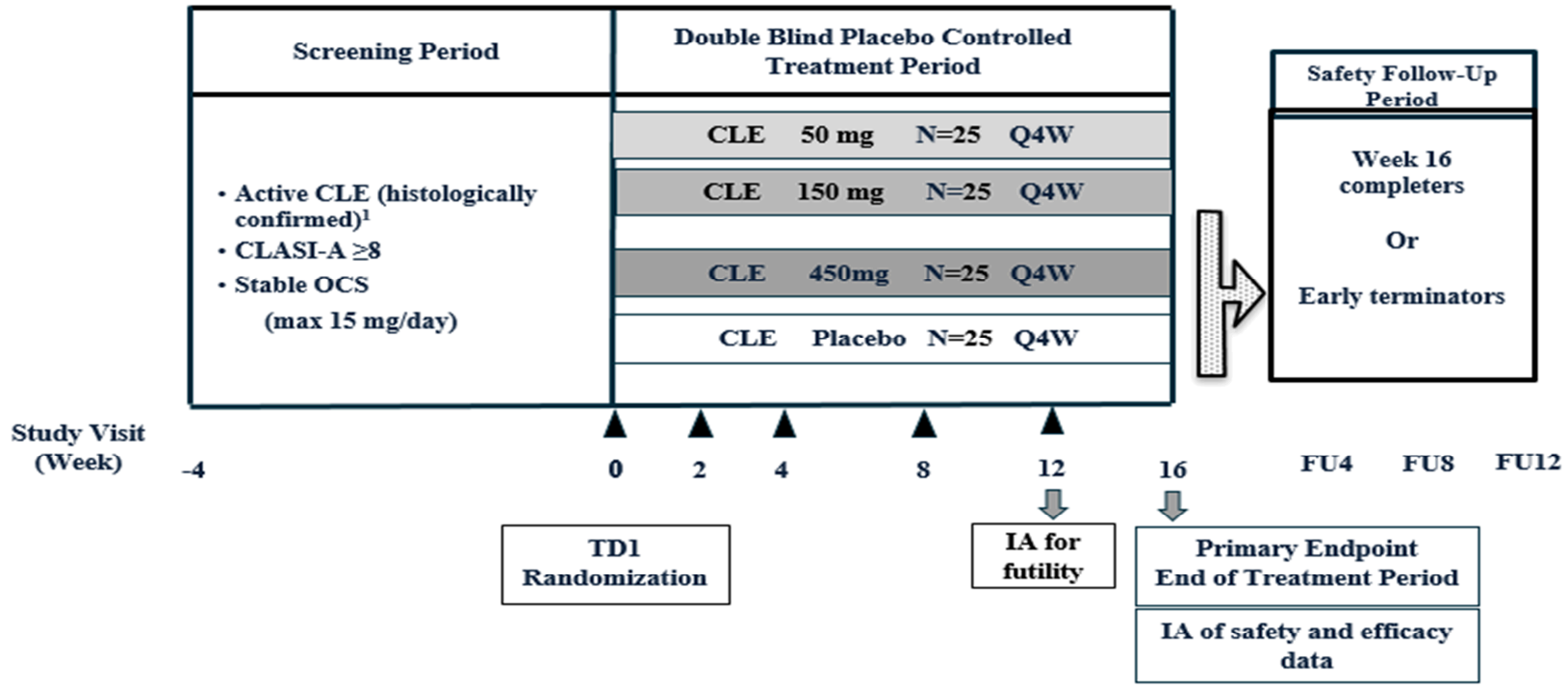
4.1. Study Schematic

Figure 1: Study Design Part A



Abbreviations: ANA=antinuclear antigen; dsDNA= double-stranded DNA; IA=interim analysis; FU=follow-up visit; MCP=metacarpophalangeal joints; OCS=oral corticosteroid; PIP=proximal interphalangeal joints; Q4W=every 4 weeks; SoC=standard of care; TD1=Treatment Day 1.
** At least 4 of the swollen joints must be PIP, MCP, and/or wrist joints. A joint that is both tender and swollen will be included in both categories (counts as 1 tender and 1 swollen).
Black triangles represent dosing visits.

Figure 2: Study Design Part B



Abbreviations: CLASI-A=Cutaneous Lupus Erythematosus Disease Area and Severity Index- Activity Scale; CLE=cutaneous lupus erythematosus; FU=follow-up visit; IA=interim analysis; OCS=oral corticosteroid; Q4W=every 4 weeks; SoC=standard of care; TD1=Treatment Day 1

[1] Histologically confirmed in the past or at Screening.

Black triangles represent dosing visits.

4.2. Schedule of Activities

Table 1: Schedule of Activities Part A

	Screening Period	Treatment Period									Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ET**	**FU4**	**FU8**	**FU12**
Study Day		**1[3]**	**8 (±2D)**	**15[3] (±2D)**	**29[3] (±3D)**	**57[3] (±3D)**	**85[3] (±3D)**	**113[3] (±3D)**	**141[3] (±3D)**	**169 (±3D)**	**197 (±5D)**	**225 (±5D)**	**253 (±5D)**
Tests and Assessments[2,3]													
Informed Consent Form(s)	X												
Inclusion/ Exclusion Criteria	X	X											
Randomization		X											
Demographic data	X												
SLE and other medical history	X												
Documentation of SLE by ACR Criteria	X												
12-lead ECG[4]	X									X			
Chest x-ray[5] (if required by local regulation)	X												
Tuberculosis test[6]	X												
Serum virology RNA (HIV, hepatitis B and C)	X												
Urine drug screen	X												

	Screening Period	Treatment Period									Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ET**	**FU4**	**FU8**	**FU12**
Study Day		**1[3]**	**8 (±2D)**	**15[3] (±2D)**	**29[3] (±3D)**	**57[3] (±3D)**	**85[3] (±3D)**	**113[3] (±3D)**	**141[3] (±3D)**	**169 (±3D)**	**197 (±5D)**	**225 (±5D)**	**253 (±5D)**
Tests and Assessments[2,3]													
Serum pregnancy test	X												
Urine pregnancy test[7]		X		X	X	X	X	X	X	X	X	X	X
Physical examination, weight, height[8]	X	X		X	X	X	X	X	X	X	X		X
Vital signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]													
BILAG-2004	X	X			X	X	X	X	X	X			
CLASI	X	X		X	X	X	X	X	X	X			X
[redacted]													
Physicians Global Assessment of SLE (VAS)[10]	X	X		X	X	X	X	X	X	X			X
Skin photography of target lesion[11]		X			X			X[12]					
Joint Count (28 joint assessment)	X	X		X	X	X	X	X	X	X			X

	Screening Period	Treatment Period									Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ET**	**FU4**	**FU8**	**FU12**
Study Day		**1[3]**	**8 (±2D)**	**15[3] (±2D)**	**29[3] (±3D)**	**57[3] (±3D)**	**85[3] (±3D)**	**113[3] (±3D)**	**141[3] (±3D)**	**169 (±3D)**	**197 (±5D)**	**225 (±5D)**	**253 (±5D)**
Tests and Assessments[2,3]													
Study treatment administration[13]		X		X	X	X	X	X	X				
Corticosteroid diary[14]		X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessment													
Hematology	X	X		X	X	X	X	X	X	X	X		X
Blood chemistry	X	X		X	X	X	X	X	X	X	X		X
Urinalysis (including microscopic examination)	X	X		X	X	X	X	X	X	X	X		X
Urine protein-creatinine Ratio (spot urine)	X	X		X	X	X	X	X	X	X	X		X
Direct Coombs Analysis	X	X			X	X	X	X	X	X			
Coagulation	X	X			X	X	X	X	X	X			
CD19+ B Cell count[15]	X												
Pharmacokinetics													
Serum BIIB059[16]		X	X		X		X	X		X	X		X
[redacted]													

	Screening Period	Treatment Period									Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ET**	**FU4**	**FU8**	**FU12**
Study Day		**1[3]**	**8 (±2D)**	**15[3] (±2D)**	**29[3] (±3D)**	**57[3] (±3D)**	**85[3] (±3D)**	**113[3] (±3D)**	**141[3] (±3D)**	**169 (±3D)**	**197 (±5D)**	**225 (±5D)**	**253 (±5D)**
Tests and Assessments[2,3]													
[redacted]													
Subject-Reported Questionnaires[20]													
[redacted]													

	Screening Period	Treatment Period									Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ET**	**FU4**	**FU8**	**FU12**
Study Day		**1[3]**	**8 (±2D)**	**15[3] (±2D)**	**29[3] (±3D)**	**57[3] (±3D)**	**85[3] (±3D)**	**113[3] (±3D)**	**141[3] (±3D)**	**169 (±3D)**	**197 (±5D)**	**225 (±5D)**	**253 (±5D)**
Tests and Assessments[2,3]													
[redacted]													
Safety													
Serum for vaccine-related immunoglobulin titers[21]		X								X			
Antibodies to BIIB059		X			X			X		X			X
Immunoglobulin (total, IgG, IgA, IgM)		X						X		X			
Concomitant medication/ procedures	Monitor and record from signing of informed consent through the end of the study												
Serious adverse events	Monitor and record from signing of informed consent through the end of the study												
Adverse events		Monitor and record from time of first dose through the end of the study											

Abbreviations: ACR=American College of Rheumatology; BILAG=British Isles Lupus Activity Group; CLASI=Cutaneous Lupus Disease Area and Severity Index; CLE=cutaneous lupus erythematosus; C=complement; CPK=creatine phosphokinase; CRP=C-reactive protein; D=day; DNA=deoxyribonucleic acid; dsDNA=double-stranded DNA; ECG=electrocardiogram; ESR=erythrocyte sedimentation rate; ET=early termination; FU=follow-up; h=hour(s); HIV=human immunodeficiency virus; Ig=immunoglobulin; [redacted]; [redacted];

RNA=ribonucleic acid; [redacted]; SLE=systemic lupus erythematosus; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; TB=tuberculosis; VAS=visual analog scale.

[1] Follow-up visit will be conducted 4, 8, and 12 weeks after the last Treatment Period Visit (Week 24 or ET).
[2] Assessments (e.g., CPK, ECG, etc.) may be performed as required to confirm SLEDAI-2K and BILAG findings.
[3] On each dosing day (Day 1, Day 15, Day 29, Day 57, Day 85, Day 113, and Day 141) all assessments should be performed prior to dosing.
[4] To be performed locally.
[5] Where mandated by local regulation, a chest x-ray will be obtained locally during the screening period, unless a previous chest x-ray or the documented results from a chest x-ray obtained within 12 weeks prior to screening are available. The chest x-ray or x-ray results will be reviewed by the Investigator (or designee) in order to exclude patients with active TB infection from entering the study.
[6] Testing to be performed locally. Indeterminate Quantiferon or T-SPOT tests may be repeated once and will be considered positive if retest results are positive or indeterminate. Subjects with documented BCG vaccination must perform a TB test at Screening and will be excluded if they exhibit skin induration ≥5 mm or a positive Quantiferon or positive or borderline T-SPOT (Elispot) test.
[7] To be performed locally.
[8] Height should be measured only once; i.e., at the Day 1/baseline visit.
[9] Vital signs include seated arterial blood pressure, heart rate, and oral body temperature.
[redacted]
[11] One lesion is to be selected at baseline as the target lesion (the most severe active CLE lesion is recommended). The target lesion must be the same lesion used for tape harvesting and the same lesion over time.
[12] If the ET Visit occurs before Week 16, skin photography should be performed at the ET Visit.
[13] Following administration of study treatment, subjects should remain at the study center for 1 hour to be observed for the development of potential allergic or anaphylactic reactions.
[14] Subject paper diaries for recording corticosteroid use will be distributed on Day 1, reviewed with site staff at each study visit, and collected by the study site at the final study visit.
[15] Only for subjects with prior B cell directed therapies within 52 weeks of Screening; this test should be performed at a central laboratory.
[16] Pharmacokinetic evaluations will be conducted as follows: Study Day 1 (predose –1 h and post-dose 4 h ±1 h), Day 8 (any time during visit), Day 29 (predose –1 h and postdose 4 h ±1 h), Day 85 (predose –1 h and postdose 4 h±1 h), Day 113 (predose –1 h), and Day 169 (any time during visit). During the Follow-up Period, 1 sample will be collected on Days 197 and 253 (any time during the visit) [Table 3]. The time and date of PK sample collection and BIIB059 dose should be recorded in the eCRF.
[redacted]
[21] Vaccine-related immunoglobulin titers for tetanus, diphtheria, and *Pneumococcus* will be collected.

Table 2: Schedule of Activities Part B

	Screening Period	Treatment Period							Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16/ ET**	**FU4**	**FU8**	**FU12**
Study Day		**1[3]**	**8 (±2D)**	**15[3] (±2D)**	**29[3] (±3D)**	**57[3] (±3D)**	**85[3] (±3D)**	**113 (±3D)**	**141 (±5D)**	**169 (±5D)**	**197 (±5D)**
Tests and Assessments[2,3]											
Informed Consent Form(s)	X										
Inclusion/Exclusion Criteria	X	X									
Randomization		X									
Demographic Data	X										
CLE, SLE and Other Medical History	X										
Documentation of SLE by ACR Criteria	X										
12-lead ECG[4]	X							X			
Chest x-ray[5] (if required by local regulation)	X										
Tuberculosis Test[6]	X										
Serum Virology (HIV, Hepatitis B and C) RNA	X										
Urine Drug Screen	X										
Serum Pregnancy Test	X										
Urine Pregnancy Test[7]		X		X	X	X	X	X	X	X	X
Physical Examination, Weight, Height[8]	X	X		X	X	X	X	X	X		X
Vital Signs[9]	X	X	X	X	X	X	X	X	X	X	X
[redacted]											
CLASI[10]	X	X		X	X	X	X	X			X

	Screening Period	Treatment Period							Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16/ ET**	**FU4**	**FU8**	**FU12**
Study Day		**1[3]**	**8 (±2D)**	**15[3] (±2D)**	**29[3] (±3D)**	**57[3] (±3D)**	**85[3] (±3D)**	**113 (±3D)**	**141 (±5D)**	**169 (±5D)**	**197 (±5D)**
Tests and Assessments[2,3]											
[redacted]											
Physicians Global Assessment of SLE (VAS) [11,12]	X	X		X	X	X	X	X			
Skin photography of target lesion[13]	X	X			X			X			
Study treatment administration[14]		X		X	X	X	X				
Corticosteroid Diary[15]		X	X	X	X	X	X	X	X	X	X
Laboratory Assessment											
Hematology	X	X		X	X	X	X	X	X		X
Blood Chemistry	X	X		X	X	X	X	X	X		X
Urinalysis (including microscopic examination)	X	X		X	X	X	X	X	X		X
Urine Protein-Creatinine Ratio (spot urine)	X	X		X	X	X	X	X	X		X
CD19+ B Cell Counts[16]	X										
Pharmacokinetics											
Serum BIIB059[17]		X	X		X		X	X	X	X	X
[redacted]											
[redacted]											

	Screening Period	Treatment Period							Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16/ ET**	**FU4**	**FU8**	**FU12**
Study Day		**1[3]**	**8 (±2D)**	**15[3] (±2D)**	**29[3] (±3D)**	**57[3] (±3D)**	**85[3] (±3D)**	**113 (±3D)**	**141 (±5D)**	**169 (±5D)**	**197 (±5D)**
Tests and Assessments[2,3]											
[redacted]											
[redacted]											
[redacted]											
Safety											
Antibodies to BIIB059		X			X			X			X
Immunoglobulin (total, IgG, IgA, IgM)		X			X			X			

	Screening Period	Treatment Period							Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16/ ET**	**FU4**	**FU8**	**FU12**
Study Day		**1[3]**	**8 (±2D)**	**15[3] (±2D)**	**29[3] (±3D)**	**57[3] (±3D)**	**85[3] (±3D)**	**113 (±3D)**	**141 (±5D)**	**169 (±5D)**	**197 (±5D)**
Tests and Assessments[2,3]											
Concomitant Medication/Procedures	Monitor and record from signing of informed consent through the end of the study										
Serious Adverse Events	Monitor and record from signing of informed consent through the end of the study										
Adverse Events	Monitor and record from time of first dose through the end of the study										

Abbreviations: ACR=American College of Rheumatology; C = complement; CLASI = Cutaneous Lupus Disease Area and Severity Index; CLE = cutaneous lupus erythematosus; CRP = C-reactive protein; D = day; DNA = deoxyribonucleic acid; dsDNA = double-stranded DNA; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; ET = early termination; FU = follow-up; HIV = human immunodeficiency virus; Ig = immunoglobulin; [redacted]; RNA = ribonucleic acid; [redacted]; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index; TB = tuberculosis; VAS = visual analog scale.

[1] Follow-up visits will be conducted 4, 8, and 12 weeks after the last Treatment Period Visit (Week 16 or ET).
[2] Assessments (e.g., CPK, ECG, etc.) may be performed as required to confirm SLEDAI-2K findings.
[3] On each dosing day (Day 1, Day 15, Day 29, Day 57, and Day 85) all assessments should be performed prior to dosing.
[4] To be performed locally.
[5] Where mandated by local regulation, a chest x-ray will be obtained locally during the screening period, unless a previous chest x-ray or the documented results from a chest x-ray obtained within 12 weeks prior to screening are available. The chest x-ray or x-ray results will be reviewed by the Investigator (or designee) in order to exclude patients with active TB infection from entering the study.
[6] Testing to be performed locally. Indeterminate Quantiferon or T-SPOT tests may be repeated once, and will be considered positive if retest results are positive or indeterminate. Subjects with documented BCG vaccination must perform a tuberculosis test at Screening and will be excluded if they exhibit skin induration ≥5 mm or a positive Quantiferon or positive or borderline T-SPOT (Elispot) test.
[7] To be performed locally.
[8] Height should be measured only once; i.e., at the Day 1/baseline Visit.
[9] Vital signs include seated arterial blood pressure, heart rate, and oral body temperature.
[10] CLASI will be assessed by the Investigator or a trained designee at all assessments (Section 19.2.2). CLASI scores at Screening will be verified by an Independent CLASI Adjudicator to confirm eligibility.
[redacted]
[14] Following administration of study treatment, subjects should remain at the study center for 1 hour to be observed for the development of potential allergic or anaphylactic reactions.

[15] Subject paper diaries for recording corticosteroid use will be distributed on Day 1, reviewed with site staff at each study visit, and collected by the study site at the final study visit.
[16] Only for subjects with prior B cell directed therapies within 52 weeks of Screening; this test should be performed at a central laboratory.
[17] Pharmacokinetic evaluations will be conducted as follows: Day 1 (pre-dose –1 h and post-dose 4 h ±1 h), Day 8 (any time during the visit), Day 29 (predose – 1 h and postdose 4 h ±1 h), Day 85 (predose –1 h and postdose 4 h ±1 h), and Day 113 (any time during the visit). During the Follow-up Period, 1 sample will be collected on Days 141, 169, and 197 (any time during the visit) [Table 3].

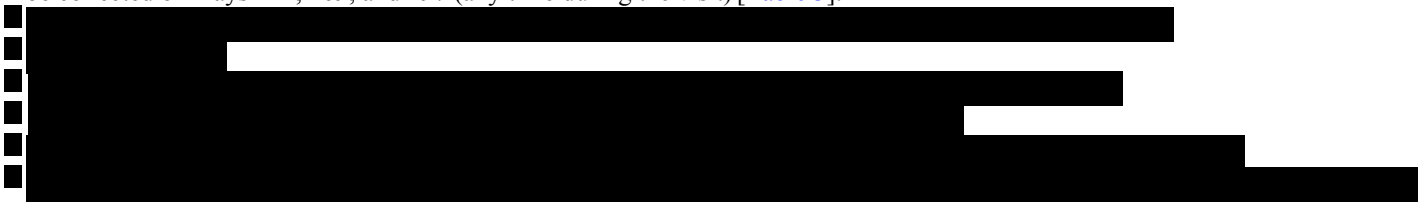


Table 3: Pharmacokinetic Assessments

Study Week	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**Follow-Up Period**
Study Day	1	8 (±2 d)	15 (±2 d)	29 (±3 d)	57 (±3 d)	85 (±3 d)	113 (±3 d)	141 (±3 d)	169 (±3 d)	Part A Day 197 and 253 (±5 d) Part B Day 141, 169, and 197 (±5 d)
Part A										
PK Sampling Timepoint(s)	• Predose (–1 h) • Postdose (4 h ±1 h)	• Any time during visit		• Predose (–1 h) • Postdose (4 h ±1 h)		• Predose (–1 h) • Postdose (4 h ±1 h)	• Predose (–1 h)		• Any time during visit	• Any time during visit
Part B										
PK Sampling Timepoint(s)	• Predose (–1 h) • Postdose (4 h ±1 h)	• Any time during visit		• Predose (–1 h) • Postdose (4 h ±1 h)		• Predose (–1 h) • Postdose (4 h ±1 h)	• Any time during visit			• Any time during visit

Abbreviations: d=days; h=hour(s); PK=pharmacokinetic

4.3. Additional Information

4.3.1. Site Personnel

For each subject, the Principal Investigator (or a qualified designee) will be responsible for administering the following instruments throughout the study. Every effort will be made to ensure that assessments are performed by the same evaluator for a given subject over time.

- Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)
- British Isles Lupus Activity Group 2004 (BILAG) [Part A only]
- Systemic Lupus Erythematosus Disease Activity Index – 2000 (SLEDAI-2K) [all subjects in Part A and subjects in Part B with SLE by American College of Rheumatology criteria at Screening]
- [redacted]
- [redacted]
- [redacted]

An unblinded pharmacist (or authorized designee) will be responsible for the storage, distribution, preparation and accountability of study treatment. The unblinded pharmacist will also be responsible for maintaining the unblinded pharmacy record separate from the main study file in order to support the study blind.

4.3.2. Skin RNA Tape Harvesting (Parts A and B)

Skin tape harvesting (tapings on the target lesion site only; the most severe active CLE lesion is recommended) will be collected at Week 0 (baseline), Week 4, and Week 16 for Part A and Part B. Only 1 affected target lesion of active CLE should be tested. The same target lesion sampled at baseline should be sampled at subsequent timepoints to study the evolution of the same lesion over time.

Refer to the Study Reference Guide for instructions on collection and processing of samples.

4.3.3. Joint Count Assessment (Part A Only)

Joint counts will be evaluated at all visits by a trained independent joint assessor. The joint counts for an individual subject must be performed by the same joint assessor throughout the trial.

For this study, the joint assessment will be carried out on 28 joints. The joints to be assessed bilaterally include the shoulders, elbows, wrists (radiocarpal, carpal, and carpometacarpal bones are considered as a single unit), metacarpophalangeal (MCP) joints (MCP 1, 2, 3, 4, and 5), proximal interphalangeal (PIP) joints (PIP 1, 2, 3, 4 and 5), and the knees. Artificial and ankylosed or fused joints will be excluded from tenderness and swelling assessments.

4.3.4. Skin Photography (Parts A and B)

Part A

In Part A, close-up clinical photographs of the target skin lesion (most severe active CLE lesion) will be obtained at Week 0 (baseline), Week 4, and Week 16 (or at early termination, if applicable). The target skin lesion is the same lesion that will be used for tape harvesting.

Part B

In Part B, for skin lesions with CLASI-A score greater than 0, photographs of each lesion and of the corresponding region with lesion(s) will be obtained at Screening, Week 0 (baseline), Week 4, and Week 16 (or at early termination, if applicable). Photographs taken at Screening will be evaluated by a central adjudicator to verify the CLASI-A score assignment by the Investigator and confirm eligibility.

One lesion is to be selected at baseline as the target lesion (the most severe active CLE lesion is recommended). The same target lesion must be photographed and used for tape harvesting and optional biopsy at each applicable timepoint.

Identical technical settings should be maintained. Biogen will provide cameras and devices for standardized photography. These photographs will be sent electronically to the central database.

On the day of photography, subjects are requested to avoid applying ointments, creams, or make-up onto their skin prior to the visit.

For further details please see the Study Reference Guide.

4.3.5. Skin Biopsy (Part B Only)

4.3.5.1. Skin Biopsy for Confirming CLE Diagnosis

For subjects without historical biopsy data, diagnosis will be confirmed during Screening by skin biopsy that can be read at a local laboratory or the central laboratory, at the discretion of the Investigator. A punch biopsy will be performed for diagnostic purposes. Subjects with an available historical biopsy do not need a screening biopsy for diagnosis.

4.3.5.2. Optional Skin Biopsy

[redacted] A punch biopsy should be performed.

Biopsies should be taken from the same lesion at both timepoints, and a biopsy from the edge of the active lesion is preferred. For further details on skin biopsy, see the Study Reference Guide.

4.3.6. CLASI Adjudication (Part B Only)

CLASI will be assessed by the Investigator or a trained designee and entered by the Investigator at all assessments (Section 19.2.2). CLASI scores at Screening will be verified by an Independent CLASI Adjudicator to confirm eligibility.

4.3.7. Blood RNA Paxgene and Skin Biopsy Immunohistochemistry Assessments

Blood samples will be collected from all subjects to evaluate biomarkers that may be related to BIIB059 activity or indicative of subjects who may respond to BIIB059. Biomarkers may include but are not limited to baseline levels of interferon (IFN)-inducible messenger RNA (mRNA) [i.e., type I IFN signature]. Effects of BIIB059 on these or other markers of disease may also be evaluated.

Classical immunohistochemistry in CLE skin biopsies (Part B) will be performed to study changes in PD biomarkers that may be related to BIIB059 activity in the skin, including but not limited to IFN-related proteins. *In situ* hybridization may also be performed to study changes in IFN-regulated or cytokine and chemokine mRNA levels after BIIB059 treatment.

5. INTRODUCTION

BIIB059 is a humanized immunoglobulin class G, type 1 (IgG1) monoclonal antibody that specifically recognizes blood dendritic cell antigen 2 (BDCA2), a type II, C-type lectin receptor expressed exclusively on the surface of human plasmacytoid dendritic cells (pDCs). BDCA2 receptor engagement in pDC prevents or diminishes toll-like receptor (TLR)7- and TLR9-induced production of IFN-α, and pDC-derived cytokines and chemokines [Cao 2007; Dzionek 2001; Fanning 2006; Röck 2007]. In non-clinical studies, BIIB059 has been shown to potently inhibit all TLR9-induced type I IFNs, as well as other pDC-derived cytokines and chemokines. BIIB059 ligation leads to rapid internalization of BDCA2 from the cell surface of human pDC and its co-localization with TLR9 in the late endolysosomal compartment, which appears to be necessary f or inhibition of TLR9 signaling. In vitro, BIIB059 also triggers internalization of CD32a which may prevent immune complex stimulation of pDC [Pellerin 2015]. By binding to BDCA2, BIIB059 treatment should target pDC in affected tissues in patients with SLE and CLE and decrease production of IFN-α, as well as other IFN subtypes and pDC-derived cytokines and chemokines that contribute to SLE and CLE pathogenesis.

5.1. Overview of Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects multiple organ systems and is unpredictable in disease severity, with periods of illness or flares alternating with periods of remission. The diverse presentation of lupus can range from rash and arthritis, anemia and thrombocytopenia, serositis, nephritis, seizures and psychosis. At its onset, SLE may involve one or more organ systems, including the musculoskeletal, cutaneous, vascular, renal, pulmonary, hematologic, and nervous systems. Disease prevalence is approximately 1 in 1000 individuals overall, but varies with race and ethnicity. SLE is more common in women than in men (up to 10 times more common). Subjects with moderate to-severe SLE consider their health-related quality of life (HRQoL) to be poor [Fauci and Longo 2008; Jiménez 2003].

Cutaneous lupus erythematosus is a chronic autoimmune disease that may present with or without SLE. Up to 80% of subjects with SLE will have cutaneous manifestations. Based on histopathological findings, the cutaneous manifestations of lupus erythematosus (LE) may be classified into LE-specific and LE-nonspecific skin lesions (e.g., urticarial vasculitis, livedo reticularis), which may be observed in other autoimmune diseases. LE-specific skin lesions may be further subdivided based on clinical and histopathological characteristics into acute cutaneous LE, subacute cutaneous LE (SCLE), and chronic cutaneous LE (CCLE), representing, respectively, 15%, 8%, and 73% of all CLE [Gilliam and Sontheimer 1981; Grönhagen and Nyberg 2014]. In CCLE, the most common form (80%) is DLE, which is rarely associated with systemic LE manifestation. Less than 10% of patients with DLE fulfill 4 of the SLE American College of Rheumatology (ACR) criteria, and between 5% and 10% of individuals with DLE will develop full SLE [Biazar 2013; Koskenmies 2008; Okon and Werth 2013; Vasquez 2013].

5.2. Current Therapies for Lupus Erythematosus

Most therapies used to treat SLE are only partially effective and have considerable toxicity. Nonsteroidal anti-inflammatory drugs (NSAIDs) and antimalarials are commonly used as

first-line therapies for mild disease. Corticosteroids and immunosuppressive drugs continue to be the mainstay for treating flares of moderate-to-severe SLE disease. Although immunosuppressive drugs can partially improve the outcome of severe SLE, very often the disease is incompletely controlled. In addition, immunosuppressive and corticosteroid drugs are associated with serious side effects [Doria 2014; Petri 2013; Ruiz-Arruza 2014]. Belimumab (Benlysta®) is the only targeted therapy approved to treat SLE. Subjects treated with belimumab and standard of care (SoC) had an increased rate of treatment response compared with those receiving placebo and SoC; however, the treatment effect was small, with 9% to 13% of patients achieving an SLE Responder Index (SRI) response of 4 in the registration studies [Furie 2011; Navarra 2011; van Vollenhoven 2012].

To date, no medications have been specifically approved for the treatment of CLE. Current therapies consist of topical corticosteroids, topical calcineurin inhibitors, and intralesional corticosteroids (for scalp lesions). For subjects who are refractory to topical therapy or who have widespread or scarring skin disease, systemic therapy, including the antimalarial agents hydroxychloroquine, chloroquine, or quinacrine, is used. Other systemic medications that can be useful in moderate and/or severe CLE subject subsets include dapsone, retinoids, azathioprine, methotrexate, thalidomide, and occasionally systemic corticosteroids [Okon and Werth 2013; Schultz 2015; Winkelmann 2013]. Unsatisfactory effectiveness and/or associated toxicities limit the use of antimalarial therapies in moderate-to-severe CLE and/or DLE. In a prospective study including 300 subjects with CLE (86 SCLE, 160 DLE, 54 others), in subjects who were treated with hydroxychloroquine, only 21% (men) to 41% (women) reported clinical remission after at least 12 weeks of therapy. Complete remission was negatively correlated with DLE diagnosis and male sex [Francès 2012]. Use of antimalarial agents is also associated with toxicities, including retinal toxicity, gastrointestinal disorders, skin hyperpigmentation, myopathy, and white discoloration of lighter skin [Chang 2011].

5.3. Profile of Previous Experience with BIIB059

5.3.1. Nonclinical Experience

Nonclinical toxicology studies in cynomolgus monkeys showed that BIIB059 administered every 2 weeks (Q2W), with up to 26-weeks of exposure at doses up to 125 mg/kg, was well tolerated, with no mortalities and no general or organ toxicity observed. No effect on the central nervous, respiratory, or cardiovascular systems, no alteration in the immune cell population, and no clinical or histopathological evidence of injection-site reactions were associated with intravenous (IV) or subcutaneous (SC) administration of BIIB059.

See the Investigator's Brochure for detailed information on nonclinical studies.

5.3.2. Clinical Experience

BIIB059 is under development as a first-in-class therapy for the treatment of SLE. It has been evaluated in a Phase 1 single-ascending-dose (SAD) and multiple-ascending-dose (MAD) study (230LE101). Briefly, this first-in-human study was a randomized, blinded, placebo-controlled study designed to evaluate the safety, tolerability and pharmacokinetics (PK) of single and multiple ascending doses of BIIB059. The study consisted of 3 parts and included healthy volunteers and subjects with SLE who fulfilled the 1997 ACR classification criteria. In Part 1,

healthy volunteers received a single IV dose of BIIB059 that ranged from 0.05 to 20 mg/kg, in order to assess the safety and tolerability of BIIB059 and determine its PK and pharmacodynamic (PD) activity. The bioavailability of a single BIIB059 50 mg (fixed) dose administered SC to healthy volunteers was also determined in Part 1. In Part 2, subjects with SLE and skin manifestations received a single BIIB059 IV dose of 20 mg/kg. In Part 3, healthy volunteers received up to 3 doses of BIIB059 that ranged from 20 mg to 300 mg every 2 weeks (Q2W) or every 4 weeks (Q4W); SLE subjects received 2 doses of BIIB059 50 mg SC Q4W or 3 doses of BIIB059 ≤300 mg SC Q2W, for a total of 3 doses.

The PK data from Study 230LE101 demonstrate that maximum observed concentration (C_{max}) and area under the concentration-time curve (AUC) for BIIB059 increased with dose following single IV administration (0.05 mg/kg to 20 mg/kg). Target-mediated clearance (CL) for BIIB059 was observed at lower doses e.g., <1 mg/kg and became saturated at doses ≥1 mg/kg. Following SC administration to healthy volunteers, BIIB059 C_{max} was reached in approximately 6 days, with a bioavailability of approximately 50%. The AUC_{∞} in SLE subjects was 39% lower when compared to healthy volunteers at IV doses of 20 mg/kg. Following multiple SC administrations (20 mg to 300 mg) the $AUC_{0\text{-}28d}$ in SLE subjects was 40% lower as compared with healthy volunteers at SC doses of 50 mg. The accumulation ratio for AUC was lower in SLE subjects (2.58) compared to healthy volunteers (2.66), after BIIB059 SC administration. Overall, the targeted mechanism of action of BIIB059, the absence of toxicological findings up to the highest dose tested, and the available clinical safety data support the ongoing evaluation of BIIB059 in subjects with SLE and CLE. The safety data obtained to date in healthy volunteers and subjects with SLE supports the evaluation of BIIB059 in this Phase 2 clinical Study 230LE201.

Study 230LE101 results indicated that complete BDCA2 internalization (i.e., target engagement and PD activity) was achieved at all dose levels, the duration of which was dose dependent. Reappearance of BDCA2 on circulating pDCs occurred when serum concentrations of BIIB059 decreased to approximately 1 µg/mL. BDCA2 internalization was similar for healthy volunteers and subjects with SLE. In addition, Study 230LE101 demonstrated proof of biological activity in SLE, whereby the IFN signature was dampened both in the blood and skin of SLE subjects, consistent with the mechanism of action of BIIB059.

Skin biopsies in 6 of 8 subjects receiving BIIB059 revealed a reduction in cutaneous myxovirus A, an IFN-associated protein, at Week 4. Notably, those same 6 subjects had at least a 4-point reduction in CLASI score at Week 4 and/or Week 12, indicating that the PD signal was associated with a clinical reduction in skin involvement in this exploratory analysis [Furie 2016].

Data from Part 1 of the first-in-human study, which included 54 healthy volunteers (38 received BIIB059), indicated that BIIB059 treatment was well tolerated at single doses up to 20 mg/kg in these SAD cohorts, with no severe AEs. Data from Part 2 (SAD), which included 12 SLE subjects (8 received BIIB059), indicated that BIIB059 treatment was well tolerated at single doses of 20 mg/kg [Furie 2016]. Data from Part 3 (MAD), which included 33 healthy volunteers (25 received BIIB059) and 10 SLE subjects (8 received BIIB059), indicated that BIIB059 treatment was well tolerated at multiple doses up to 300 mg in this study. Three SLE subjects experienced SAEs: 1 subject enrolled in Part 2 of the study (BIIB059 20 mg/kg IV) and 2 subjects enrolled in Part 3b of the study (BIIB059 50 mg SC and BIIB059 300 mg SC). None of

the SAEs was considered related to BIIB059 as assessed by the Investigator. No SAEs were reported in healthy volunteers in Part 1 or 3a of the study. In Part 3a, 1 subject discontinued study treatment due to an AE not related to BIIB059; however, none withdrew from the study due to an AE.

See the Investigator's Brochure for detailed information on BIIB059 clinical studies.

5.4. Study Rationale

A hallmark of SLE and CLE is the production of autoantibodies to a variety of nuclear antigens that account for some of the pathological manifestations [Achtman and Werth 2015; Fauci and Longo 2008; Rahman and Isenberg 2008]. Although the pathogenesis of SLE and CLE is not fully understood, there is increasing evidence that the cytokine family of type I IFNs, most notably IFN-α, plays a central role in the pathogenesis of SLE, including the cutaneous manifestations seen in CLE. In both CLE and SLE, type I IFN expression correlates with both disease activity and severity [Braunstein 2012; Dall'era 2005; Hellquist 2009; Järvinen 2010; Niewold 2012]. Furthermore, the "IFN signature" that represents a messenger RNA expression pattern of IFN-inducible genes has been observed in more than half of SLE patients and in 70% to 75% of patients with active disease [Furie 2015; Kalunian 2016]. Although not predictive of flares or changes in disease activity, a high IFN signature is associated with greater disease activity [Baechler 2003; Petri 2009].

In CLE, type I IFNs are thought to be involved in amplifying intralesional inflammation by inducing IFN-inducible chemokines and recruitment of T cells into the skin. As pDC have been identified as the main IFN-producing cells in CLE [Farkas 2001; Ghoreishi 2012; Vallin 1999] blocking pDC and the IFN pathway may provide clinical benefit. Recent data from Phase 2 studies with IFN-α-blocking agents (sifalimumab and anifrolumab) demonstrated improvement in systemic lupus disease activity and, more specifically, cutaneous manifestations, further supporting the rationale for blocking the IFN pathway in patients with SLE and CLE with or without systemic manifestations [Furie 2015; Khamashta 2014].

BDCA2 is a type II, C-type lectin receptor that is uniquely expressed on the cell surface of pDC and was the first receptor described to negatively down-regulate the type I IFN response in these cells [Cao 2007; Dzionek 2001; Fanning 2006; Röck 2007]. In SLE, pDC are found to be decreased in the blood and to be present in target organs such as the skin or the kidney [Farkas 2001; Vermi 2009]. By binding to BDCA2, BIIB059 treatment should target pDC in affected tissues in patients with SLE and CLE and decrease production of IFN-α, as well as other IFN subtypes and pDC-derived cytokines and chemokines that contribute to SLE and CLE pathogenesis. In addition, BIIB059 may decrease localization of pDC in SLE- or CLE-affected organs such as the skin and restore the number of circulating pDC in the blood.

Altogether, given the lack of highly efficacious and safe treatments for active SLE and CLE, and the large impact of this disease on health-related quality of life (HRQoL) in SLE and CLE patients, there is currently a large unmet need for new targeted therapies. Based on its mechanism of action, BIIB059 has the potential to decrease skin disease activity. In addition, based on data currently available, BIIB059 presents an acceptable safety profile, and hence it is therefore justified to evaluate its potential efficacy in subjects with active SLE or CLE.

5.5. Rationale for Dosing Regimen

5.5.1. Part A

Single IV as well as multiple SC doses of BIIB059 up to and including 20 mg/kg and 300 mg, respectively, in healthy volunteers have demonstrated acceptable tolerability in the Phase 1 Study (230LE101). In general, BIIB059 serum concentrations were slightly lower in subjects with SLE than in healthy volunteers following dosing with BIIB059 50 mg SC (single and multiple dose administration). Additionally, the median percent change from baseline in BDCA2 on pDC surfaces was equivalent between SLE and healthy subjects following SC doses of 50 mg.

Single doses of 450 mg administered SC Q4W, with an additional dose at Week 2, will be used in Part A. The dosing regimen was selected based on Phase 1 safety, PK, PK-BDCA2 internalization relationship and extrapolated inhibitory potency (concentration resulting in 90% inhibition of response [IC_{90}]) of pDC IFN-α production [Pellerin 2015]. The BIIB059 fixed dose of 450 mg SC Q4W, with an additional dose at Week 2, was selected to achieve C_{min} levels similar to 3-fold of the calculated IC_{90} for IFN-α inhibition. Furthermore, this dose regimen with an additional dose of 450 mg at Week 2 and a bioavailability (F) of 0.45 is expected to result in cumulative exposure comparable to or lower than that achieved by the single dose of 20 mg/kg IV for a 65-kg person, the highest dose tested in healthy volunteers.

5.5.2. Part B

The dosing regimen was selected based on the Phase 1 safety, PK, PK-BDCA2 internalization relationship, and extrapolated inhibitory potency (concentration resulting in 90% inhibition of response [IC_{90}]) of pDC IFN-α production [Pellerin 2015]. BIIB059 fixed doses of 50, 150 and 450 mg SC Q4W, with an additional dose at Week 2, were selected for the Phase 2 study because simulations conducted, based upon the population PK model developed using the phase 1 data, predicted that:

- At the low dose of 50 mg SC Q4W, BIIB059 is expected to achieve plasma concentrations sufficient to maintain 90% BDCA2 internalization for the majority of the dosing interval.
- At the middle dose of 150 mg SC Q4W, BIIB059 is expected to achieve plasma concentrations similar to or in excess of the calculated IC_{90} for IFN-α for the majority of the dosing interval.
- At the top dose of 450 mg SC Q4W, BIIB059 is expected to achieve C_{min} levels similar to 3-fold of the calculated IC_{90} for IFN-α inhibition.

The selected doses are considered safe and tolerable, based upon the results of the Phase 1 study. The dosing regimen of 450 mg SC Q4W, with an additional dose of 450 mg at Week 2 and a bioavailability (F) of 0.45, is expected to result in cumulative exposure over 12 weeks that is comparable to or lower than that achieved by the single dose of 20 mg/kg IV for a 65-kg person, the highest dose tested in healthy volunteers.

5.5.3. Rationale for Placebo

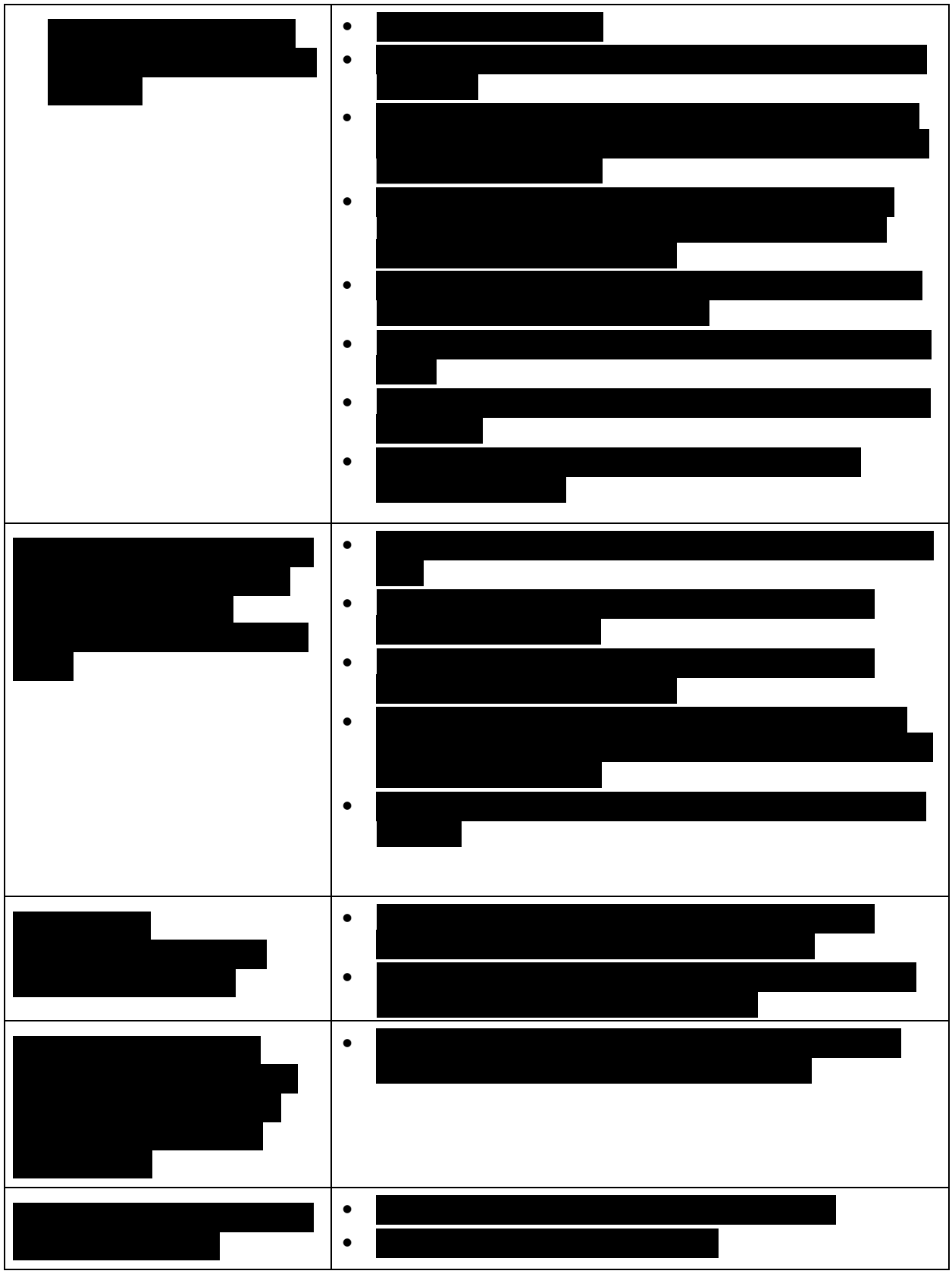
The use of placebo is justified because subjects assigned to placebo may also be receiving background lupus SoC. Any prior lupus background medication allowed in this study that has been initiated prior to Screening will be authorized according to the protocol specifications (Section 11.4.1.1.1).

6. STUDY OBJECTIVES AND ENDPOINTS

Table 4: Study Objectives and Endpoints

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of BIIB059 in reducing disease activity in subjects with SLE with active cutaneous manifestations and joint involvement (Part A), and in subjects with active CLE (SCLE or chronic CLE, including DLE) with or without systemic manifestations (Part B).	Part A: Change in active joint count (28-joint assessment) from Baseline to Week 24; the active joint count is defined as the sum of tender and swollen joint counts. Part B: Percent change in CLASI-A score from Baseline to Week 16.
Secondary Objectives	**Secondary Endpoints**
To evaluate additional efficacy parameters of BIIB059 in reducing SLE/CLE disease activity.	
Skin related (Part A and Part B):	• CLASI-50, defined as a 50% improvement from baseline in CLASI-A score at Week 24 (Part A) and Weeks 12 and 16 (Part B) • Percent change in CLASI-A score from baseline to Weeks 12, 16, and 24 (Part A) and Week 12 (Part B) • A ≥4-point reduction in CLASI-A score relative to baseline at Week 24 (Part A) and at Weeks 12 and 16 (Part B)
SLE disease activity related (Part A only):	• Proportion of subjects with a composite response, defined as: – SLE Responder Index (SRI) of ≥4 (SRI-4) at Week 24, where SRI-4 is defined as: o A reduction from baseline of ≥4 points in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) and o No new organ system affected, as defined by no new BILAG-2004 A and no more than one new BILAG-2004 B and o No worsening from baseline in subject's lupus disease activity defined by <0.3 point

	increase in PGA (VAS) – No protocol-prohibited medication or treatment. – Concomitant corticosteroid dosage at Week 24 to be ≤10 mg/day – Concomitant corticosteroid dosage at Week 24 to be ≤Day 1 corticosteroid dosage – No increase in corticosteroid dose between Weeks 17 and 24 • Change from baseline to Week 24 in SLEDAI-2K score • Proportion of subjects with no new organ system affected, as defined by no new BILAG-2004 A and no more than one new BILAG-2004 B from baseline to Week 24 • Change from baseline to Week 24 in PGA VAS score
To evaluate pharmacokinetic parameters of BIIB059 (Parts A and B)	• BIIB059 clearance, volume of distribution, and absorption rate
To evaluate the safety and tolerability of BIIB059 (Parts A and B)	• Nature, severity, relationship to study treatment and incidence of AEs and SAEs • Change from baseline in standard laboratory parameters, vital signs and ECGs • Immunogenicity (antibodies to BIIB059) • Absolute and percent change from baseline over time in immunoglobulin levels and vaccine-related immunoglobulin titers
[redacted]	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted]



	– [redacted] – [redacted] – [redacted]

Abbreviations: ACR = American College of Rheumatology; AE = adverse event; BILAG = British Isles Lupus Activity Group; CLASI-A = Cutaneous Lupus Erythematosus Disease Area and Severity Index – Activity; [redacted]; CLE = cutaneous lupus erythematosus; ECG = electrocardiogram; [redacted]; PGA = Physician's Global Assessment; [redacted]; SAE = serious adverse event; [redacted]; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index – 2000; SRI-4 = SLE Responder Index of ≥4; VAS = visual analog scale.

[redacted]

7. STUDY DESIGN

7.1. Study Overview

This is a 2-part randomized, double-blind, parallel-group, placebo-controlled, multicenter Phase 2 trial designed to evaluate the efficacy and safety of BIIB059 in subjects with SLE with active skin manifestations and joint involvement (Part A) or active CLE, defined as SCLE or CCLE, including DLE, with or without SLE (Part B). The study will be conducted at approximately 130 centers in the United States, Europe, Latin America, and Asia.

Study treatment will begin following a 28-day Screening period.

In Part A, subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio and will receive either BIIB059 (450 mg) or placebo subcutaneously every 4 weeks (Q4W) for 24 weeks, with an additional dose at Week 2, for a total of 7 doses (Figure 1). The maximum number of subjects in Part A is approximately 190 subjects. Of these 190 subjects, approximately 100 subjects will be enrolled under protocol version 2 or subsequent versions. If the study is not stopped for futility at the interim analysis (IA), then up to 70 additional subjects may be added (up to a total of approximately 170 subjects under protocol version 2 or subsequent versions). Subjects enrolled under protocol version 1 will remain on their original treatment assignment (up to a total of approximately 20 subjects) and will not be reconsented under protocol version 2. Randomization will be stratified by oral corticosteroid usage (≤10 mg vs. >10 mg) and by geographic region (United States vs. Asia vs. Latin America and Europe).

In Part B, approximately 130 subjects will be randomized; of these, approximately 100 subjects will be enrolled under protocol version 2 or subsequent versions. Subjects enrolled under protocol version 1 will remain on their original treatment assignment and may be reconsented under protocol version 2 unless they have completed the Week 12 / Early Termination Visit. Subjects enrolled in protocol version 2 or subsequent versions will be randomly assigned to 1 of 4 treatment groups in a 1:1:1:1 ratio, with approximately 25 subjects per treatment arm to receive either a fixed dose of BIIB059 (50 mg, 150 mg, or 450 mg) or placebo SC every 4 weeks (Q4W) for 16 weeks, with an additional dose at Week 2, for a total of 5 doses (Figure 2). Randomization will be stratified by CLASI-A score (≤10 vs. >10) and DLE (presence, absence).

An IA (IA 1) for futility of Part B and possible expansion of Part A will be performed. IA 1 will be performed after approximately 45% of Part B subjects under protocol version 2 or subsequent versions have completed their Week 12 Treatment Visit. At the time of this IA, it is estimated that over 50% of subjects in Part A will have completed their Week 12 treatment visit. Following the IA, up to an additional 70 subjects maybe enrolled in Part A and BIIB059 dose may by adjusted. The additional subjects in Part A may be enrolled based on a more inclusive criteria to include an expanded SLE population. Details are provided in Section 16.7.1.

An interim database lock and IA (IA 2) of efficacy and safety data will occur after the last subjects complete the Double-Blind Treatment Periods for Part A (at Week 24) and Part B (at Week 16). Details are provided in Section 16.7.2.

For both IAs (1 and 2), all Investigators, study site personnel, and subjects will remain blinded to treatment assignments until after the final database lock.

7.2. Overall Study Duration and Follow-Up (Part A)

The total duration of study participation for each subject who completes Part A of the study will be approximately 40 weeks (a 4-week Screening Period, a 24-week double-blind Treatment Period, and a 12-week Follow-up Period). Details on the timing of assessments during the study are presented in Table 1.

7.2.1. Screening

Subject eligibility for the study will be determined within 4 weeks prior to randomization. Laboratory assessments for eligibility may be repeated once if the results are out of eligibility range, but considered not clinically significant by the Investigator.

See Section 9 for details on screening and registration of subjects.

7.2.2. Treatment

Subject eligibility will be reconfirmed prior to randomization on Day 1. Eligible subjects will receive study treatment on Day 1 and return to the study site for additional dosing every 4 weeks through Week 20, with an additional dose at Week 2. Following each administration of study treatment, subjects should remain at the study center for 1 hour to be monitored for the development of potential allergic or anaphylactic reactions. Subjects will receive study treatment at baseline (Day 1), Week 2 (Day 15), Week 4 (Day 29), Week 8 (Day 57), Week 12 (Day 85), Week 16 (Day 113), and Week 20 (Day 141) for a total of 7 doses.

Subjects will undergo study assessments (see Table 1) at each of the dosing visits and will also undergo assessments at Week 1 (Day 8) and Week 24 (Day 169), though study treatment is not administered at these visits. The last dose of study treatment will be administered at Week 20 (Day 141).

7.2.3. Follow-Up

Subjects are to return to the study site for follow-up (FU) visits at 4, 8, and 12 weeks after the last Treatment Period visit (Week 24 or Early Termination [ET] Visit). Follow-up visits will be conducted at Week FU4 (Day 197), Week FU8 (Day 225) and Week FU12 (Day 253). The final study visit will be Week FU12.

Subjects who prematurely **discontinue study treatment** during the Double-blind Treatment Period should complete all study assessments for the Week 24/ET Visit as soon as possible, but within 4 weeks. Subjects who discontinue study treatment should also complete the study assessments for the Safety FU Visits at Week FU4, Week FU8, and Week FU12 after their ET Visit.

Subjects who are prematurely **withdrawn from the study** during the Double-blind Treatment Period should complete all study assessments for the Week 24/ET Visit as soon as possible, but within 4 weeks. Withdrawn subjects should also be encouraged to complete the study assessments for the Safety FU Visits at Week FU4, Week FU8, and Week FU12, after their ET Visit. However, if the subject is unwilling or unable to attend the study FU Visits, or at minimum the ET Visit, and decides to withdraw consent, the reason for withdrawal will be documented and no further assessments will be obtained.

7.3. Overall Study Duration and Follow-Up (Part B)

The total duration of study participation for each subject who completes Part B of the study will be approximately 32 weeks (a 4-week Screening Period, a 16-week double-blind Treatment Period, and a 12-week Follow-up Period). Details on the timing of assessments during the study are presented in Table 2.

7.3.1. Screening

Subject eligibility for the study will be determined within 4 weeks prior to randomization. Laboratory assessments for eligibility may be repeated once if the results are out of eligibility range but considered not clinically significant by the Investigator.

For subjects without a historical biopsy-proven diagnosis of CLE, eligibility will be confirmed during Screening by a skin biopsy that can be read at a local laboratory (if a pathologist is present) or at a central laboratory. Subjects with a documented historical biopsy do not need a Screening biopsy for diagnosis.

See Section 9 for details on screening and registration of subjects.

7.3.2. Treatment

Subject eligibility will be reconfirmed prior to randomization on Day 1. Eligible subjects will receive study treatment on Day 1 and return to the study site for additional dosing every 4 weeks through Week 12, with an additional dose at Week 2. Following each administration of study treatment, subjects should remain at the study center for 1 hour to be monitored for the development of potential allergic or anaphylactic reactions. Subjects will receive study treatment at baseline (Day 1), Week 2 (Day 15), Week 4 (Day 29), Week 8 (Day 57), and Week 12 (Day 85), for a total of 5 doses.

Subjects will undergo study assessments (see Table 2) at each of the dosing visits and will also undergo assessments at Week 1 (Day 8) and Week 16 (Day 113), though study treatment is not administered at these visits. The last dose of study treatment will be administered at Week 12 (Day 85).

7.3.3. Follow-Up

Subjects are to return to the study site for follow-up visits on Week FU4 (Day 141), Week FU8 (Day 169), and Week FU12 (Day 197) after the last Treatment Period visit (Week 16 or ET Visit). The final study visit will be Week FU12.

Subjects who prematurely **discontinue study treatment** during the Double-blind Treatment Period should complete all study assessments for the Week 16/ET Visit as soon as possible, but within 4 weeks. Subjects who discontinue study treatment should also complete the study assessments for the Safety FU Visits at Week FU4, Week FU8, and Week FU12 after their ET Visit.

Subjects who are prematurely **withdrawn from the study** during the Double-blind Treatment Period should complete all study assessments for the Week 16/ET Visit as soon as possible, but within 4 weeks. Withdrawn subjects should be encouraged to complete the study assessments for the Safety FU Visits at Week FU4, Week FU8, and Week FU12 after their ET Visit.

However, if the subject is unwilling or unable to attend the study FU Visits, or at minimum the ET Visit, and decides to withdraw consent, the reason for withdrawal will be documented and no further assessments will be obtained.

7.4. Study Stopping Rules

Biogen will notify Investigators, ethics committees and any applicable regulatory agencies when the study is to be placed on hold, completed, or terminated.

Conditions that may warrant termination of the study include, but are not limited to the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of Biogen to suspend or discontinue testing, evaluation, or development of the product

7.5. End of Study

The end of study is last subject's last visit.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

8.1.1. Inclusion Criteria (Parts A and B)

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening or at the time point specified in the individual eligibility criterion listed:

1. Ability of the subject to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Age 18 to 75 years old, inclusive, at the time of informed consent.
3. All women of childbearing potential and all men must practice effective contraception during the study and for 16 weeks after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.

8.1.2. Inclusion Criteria (Part A Specific)

1. Diagnosis of SLE fulfilling at least 4 out of 11 of the 1997 revised ACR classification criteria for SLE (Appendix C), with a diagnosis made ≥24 weeks prior to signing the informed consent form (ICF).
2. Positive antinuclear antibody test at Screening (central laboratory titer ≥1:80) and/or elevated anti-double-stranded DNA (≥30 IU/mL).
3. At least one sign of active skin disease, including acute, subacute, and/or chronic cutaneous lupus (e.g., discoid lupus erythematosus), with skin activity defined by SLEDAI-2K.
4. Must have at least 4 tender joints based on assessment of 28 joints as described in Section 4.3.3.
5. Must have at least 4 swollen joints based on assessment of 28 joints as described in Section 4.3.3, with at least 4 occurring in the PIP, MCP, or wrist joints. Note: A joint that is both tender and swollen will be included in both categories (counts as 1 tender and 1 swollen).
6. To allow for accurate assessment of joint tenderness and swelling, subjects who may be taking NSAIDs or other analgesics, including narcotics or medical marijuana, must agree not to take a dose of these medications within 24 hours prior to the joint assessment visits.

8.1.3. Inclusion Criteria (Part B Specific)

1. Must have diagnosis of CLE that has been histologically confirmed (in the past or at Screening), with or without systemic LE manifestations. The histological diagnosis confirmation should be documented at Screening. For subjects without historical biopsy

data, a skin biopsy must be performed at Screening to confirm CLE diagnosis prior to randomization. All subjects must also have active skin manifestations that fulfill the following:

- Subacute CLE with a CLASI-A erythema score of ≥2

  and/or

- Chronic CLE, including DLE, with at least 1 active DLE lesion with a minimum CLASI-A erythema score ≥2 and in addition, CLASI-D scarring score ≥1

2. CLASI-A ≥8 at Screening and randomization.
3. Must have active CLE despite an adequate trial of conventional therapies (defined as either topical corticosteroids or an antimalarial agent used for at least 12 weeks prior to Screening) OR previously documented failure to respond to these agents when used for at least 12 weeks OR the requirement to discontinue these agents due to side effects or poor tolerability.

8.2. Exclusion Criteria

8.2.1. Exclusion Criteria (Parts A and B)

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening, or at the timepoint specified in the individual criterion listed:

1. Current enrollment or a plan to enroll in any interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered. A washout period of at least 12 weeks or 5 half-lives (whichever is longer) is required prior to randomization. Participation in observational registries is allowed.
2. For subjects who previously received an investigational or approved treatment that blocks IFN-α, a washout period of 24 weeks is required prior to randomization.
3. For subjects who previously received BIIB059 in the phase 1 study, a washout period of 24 weeks is required prior to randomization in the present study. Subjects who discontinued previous BIIB059 study participation due to AEs are not eligible.
4. Inability to comply with study requirements.
5. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

Medical Condition

6. History or positive test result at Screening for human immunodeficiency virus.
7. Current active hepatitis C virus (HCV) infection, determined as HCV RNA above the limit of detection, in subjects with positive HCV antibody titer.
8. Positive test result at Screening for hepatitis B virus (HBV; defined as positive for either hepatitis B surface antigen or hepatitis B core antibody).

9. Active lupus nephritis or moderate-to-severe or chronic kidney disease (urine protein to creatinine ratio >2.0 or estimated glomerular filtration rate <30 mL/min/1.73 m^2 calculated using the abbreviated Modification of Diet in Renal Disease equation) [Stevens 2007].
10. Subjects with a history of suicide attempt or suicidal ideation within 1 year prior to Screening.
11. Active neuropsychiatric SLE including but not limited to the following: seizure, new or worsening impaired level of consciousness, psychosis, delirium or confused state, aseptic meningitis, ascending or transverse myelitis, chorea, cerebellar ataxia, mononeuritis multiplex, or demyelinating syndromes.
12. Any active skin conditions other than CLE that may interfere with skin assessments (e.g., psoriasis, non-LE skin lesions, non-LE alopecia areata, drug-induced lupus).
13. History of severe herpes infection, such as herpes encephalitis, ophthalmic herpes, or disseminated herpes.
14. History of chronic, recurrent (3 or more of the same type of infection in a 52-week period), or recent serious infection (e.g., pneumonia, septicemia, herpes zoster) as determined by the Investigator and requiring anti-infective treatment within 12 weeks prior to Screening.
15. Signs of herpes or varicella zoster viral infection (specifically chicken pox, shingles, or herpes zoster) within 12 weeks prior to Screening.
16. History of or current diagnosis of active tuberculosis (TB), or untreated latent TB infection (LTBI), determined by a TB skin test with purified protein derivative as evidenced by induration ≥5 mm or a positive Quantiferon, positive or borderline T-SPOT (Elispot) test performed locally, either at Screening or documented with results within 12 weeks of the Screening Visit. Subjects who have previously completed appropriate and documented LTBI treatment will not be required to be tested. Subjects must have received complete LTBI treatment prior to Screening without evidence of re-exposure prior to entering the study.
    - Subject with current household contacts with active TB will also be excluded unless the subject is being treated and there is evidence that household contacts are being treated.
    - Indeterminate Quantiferon or T-SPOT tests may be repeated once, and will be considered positive if retest results are positive or indeterminate. Subjects with documented BCG vaccination must perform a TB test at Screening and will be excluded if skin induration ≥5 mm or a positive Quantiferon or positive or borderline T-SPOT (Elispot) test.
17. Presence of New York Heart Association class III or IV congestive heart failure.
18. Known hypersensitivity to BIIB059 or any of the components of the formulated BIIB059 or matching placebo.

19. History of, or ongoing, malignant disease, including solid tumors and hematologic malignancies with the exception of basal cell carcinomas and squamous cell carcinomas and carcinoma in situ of the cervix that have been completely excised and considered cured >2 years prior to Screening.
20. History of any clinically significant cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric and renal, or other major disease, as determined by the Investigator. Specifically, a diagnosis of any other systemic autoimmune disease other than secondary Sjögren's syndrome, such as rheumatoid arthritis, psoriatic arthritis, dermatopolymiositis, systemic sclerosis (scleroderma), etc, which may confound the evaluation of the effect of investigational product.
21. History of substance abuse (except for cannabinoid) within 24 weeks prior to Screening, based on the Investigator's opinion.
22. Female subjects who are pregnant, currently lactating, have stopped lactating in the past 12 weeks, or are planning to become pregnant during the study and for 16 weeks after the last dose of study treatment.

Previous Therapies

23. Use of IV or intramuscular (IM), or intra-articular (Part A only) corticosteroids within 12 weeks prior to randomization.
24. Use of high-potency topical corticosteroid and/or topical agents (immunosuppressant) for skin lesions within 7 days prior to randomization.
25. Use of high-potency intralesional corticosteroid within 4 weeks prior to randomization.
26. Part A subjects who are receiving systemic corticosteroid treatment at a dose exceeding 20 mg/day prednisone (or its equivalent), or if any dose of prednisone (or its equivalent) has not been stable for ≥4 weeks prior to randomization.
27. Part B subjects who are receiving systemic corticosteroid treatment at a dose exceeding 15 mg/day of prednisone (or its equivalent), or if any dose of prednisone (or its equivalent) has not been stable for ≥4 weeks prior to randomization.
28. Use of thalidomide or lenalidomide, IV or SC immunoglobulin, or plasmapheresis within 12 weeks of randomization.
29. Use of tacrolimus, pimecrolimus, or sirolimus within 4 weeks prior to randomization.
30. Use of oral or parenteral rituximab, ocrelizumab, or other B cell-directed biologic therapies within 24 weeks prior to randomization. Subjects with prior B cell-directed therapies within 52 weeks of Screening will be excluded if total CD19 B cell level is <25 cells/μL as measured at Screening at the central laboratory.
31. Use of cyclophosphamide, cyclosporine, mixoribine, atacicept, abatacept, belimumab, tocilizumab, or tumor necrosis factor (TNF) inhibitors within 12 weeks or 5 half-lives (whichever is longer) prior to randomization.

32. Use of immunosuppressive or disease-modifying treatments for SLE or CLE (via an oral, IV, or SC route) that were initiated less than 12 weeks prior to randomization, have not been at a stable dose for at least 4 weeks prior to randomization, or have been taken during the last 12 weeks at doses above the prescribed maximum listed here (medication list includes, but is not limited to the following): antimalarial medications (hydroxychloroquine up to 400 mg/day, quinacrine 100 mg/day maximum, chloroquine 250 mg/day), dapsone 150 mg/day, methotrexate 25 mg/week, azathioprine 200 mg/day, 6-mercaptopurine 100 mg/day, and mycophenolate mofetil (MMF) 3 g/day or mycophenolate sodium (MPS) 2160 mg/day.
33. Immunizations with live or live-attenuated vaccines within 4 weeks before Screening and throughout the study and for 16 weeks after the last dose of study treatment.

Laboratory abnormalities

34. Aspartate aminotransferase or alanine aminotransferase >2.0 times the upper limit of normal at Screening.
35. Hemoglobin <5.5 mmol/L [9 g/dL], neutrophils <1.5 x 10^3/μL, platelets <75 x 10^9/L at Screening.
36. Any abnormal laboratory test result at Screening that is considered clinically significant and unrelated to the underlying disease (SLE/CLE), as determined by the Investigator, and would preclude the subject from participating in the study. Clinical laboratory tests may be repeated one time, at the discretion of the Investigator, if there are questionable results, or if abnormalities are felt to be due to inherent variability of the test procedure.

9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Registration

Subjects (or their legally authorized representative [e.g., parent or legal guardian], where applicable) must provide informed consent before any screening tests are performed (see Section 17.3). When a subject signs the ICF, that subject is considered to be enrolled in the study. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log.

For subjects entering Part A, screening tender and swollen joint counts will be performed by an independent joint assessor at each site prior to study entry.

For subjects entering Part B, screening CLASI scores will be verified by an independent CLASI Adjudicator (Section 19.2.2) prior to study entry.

Subjects will be registered at the Screening Visit; as part of study screening, potential subjects will have the study risks and benefits explained to them, the associated ICF reviewed with them, and all their questions answered.

If a subject initially fails any of the screening criteria and is deemed as a screen failure by the end of the initial 28-day screening period, they will be allowed to be rescreened one time at the discretion of the Investigator. Upon rescreening, and in consultation with the Medical Monitor , subjects should repeat the Screening assessments and receive a new Screening Number.

9.2. Randomization of Subjects

Subjects will be randomized at the Day 1 Visit only after all screening assessments have been completed and the Investigator has verified that the subjects are eligible per criteria in Section 8. In addition, subjects will only be randomized after review of the narrative of SLE and CLE disease history, including relevant medical history that encompasses past infection, histological confirmation of CLE diagnosis (Part B) and receipt of the approval from the Medical Monitor. Randomization will be stratified by randomization factors (Section 7.1).

No subject may begin treatment prior to assignment of a unique identification number (registration) and randomization through the interactive response technology (IRT) system. Any subject identification numbers or randomization schedule assignments that have been assigned will not be reused even if the subject does not receive treatment. Rescreened subjects will be assigned a new number.

Subjects who withdraw from the study after randomization may not be replaced.

Refer to the Study Reference Guide for details on registration and randomization.

9.3. Blinding Procedures

This is a randomized, double-blind, placebo-controlled study.

All study staff will be blinded to the subject treatment assignments. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the study team, either at the study site or at Biogen, except the unblinded Pharmacist (or designee) and the unblinded Pharmacy Monitor.

[redacted] Efforts will be made to ensure that no members of the team involved in study conduct will be unblinded. Unblinding is permitted only in the case of a medical emergency or serious medical condition, when knowledge of the study treatment is essential for the immediate clinical management or welfare of the study subject, as judged by the Investigator.

Refer to the Study Reference Guide for details about unblinding.

There will be two IAs in the study.

For IA 1, a team of Biogen personnel independent of the study team will be set up to conduct the unblinded analysis for futility, as discussed in Section 16.7.1.

For IA 2, members of the Biogen study team not in direct contact with the study sites will have access to the study data after all subjects complete all Week 24 assessments in Part A and all Week 16 assessments in Part B. Members of the Biogen study team who become unblinded to the data for the IA at the end of the treatment periods, as described in Section 16.7.2, will have no further contact with study sites until after the final database lock.

All Investigators, study site personnel, and subjects will remain blinded to treatment assignments until after the final database lock.

10. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue study treatment for any of the following reasons:

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.4.1.
- The subject withdraws consent to continue study treatment.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- The subject experiences a medical emergency that necessitates unblinding of the subject's treatment assignment.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator for medical reasons.

The reason for discontinuation of study treatment must be recorded in the subject's electronic case report form (eCRF).

Subjects who prematurely **discontinue study treatment** during the Double-blind Treatment Period should complete all study assessments for the ET Visit as soon as possible, but within 4 weeks. Subjects who discontinue study treatment should also complete the study assessments for the Safety FU Visits at 4, 8, and 12 weeks after the ET Visit.

10.2. Withdrawal of Subjects From Study

Subjects must be withdrawn from the study for any one of the following reasons:

- The subject withdraws consent.
- The subject enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.
- The subject is unwilling or unable to comply with the protocol.

Subjects who are prematurely **withdrawn from the study** during the Double-blind Treatment Period should complete all study assessments for the ET Visit as soon as possible, but within 4 weeks. Withdrawn subjects should be encouraged to complete the study assessments for the Safety FU Visits at 4, 8, and 12 weeks after the ET Visit. However, if the subject is unwilling or unable to attend the study FU Visits, or at minimum the ET Visit, and decides to withdraw consent, the reason for withdrawal will be documented and no further assessments will be obtained.

The reason for the subject's withdrawal from the study must be recorded in the subject's eCRF. The level of consent withdrawal (e.g., whether samples collected but not yet analyzed can still be used/analyzed, and so on) should also be recorded in the eCRF.

11. STUDY TREATMENT USE

11.1. Study Treatment Regimen

11.1.1. Part A

Subjects will be randomized in a 1:1 ratio to 1 of the following 2 treatment groups:

- BIIB059 450 mg
- Placebo

Dose regimen: every 4 weeks (Q4W) SC, with an additional dose at Week 2, for a total of 7 doses.

11.1.2. Part B

Subjects will be randomized in a 1:1:1:1 ratio to 1 of the following 4 treatment groups:

- BIIB059 50 mg
- BIIB059 150 mg
- BIIB059 450 mg
- Placebo

Dose regimen: every 4 weeks SC (Q4W), with an additional dose at Week 2, for a total of 5 doses.

11.1.3. BIIB059

Biogen will provide BIIB059 to sites.

11.1.4. Placebo

Placebo (0.9% sodium chloride) will be commercially available saline supplied by the study site or Sponsor based on local regulations.

11.2. Study Treatment Precautions

Following administration of study treatment, subjects should remain at the study center for 1 hour to monitor for the development of potential allergic or anaphylactic reactions.

Epinephrine for SC injection, diphenhydramine (or equivalent) for IV injection, and any other medications and resuscitation equipment for the emergency management of anaphylactic reactions must be available in the room where the infusion is being performed.

BIIB059 or placebo should be administered within the stated window of the scheduled visit (±2 or 3 days; see Table 1 and Table 2). If a subject misses a planned dose (i.e., outside of the 2- or 3-day window), the missed dose should be administered as soon as possible, and no later than 5 days after the last day of the planned window. If the Week 2 dose (the second dose to be

administered in the study) can't be given within the planned window, the missed dose should be skipped and the subject should receive the next scheduled dose as per protocol.

11.3. Study Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff.

11.4. Concomitant Therapy and Procedures

11.4.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between Screening and the final study visit.

11.4.1.1. Allowed Concomitant Therapy

All permitted therapies, unless indicated otherwise, should be taken at a stable dose starting from the Screening Visit until the end of the Treatment Period. A stable dose is defined as no increase or decrease during a specified time period. Dose decrease is allowed where specified by protocol.

Any medications, other than those excluded per Section 8.2, that are considered necessary for the subject's welfare and that do not interfere with the trial conduct or assessments, may be given at the Investigator's discretion and should be recorded in the eCRF dedicated page.

11.4.1.1.1. Background Therapies for Lupus

11.4.1.1.1.1. Systemic Lupus Erythematosus

Standard of care therapy that may be continued during the study for SLE includes 1 of the following single immunosuppressants or immunomodulators, delivered via IV, SC, or oral administration: azathioprine (up to 200 mg/day), 6-mercaptopurine (up to 100 mg/day), mycophenolate (either as MMF at up to 3 g/day or MPS up to 2160 mg/day), and methotrexate (up to 25 mg/week). Other permitted SoC therapies include antimalarial medications such as (hydroxychloroquine (up to 400 mg/day), quinacrine (100 mg/day), chloroquine (up to 250 mg/day), and dapsone (up to 150 mg/day) as well as corticosteroids (see Section 11.4.1.1.2) and NSAIDs (see Section 11.4.1.1.3.1).

All background therapy for SLE given prior to Screening or randomization must have been kept stable or discontinued as specified in the inclusion/exclusion criteria for a subject to be eligible for the study. These medications must remain stable during Screening or randomization as well as the 24-week (Part A) or 16-week (Part B) Treatment Period, with the exception of the 2 corticosteroid rescue attempts allowed during corticosteroid tapering in Part A of the study (Section 11.4.1.1.2). No initiation of new immunosuppressant therapy or increase in dose of current immunosuppressant is allowed. Subjects who initiate SLE SoC therapy during the study will be considered treatment failures. They are encourage to continue receiving study treatment and complete the study at the Investigator's discretion.

Standard of care medications that are part of the subject's previous SLE treatment will not be provided by Biogen.

11.4.1.1.1.2. Cutaneous Lupus Erythematosus

All background therapy for CLE given prior to Screening must have been kept stable or discontinued as specified in the inclusion/exclusion criteria (Section 8) for a subject to be eligible for the study. These medications must remain stable during the Screening Period as well as the Treatment Period.

11.4.1.1.2. Corticosteroid Usage During the Study

In Part A, corticosteroid use at doses above 20 mg/day of prednisone or prednisone equivalent is not allowed (with the exception of Rescue 1 during corticosteroid tapering; see Table 7). In Part B, corticosteroid use at doses above 15 mg/day of prednisone or prednisone equivalent is not allowed. Doses stated are for a total daily dose of prednisone or prednisolone; other corticosteroids may be used instead at the equivalent doses listed. See Table 5 for prednisone equivalence values of commonly used corticosteroids.

Systemic (IM or IV) or intra-articular (Part A) administration of corticosteroids is not allowed for the duration of the study; a washout period of 12 weeks must be observed prior to randomization.

Nonsystemic corticosteroids (defined as otic, intranasal, inhaled, or ophthalmic) are permitted without restriction. See Section 11.4.1.1.2.1 for guidance on the use of topical steroids.

Table 5: Prednisone Equivalence Values for Common Alternatives

Medication	Equivalent (mg) to 1 mg of Prednisone
Betamethasone	0.15
Cortisone	5
Dexamethasone	0.15
Hydrocortisone	4
Prednisolone	1
Methylprednisolone	0.8
Triamcinolone	0.8

11.4.1.1.2.1. Topical and Intralesional Corticosteroids

Intralesional corticosteroids are not allowed during the screening and treatment periods. The use of low or lower mid-potency topical steroids is allowed during the study. Table 6 provides guidance for topical corticosteroid use. Subjects are requested to avoid use of topical corticosteroids on the day of CLASI assessments throughout the study, and for 24 hours prior to the primary endpoint CLASI assessment at the Week 16 Visit.

High-potency steroids and/or topical agents (immunosuppressant) for skin lesions, including intralesional corticosteroids, are prohibited.

Table 6: Topical Corticosteroids Allowed During the Study

Examples of Low-Potency or Lower Mid-Potency Topical Corticosteriods	
Low-Potency	Lower Mid-Potency
Hydrocortisone acetate 0.1 to 0.25%	Fluocinolone acetonide 0.025% cream
Desonide 0.05% cream	Triamcinolone acetonide 0.1%
Methylprednisolone 0.25%	Fluticasone propionate 0.05% cream
Fluocinolone acetonide 0.01%	Hydrocortisone butyrate 0.1% cream
	Betamethasone valerate 0.05%
	Clobetasone butyrate 0.05%.

For a list of commonly used topical corticosteroids that are not permitted during the study, see Appendix B. The Investigator is invited to contact the Sponsor's Medical Monitor with questions about topical corticosteroid use during the study.

11.4.1.1.2.2. Part A Specific Instructions

Intra-articular Corticosteroids

Intra-articular administration of corticosteroids is not allowed for the duration of the study; a washout period of 12 weeks must be observed prior to randomization.

Oral Corticosteroids

Eligible subjects will have active SLE with joint and skin manifestations at Screening and randomization. Subjects may be treated with SLE background SoC therapies as per exclusion criterion #31 and, if taking corticosteroids, must have been on stable dosage for at least 4 weeks prior to randomization. Subjects who are not receiving corticosteroids at Screening or baseline are permitted to participate in the study.

Doses of corticosteroid must remain stable during Screening and during the first 4 weeks after the first dose of study treatment (i.e., until Day 28). The tapering schedule should begin 4 weeks (Week 5; Days 29 to 35) after the first dose of study treatment. The tapering regimen is intended to reduce the daily dose of prednisone (or equivalent) to 10 mg/day or lower by Week 12 (Day 85) of the study, as outlined in Table 7.

If a subject deviates from the planned tapering schedule, they might be considered a treatment failure (see Section 16.1.2.1). Subjects are allowed to continue to receive the investigational product and to complete the study at the discretion of the Investigator.

Subjects who achieve the Week 12 dose of 10 mg of prednisone (or equivalent) or lower may remain on this dose or continue to taper between Week 13 and Week 16 at the discretion of the Investigator. The dose of prednisone (or equivalent) will remain stable (at the Week 16 dose) between Week 17 and Week 24.

***Screening*:**

Subjects who are receiving corticosteroids must receive a stable dose throughout the Screening period; no initiation, increase, or decrease of corticosteroid dose is permitted.

The maximum daily dose of corticosteroid allowed is 20 mg of prednisone (or equivalent).

Treatment period:

Oral corticosteroid dose tapering (as described in Table 7) is mandatory within the rules for dose changes outlined below.

Briefly, oral corticosteroids dosing guidelines are as follow:

- Stable corticosteroid dose from Day 1 to Week 4 (Day 1 to Day 28)
- Decrease in corticosteroid dose from baseline between Week 5 and Week 11 (Days 29 to 78)
- Stable corticosteroid dose at Week 12 (Days 79 to 85)
- Stable Week 12 corticosteroid dose, or decrease by 2.5 mg between Week 13 and Week 16 (Day 86 to 113)
- Stable corticosteroid dose (at Week 12 dose) between Week 17 and Week 24 (Days 114 to 169)

Between Day 1 to Week 4, the corticosteroid dose can be increased to a maximum of 10 mg/day above Day 1 dosage, but must return to Day 1 level within 7 days (Rescue 1). Between Week 5 and Week 7 (Rescue 2), OR between Week 9 and Week 11 (Rescue 3), the corticosteroid dose can be increased to the previous dosage level for up to 1 week before resuming the tapering schedule. Only two rescues out of the three described above are allowed, at the discretion of the Investigator.

Overall, TWO corticosteroid rescues are allowed:

- Rescue 1 and Rescue 2; OR
- Rescue 1 and Rescue 3; OR
- Rescue 2 and Rescue 3.

Any other increase in corticosteroid dose may be considered a treatment failure and/or a protocol deviation (depending on the timing or severity of the deviation) for the analysis (see Section 16.1.2.1). Subjects who cannot fulfill the corticosteroid tapering schedule should still complete the study and remain on the investigational product. Corticosteroid dose should be recorded in the subject diary (Section 11.4.1.1.2.4).

Day 1 to Week 4:

Stable dosage at Day 1 dose level, 1 oral corticosteroid rescue (Rescue 1) for SLE activity is allowed up to a dose no higher than 10 mg above the baseline level (maximum of 30 mg/day), but the dose must return to baseline (Day 1) level within 7 days. A dose increase is strongly recommended to be avoided within 1 week of a planned study visit.

Week 5 to Week 7:

Decrease as per the tapering schedule. One oral corticosteroid rescue (Rescue 2) for SLE activity is allowed up to a dose no higher than the previous dosage level, but the dose must be

returned to the last oral corticosteroid dosage prior to rescue level within 7 days. A dose increase is not permitted within 1 week of a planned study visit.

Week 8:

Decrease as per tapering schedule. No increases are allowed.

Week 9 to Week 11:

Decrease as per tapering schedule. One oral corticosteroid rescue (Rescue 3) for SLE activity is allowed up to a dose no higher than the previous dosage level, but the dose must be returned to last oral corticosteroid dosage prior to rescue level within 7 days. A dose increase is not permitted within 1 week of a planned study visit.

Week 12:

No increase or decrease allowed.

Week 13 to Week 16:

Stable dosage or decrease as per the tapering schedule (no increase is allowed). The corticosteroid dose must always be ≤Week 12 dose.

Week 17 to Week 24:

Stable dosage at Week 16 dosage, no increases or decreases are allowed.

Table 7: Oral Corticosteroid Tapering Schedule

Allowable OCS Rescue Dosing[1]	Timing by Weeks (Days)	OCS Starting Dose Prior to Tapering (mg/day)							
		20 mg	17.5 mg	15 mg	12.5 mg	10 mg	7.5 mg	5 mg	2.5 to <5 mg
Rescue 1	Week 1-4[2] (Day 1 to 28)	Stable 1 OCS rescue for SLE activity allowed up to maximum 10 mg/day above Day 1 dosage, but must return to Day 1 level within 7 days							
Rescue 2	Week 5[3] (Day 29 to 35)	17.5	15	12.5	10	7.5	5	5 or 2.5	2.5 to <5
	Week 6[3] (Day 36 to 43)	17.5	15	12.5	10	7.5	5	5 or 2.5	2.5 to <5
	Week 7[3] (Day 44 to 50)	15	12.5	12.5	10	7.5	5	5 or 2.5	2.5
	Week 8 (Days 51 to 57)	15	12.5	10	7.5	7.5	5	5 or 2.5	2.5
Rescue 3	Week 9[3] (Days 58 to 64)	12.5	10	10	7.5	5	2.5	2.5	0 to 2.5
	Week 10[3] (Days 65 to 71)	12.5	10	10	7.5	5	2.5	2.5	0 to 2.5
	Week 11[3] (Days 72 to 78)	10	7.5	7.5	5	2.5 to <5	2.5	2.5	0 to 2.5
	Week 12 (Days 79 to 85)	10	7.5	7.5	5	2.5 to <5	2.5	2.5	0 to 2.5
	Week 13-16 (Days 86 to 113)	Stable at Week 12 dose or decrease							
	Week 17-24 (Days 114 to 169)	Stable at Week 16 dose							

Abbreviations: OCS = oral corticosteroids; SLE = systemic lupus erythematosus.
[1] Two rescues are allowed out of the three described.

[2] Between Weeks 1 and 4 (Rescue 1). Once a dose is reduced it must not be re-increased, with the exception of the 1 time rescue.
[3] Between Weeks 5 and 7 (Rescue 2) and between Weeks 9 and 11 (Rescue 3), the dose can be increased to the previous dose level for up to 1 week before restarting the tapering schedule.

11.4.1.1.2.3. Part B Specific Instructions

Oral Corticosteroid

No corticosteroid tapering schedule is planned for subjects in Part B. The dose of corticosteroids given at Screening should not exceed 15 mg/day and should remain stable (no increase throughout the Screening, Treatment, and Follow-up Periods) .

An increase of corticosteroid dose will be considered a treatment failure (see Section 16.1.2.1). Subjects are allowed to remain in study and receive the investigational product.

11.4.1.1.2.4. Subject Diaries

Subjects will be issued a paper diary to record daily corticosteroid use (topical and oral) between study visits. Subjects will be instructed to bring the diary to the clinic at each visit, where it will be collected and reviewed by site personnel.

11.4.1.1.3. Pain Medication

11.4.1.1.3.1. Nonsteroidal Anti-inflammatory Treatments

Subjects taking stable doses of NSAIDs (e.g., ibuprofen, naproxen, aspirin) for SLE symptoms at Screening should continue to do so throughout the trial; however, subjects should refrain from using NSAIDs within 24 hours before each study visit. Subjects taking stable doses of NSAIDs for reasons other than SLE are encouraged to titrate down as tolerated.

Low-dose aspirin (<350 mg/day) at stable doses for cardiovascular prophylaxis is permitted during the study.

11.4.1.1.3.2. Acetaminophen

Acetaminophen (paracetamol) may be initiated for pain control of SLE symptoms during the study. The medication should be titrated down as tolerated. The maximum dose of acetaminophen or pain medications that contain acetaminophen is 3 g/day.

11.4.1.1.3.3. Other Pain Medications

Other pain medications, including opiates, other narcotics, and medical marijuana, may be used to treat symptoms of arthritis and other extra-articular conditions in SLE as needed; however, these medications may not be used within 24 hours of a study visit if they are used as needed. If opiates are chronically taken prior to Screening, a stable dose should be maintained from Screening until the end of the Treatment Period.

11.4.1.1.4. Vitamin D and Calcium Supplements

Use of vitamin D_3 (≥400 IU/day) and calcium supplements (≥800 mg/day) is recommended for prevention of glucocorticoid- or postmenopausal-induced bone loss. Subjects should continue these medications per SoC with no change in dose during the study.

11.4.1.1.5. Vaccines

Live and live-attenuated vaccines are not permitted within 4 weeks before Screening and throughout the study, and for 16 weeks after the last dose of study treatment.

11.4.1.2. Disallowed Concomitant Therapy

Table 8 provides a list of medications prohibited during study participation (and during the prescribed washout period prior to randomization).

Table 8: Disallowed Concomitant Therapy and Required Washout Periods Prior to Randomization

Generic Name	Washout Period Prior to Randomization
Biologics (monoclonal antibodies and and fusion proteins)	
Rituximab, ocrelizumab, other B-cell directed therapies[1]	24 weeks
Abatacept, belimumab, tocilizumab, TNF inhibitors	12 weeks or 5 half-lives (whichever is longer)
Immunosuppressants	
Tacrolimus, pimecrolimus, sirolimus	4 weeks
High-potency topical corticosteroid and/or topical agents (immunosuppressive) for skin lesions	7 days
High-potency intralesional corticosteroids	4 weeks
IV or IM corticosteroids (Parts A and B)	12 weeks
Intra-articular corticosteroids (Part A)	12 weeks
Cyclophosphamide, cyclosporine, mixoribine	12 weeks or 5 half-lives (whichever is longer)
Other	
IV and SC immunoglobulin	12 weeks
Plasmapheresis	12 weeks
Thalidomide or lenalinomide	12 weeks
Investigational or approved agent that blocks IFN-α	24 weeks
Any investigational therapy, including BIIB059, and any not mentioned above	24 weeks

IFN = interferon; IM=intramuscular; IV = intravenous; SC=subcutaneous; TNF = tumor necrosis factor
[1]Subjects with history of B-cell directed therapies more than 24 weeks but less than 52 weeks prior to Screening will be excluded if the total CD19 B-cell level is <25 cells/μL as measured at Screening.

11.4.1.3. Rescue Medication Usage Guidelines During the Treatment Period

Rescue medications to mitigate local effects that have occurred at the administration site (e.g., injection-site reactions) of study treatment are allowed. These may include topical or systemic antihistamines, acetaminophen, NSAIDs, or low-potency topical corticosteroids. Any medications used should be recorded in the eCRF.

Treatment for severe SLE flares leading to the use of rescue medication per SoC will be considered as a protocol deviation for the analysis. Subjects are allowed to stay in the study and remain on the investigational product. Any medications used should be recorded in the eCRF.

See Section 11.4.1.1 for medications permitted during the Treatment Period.

See Section 11.4.1.1.2 for detailed guidance on oral corticosteroid use.

See Section 11.4.1.3 for detailed guidance on the use of oral corticosteroid as rescue medication for SLE disease activity (Part A only).

11.4.1.4. Rescue Medication Usage Guidelines During the Safety Follow-Up Period

Subjects will be treated according to local SoC during the Follow-up Period. The initiation of immunosuppressants, immunomodulators, and/or biologics should be avoided during the Follow-up Period (approximately 5 half-lives of study treatment) at the discretion of the Investigator. Any medications used should be recorded in the eCRF.

11.4.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time the subject is enrolled in the study and the last Follow-up Visit.

The following nondrug therapy is not permitted during the study (from the initial Screening Visit until the last Follow-up Visit, unless the subject has been previously stabilized on the therapy):

- Allergen desensitization

The following nondrug procedures are not permitted during the study (from initial Screening Visit until the last Follow-up Visit):

- Major medical procedures (e.g., invasive diagnostic procedures, such as arthroscopy)
- Surgical procedures and acupuncture

The use of concomitant treatment or procedures defined above must be recorded on the subjects' eCRF according to the instructions for eCRF completion. AEs related to the administration of these therapies or procedures must be documented on the appropriate eCRF.

11.5. Continuation of Treatment

No further provisions are made for access to the study treatment. If BIIB059 is proven to be beneficial, all regulatory requirements regarding post-study access will be met.

12. STUDY TREATMENT MANAGEMENT

Study site staff should follow the Directions for Handling and Administration (DHA) for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Following administration of study treatment, subjects should remain at the study center for 1 hour to observe for the development of potential allergic or anaphylactic reactions. Study treatment is for one-time use only; do not use any study treatment remaining in the vial for another subject.

12.1. BIIB059

BIIB059 is a fully humanized antibody consisting of 2 glycosylated human IgG1 heavy chains and 2 human kappa light chains. The deglycosylated antibody has a calculated molecular mass of 146.4 kDa. The antibody is produced in Chinese hamster ovary cells stably transfected with expression vectors containing the human anti-BDCA2 heavy- and light-chain genes. BIIB059 is manufactured in accordance with Good Manufacturing Practice.

BIIB059 is supplied as a sterile liquid drug product containing 150 mg/mL BIIB059, 20 mM histidine, 100 mM L-arginine hydrochloride, 3% sucrose, 0.05% polysorbate 80 and at a pH of 5.5. It is provided in 3-mL vials containing 255 mg of BIIB059 per vial.

The BIIB059 label includes conditions for storage, batch/lot number, and other pertinent information such as Sponsor, caution statement, and, when required, manufacturer. The expiration date will be provided separately if one is not provided on the kit. BIIB059 should not be used after the expiration date.

The contents of the BIIB059 label will be in accordance with all applicable regulatory requirements

12.1.1. BIIB059 Preparation

The individual preparing BIIB059 should carefully review the instructions provided in the DHA.

If the packaging is damaged or if there is anything unusual about the appearance or attributes of the vials, the study treatment should not be used. The vial in question should be saved at the study site, and the problem should be immediately reported to Biogen.

12.1.2. BIIB059 Storage

BIIB059 must be stored at 2°C to 8°C (36°F to 46°F) in a secure location, preferably a locked refrigerator with limited access. BIIB059 vials are to be protected from light and are not to be frozen. If BIIB059 is frozen, Biogen should be notified immediately, and the drug should not be used. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

12.1.3. BIIB059 Handling and Disposal

The Investigator must return all used and unused vials of BIIB059 as instructed by Biogen unless approved for onsite destruction.

If any BIIB059 supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from Biogen, by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen must be notified, in writing, of the details of the study treatment destroyed (e.g., lot numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. BIIB059 Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed or lost.

Unless otherwise notified, all vials both used and unused, must be saved for study treatment accountability. At the end of the study, reconciliation must be made between the amount of BIIB059 supplied, dispensed, and subsequently destroyed or returned to Biogen. A written explanation must be provided for any discrepancies.

12.2. Placebo

The placebo (control agent) to be used in this study will be sterile normal saline (0.9% sodium chloride for SC administration). Sterile normal saline will be supplied by the study site or Sponsor (based on local regulations). The manufacturer's directions for material storage and handling are to be followed, as are standard clinical practices for ensuring sterility of the material.

13. EFFICACY ASSESSMENTS

See Section 4 for the timing of all assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of BIIB059.

- CLASI-A and [redacted]
- [redacted]
- BILAG-2004 (Part A only)
- Joint counts (tender joint count and swollen joint count based on a 28-Joint Assessment) [Part A only]
- PGA of SLE (in Part B, only for subjects with SLE at Screening)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Descriptions of the efficacy instruments are provided in Appendix A.

13.2. Pharmacokinetic Assessments

Sparse PK serum samples to measure levels of BIIB059 over time will be obtained from all subjects at timepoints specified in the Schedule of Assessments (Table 3).

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

14. SAFETY ASSESSMENTS

Refer to Section 4 for the timing of all safety assessments.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of BIIB059:

- AE and SAE recording
- Physical examinations, including weight and height measurements (height will be measured only on Day 1/baseline)
- Vital signs (e.g., seated arterial blood pressure, heart rate, and oral body temperature)
- 12-lead ECG
- Concomitant therapy and procedure recording

14.2. Laboratory Safety Assessments

The following laboratory assessments will be performed to evaluate the safety profile of BIIB059:

- Hematology: Complete blood count with differential and platelet count, and absolute neutrophil count
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium and potassium. Creatine phosphokinase (CPK) will also be assessed in subjects in Part A.
- Coagulation
- Direct Coombs Test
- Immunoglobulins IgG, IgM, and IgA
- Immunoglobulins and vaccine-related immunoglobulin titers
- Urinalysis: dipstick for blood, protein, and glucose (microscopic examination, if abnormal)
- Urine protein: creatinine ratio (spot urine)

14.3. BIIB059 Specific Safety Assessments

The following assessment will be performed to determine the safety of BIIB059

- Immunogenicity (anti-BIIB059 antibodies)

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

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

Determination of whether an abnormal laboratory value meets the definition of an AE will be made by the Investigator. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the subject to receive specific corrective therapy
- A laboratory abnormality that the Investigator considers to be clinically significant

15.1.2. Serious Adverse Event

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

- Results in death
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm

requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

15.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject is hospitalized. The study site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
    - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2.
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment.

Relationship of Event to Study Treatment	
Not related	An AE will be considered "not related" to the use of the investigational drug if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to: the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the investigational drug if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of an alternative explanation for the AE.

15.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptoms barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms but may be given because of personality of subject.
Moderate	Symptoms of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptoms may be needed.
Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptoms may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the Investigator's Brochure.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and final follow-up visit is to be recorded on the eCRF, regardless of the severity of the event or its relationship to study treatment.

15.3.2. Serious Adverse Events

Any SAE experienced by the subject between the time of the signing of the ICF and final follow-up visit is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to the safety vendor listed in the Study

Reference Guide within 24 hours as described in Section 15.3.3. Follow-up information regarding an SAE also must be reported with 24 hours.

Events occurring after the final follow-up visit should be reported as described in the Study Reference Guide only if the Investigator considers the SAE to be related to study treatment.

Any SAE that is ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

15.3.3. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify the safety contact as described in the Study Reference Guide within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time that the subject has signed the ICF and final follow-up visit must be reported as described in the Study Reference Guide within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported only if the Investigator considers it related to study treatment.

A report ***must be submitted*** as described in the Study Reference Guide regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event
- The relationship of the event to study treatment

To report initial or follow-up information on an SAE, fax, or email a completed SAE form as described in the Study Reference Guide.

15.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate eCRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports as described in the Study Reference Guide. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered.

Appropriate personnel at Biogen will unblind SUSARs for the purpose of regulatory reporting. Biogen or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Biogen or designee will submit SUSARs to Investigators in a blinded fashion.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant or impregnate their partners during the study and for 16 weeks after their last dose of study treatment. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy occurring in a female subject by faxing or emailing the appropriate form as described in the Study Reference Guide within 24 hours of the study site staff becoming aware of the pregnancy. The Investigator or study site staff must report the outcome of the pregnancy to Biogen or designee.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment administered to a subject or taken by a subject that exceeds the dose assigned to the subject according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the eCRF; however, all overdoses must be recorded on an Overdose form and faxed to Biogen or designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Biogen or designee even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed to Biogen or designee. All study treatment-related dosing information must be recorded on the dosing eCRF. Refer to the Study Reference Guide for additional details.

15.4.3. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current SoC. The Investigator (or designee) should contact the study's Medical Director. Refer to the Study Reference Guide's Official Study Contact List for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

In a medical emergency when knowledge of the subject's treatment assignment may influence the subject's clinical care, the Investigator and, if applicable, designated personnel at Biogen may access the subject's treatment assignment by IRT. The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, nor to personnel involved with the analysis and conduct of the study. The Investigator can contact Biogen or designee to discuss such situations.

15.5. Contraception Requirements

All women of childbearing potential and all men must practice highly effective contraception during the study and for 16 weeks after their last dose of study treatment. In addition, subjects should not donate sperm or eggs for the duration of the study and for at least 16 weeks after their last dose of study treatment.

For the purposes of this study, women who do not meet one of the following criteria listed below are considered to be physiologically capable of becoming pregnant and are, therefore, defined as women of childbearing potential:

- Postmenopausal
    - 12 months of natural (spontaneous) amenorrhea without an alternative medical cause and a serum follicle-stimulating hormone level >40 mIU/mL
    - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy
- Female surgical sterilization (e.g., bilateral tubal ligation)

For the purposes of the study, highly effective contraception is defined as the use of one of the following:

For females:

- Established use of oral (birth control pills), injected, or implanted hormonal methods of contraception
- Placement of an intrauterine device or intrauterine system.
- Vasectomy of male sexual partner (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

For males:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms with spermicide.

Complete abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and follow up on the outcome per Section 15.4.1
- Complete an SAE form for each SAE and send it to Biogen or designee within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to Biogen or designee within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable.
- Report SAEs to local ethics committees, as required by local law.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Table 4.

This is a 2-part study consisting of Part A and Part B.

For Part A, subjects will be randomized in a 1:1 ratio (50 subjects each to 450 mg and placebo), and the randomization will be stratified by prior oral corticosteroid usage (≤10 mg/day vs. >10 mg/day) and by geographic region (United States vs. Asia vs. Latin America and Europe). This randomization scheme will apply to the approximately 100 subjects randomized under protocol version 2 or subsequent versions.

For Part B, subjects will be randomized in a 1:1:1:1 ratio (25 subjects each to 50 mg, 150 mg, and 450 mg and placebo), and the randomization will be stratified by CLASI-A score (≤10 vs. >10) and DLE (presence, absence). This randomization scheme will apply to the approximately 100 subjects randomized under protocol version 2 or subsequent versions.

For Part A and Part B, baseline is defined as the last nonmissing measurement prior to randomization to study treatment (Screening or Day 1), change from baseline is defined as post-baseline value minus baseline value, and percent change is defined as 100 × (change/baseline).

For each part, all primary, secondary and exploratory endpoints will be summarized by treatment group and, where applicable, by treatment group and visit, unless otherwise specified in the SAP.

Additional information is provided in the subsections below, analysis details will be provided in the SAP.

16.1. Efficacy

16.1.1. Analysis Population

For Part A and Part B, analysis of efficacy endpoints will be based on the intent-to-treat (ITT) population and the per-protocol (PP) population.

The ITT population is defined as all randomized subjects who received at least 1 dose of study treatment (whether or not the subjects adhered to the protocol). Subjects will be analyzed according to the study treatment to which they were randomized. Analysis of other non-safety endpoints (e.g., demographics) will also be based on the ITT population, unless otherwise specified in the SAP.

The PP population is defined as all subjects in the ITT population who do not meet the criteria for exclusion from analysis. The exclusion criteria will be defined prior to database lock for the final analysis.

16.1.2. Methods of Analysis

Continuous endpoints will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation, median, minimum, and maximum), and categorical endpoints using frequency and percentage of subjects.

16.1.2.1. Analysis of the Primary Endpoint

Part A:

A Mixed Effect Model Repeat Measurement (MMRM) model will be used as the primary method to analyze change from baseline in the active joint count using treatment group, study visit, prior oral corticosteroid usage, region, and study visit-by-treatment interaction as fixed effect factors and baseline active joint count as covariate. The primary treatment comparison will be the difference between the 450 mg dose and placebo at the end of the Week 24 on the change from baseline in active joint count.

In addition, sensitivity analysis based on the MMRM model, with missing values imputed, will also be performed (imputation methods are defined in the SAP).

Due to the impact of corticosteroid and rescue medication use on active joint count, if a subject has an increase from baseline in corticosteroid use after Week 4 (excluding allowed corticosteroid use as described in Section 11.4.1.1.2) or uses any SLE rescue medication (as described in Section 11.4.1.1.1) during the 24-week treatment period of the study, the subject will be a treatment failure. The subject's joint count after the increased corticosteroid use or after SLE rescue medication will not be included in the primary analysis. For subjects who are treatment failures prior to the Week 24 assessment of joint count, a worst observation carried forward (WOCF) method will be applied using the patient's last post-baseline joint count prior to treatment failure. In addition, if a subject deviates from the planned tapering schedule (Table 7), they might be considered as a treatment failure depending on the severity and timing of deviation. Additional details will be provided in the SAP.

Part B:

An MMRM model will be used to analyze the percent change from baseline in CLASI-A score using treatment group, study visit, study visit-by-treatment interaction, DLE (presence or absence), and SLE (presence or absence) as fixed effect factors, and baseline CLASI-A scores as a covariate.

The primary analysis of the primary endpoint is a test of dose-response, using the Multiple Comparison Procedure – Modelling (MCP-Mod) methodology [Bretz 2005].

Five dose-response trends will be tested using the appropriate contrasts, as determined by the MCP-Mod methodology, on the treatment effects obtained from the MMRM model. Additional information will be provided in the SAP.

[redacted]

[redacted]

The following analyses of the primary endpoint will also be performed:

- Pairwise comparison of each BIIB059 treatment group versus placebo, based on the MMRM model.
- Sensitivity analysis based on the MMRM model, with missing values imputed (imputation methods defined in the SAP).

Due to the impact of corticosteroid use on CLASI-A scores, if a subject has an increase from Screening in corticosteroid use, the subject's CLASI-A scores after the increased corticosteroid use will not be included in the primary analysis. The missing data handling methodology will follow the methods described for Part A. For subjects in Part B with a diagnosis of SLE in addition to CLE, see Section 11.4.1.1.1. Additional details will be provided in the SAP.

16.1.2.2. Analysis of the Secondary Endpoints

Part A:

The secondary efficacy endpoints are defined in Table 4. All continuous endpoints, such as change from baseline over time in CLASI-A score and active joint count, will be summarized using standard descriptive statistics. All categorical endpoints, such as CLASI-50 response at Week 12, will be summarized using frequency and percentage of subjects.

In addition, statistical hypothesis testing will be performed for all secondary endpoints, defined below, unless otherwise specified in the SAP.

For the continuous endpoints, p-values for the pairwise comparison of each BIIB059 treatment group versus placebo and corresponding confidence intervals will be provided based on the MMRM model specified above for the primary analysis for Part A, with the analysis performed by visit. For the categorical endpoints, p-values will be based on the Cochran-Mantel-Haenszel test stratified by geographic region (United States vs. Asia vs. Latin America and Europe) and prior oral corticosteroid usage (≤10 mg/day at baseline vs. >10 mg/day at baseline) comparing the BIIB059 treatment group versus placebo.

Part B:

The secondary efficacy endpoints are defined in Table 4. All continuous and categorical endpoints will be summarized descriptively, as indicated for Part A.

In addition, hypothesis testing will be performed for all secondary endpoints, defined below, unless otherwise specified in the SAP.

For the continuous endpoints, p-values and confidence intervals will be based on the MMRM model specified above for the primary analysis for Part B, with the model performed by visit. For the categorical endpoints, p-values will be based on the Cochran-Mantel-Haenszel test stratified by CLASI-A score (≤10 vs. >10), and DLE (presence or absence)comparing each BIIB059 treatment group versus placebo.

For both Parts A and B, a WOCF method will be applied as outlined in Section 16.1.2.1 for subjects who are treatment failures. Additional details will be provided in the SAP.

16.1.2.3. Exploratory Endpoints Analysis

[redacted]

16.2. Pharmacokinetics

16.2.1. Analysis Population

For Part A and Part B, the PK population is defined as the ITT population with sufficient concentration data for the calculation of BIIB059 PK parameters.

16.2.2. Methods of Analysis

The serum concentration of BIIB059 will be summarized by visit using standard descriptive statistics. Additionally, a population PK analysis will be conducted to characterize the PK of BIIB059 in subjects with SLE and CLE, estimate population PK parameters of BIIB059, estimate random inter- and intrasubject variability, and estimate random residual variability associated with the estimation of PK model parameters. Population PK analysis may also be used to identify sources of variability (continuous and categorical covariates) that may influence the PK of BIIB059. In addition, exposure-response (efficacy) analysis will be performed to evaluate the relationship between exposure of BIIB059 and clinical endpoints, which will be used to justify doses for Phase 3 studies. The results of the analysis will be included in a separate population PK-PD report.

[redacted]

[redacted]

16.5. Safety

16.5.1. Analysis Population

For Part A and Part B, analysis of safety endpoints will be based on the safety population, defined as all subjects who received at least 1 dose of study treatment (whether randomized or not, or randomized in error). Subjects will be analyzed according to the study treatment actually received.

16.5.2. Methods of Analysis

For Part A and Part B, all continuous endpoints will be summarized by treatment group (50 mg, 150 mg, 450 mg, and placebo) and, where applicable, by treatment group and visit, using standard descriptive statistics, and all categorical endpoints using frequency and percentage of subjects. In addition to the by-treatment group summaries, AEs will also be summarized for all BIIB059 treatment groups combined versus placebo.

No statistical hypothesis testing is planned.

16.5.2.1. Adverse Events

For Part A and Part B, AEs will be coded using the available, current version of the Medical Dictionary for Regulatory Activities (MedDRA). A TEAE will be defined as any AE that started or worsened in severity after initial dose of study treatment through the follow-up period; hereafter referred to simply as AE. AEs will be grouped by system organ class, preferred term, and overall, and then summarized. The incidence, severity, and relationship to study treatment will be summarized, separately for all AEs, treatment-related AEs, and SAEs.

16.5.2.2. Clinical Laboratory Evaluations and Vital Signs

For Part A and Part B, the raw values, changes from baseline, and shifts for clinical laboratory and vital signs parameters will be summarized, as appropriate. In addition, clinical relevant abnormalities (values outside the normal range for each parameter) will be summarized. Clinical abnormalities will be defined in the SAP.

[redacted]

16.7. Interim Analyses

16.7.1. Interim Analysis 1: Futility

Parts A and B:

An IA for futility of Part B and possible expansion of Part A will be performed. The IA will be performed after approximately 45% of Part B subjects under protocol version 2 or subsequent versions have completed their Week 12 Treatment Visit. At the time of the IA, it is estimated that over 50% of subjects in Part A will have completed their Week 12 treatment visit. Following the IA, up to 70 additional subjects may be enrolled in part A and BIIB059 dose may by adjusted. At the IA, unblinded subject baseline characteristics (e.g., Joint Count, SLEDAI-2K) will be assessed. The randomization stratification factors will be re-evaluated in the expanded enrollment to achieve balance between treatment groups. The 3 objectives for adding additional subjects to Part A after the IA are to: 1) potentially include an expanded SLE patient population based on more inclusive criteria, 2) potentially adjust the dose of BIIB059 and, 3) to provide greater precision for the Week 24 endpoints, including the SRI-4. Unblinded tables, listings, or graphs (TLGs) will be generated by independent personnel (internal or external) not involved in the conduct of the study. The IA will be performed by independent personnel (internal and/or external) not involved in the conduct of the study. At the discretion of Biogen, unblinded TLGs and/or data may be shared with Sponsor personnel who are not directly involved in the conduct of the study. Additional information will be provided in an unblinding plan. Details of the data to be used for the IA and the analyses planned for futility and possible expansion will be provided in the SAP.

16.7.2. Interim Analysis 2: End of Treatment Periods

After the last subjects complete the Double-Blind Treatment Periods for Part A (at Week 24) and Part B (at Week 16), an interim database lock will occur and an IA of efficacy and safety data will be conducted. All Investigators, study site personnel, and subjects will remain blinded to treatment assignments until after the end of the study. Members of the Biogen study team not in direct contact with the study sites will have access to the study data after all subjects complete all Week 24 assessments in Part A and all Week 16 assessments in Part B. Members of the Biogen study team who become unblinded to the data for this IA will have no further contact with study sites until after the final database lock.

Unblinding details will be provided in an unblinding plan. Details of the data to be used for the IA and the specific analyses to be performed will be provided in the SAP.

A complete final CSR will be written for the entire study after the final database lock (i.e., after the completion of the Safety Follow-up periods for Part A and Part B of the study).

16.8. Sample Size Considerations

Part A:

The sample size for Part A is 100 subjects, randomized in a 1:1 ratio, with 50 subjects allocated to each treatment group. This sample size will provide approximately 71% power to detect a statistically significant difference in the Week 24 absolute change from baseline active joint count, assuming a standard deviation of 6, a maximal difference of BIIB059 over placebo of 2.5, a 20% dropout rate, and a 2-sided testing at the 0.2 level significance. Additional information will be provided in the Statistical Analysis Plan (SAP). If the study is not stopped for futility at the IA (details in Section 16.7), then up to 70 additional subjects may be added to Part A. If an additional 70 subjects are added, the power will increase to approximately 87% at Week 24.

Part B:

The planned sample size for Part B is 100 subjects, randomized in a 1:1:1:1 ratio, with 25 subjects per dosage arm of BIIB059 (50 mg, 150 mg, and 450 mg) and placebo. This sample size will provide approximately 90% power to detect a dose-response relationship in the Week 16 percent change from baseline score in CLASI-A score, assuming a standard deviation of 30, a maximal difference of BIIB059 over placebo of 27.5%, and a 20% dropout rate. Five different dose-response relationships will be tested at the 2-sided 10% significance level with the MCP-Mod method being used to control for multiplicity [Bretz 2005].

17. ETHICAL REQUIREMENTS

Biogen, the Investigator, and any CRO or vendor assisting with the study must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated.

17.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. Biogen will submit documents on behalf of the investigational sites in countries other than the United States.

If the Investigator makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Biogen.

It is the responsibility of the Investigators to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

Biogen must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the ethics committee and Biogen.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the

subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

Subjects will be informed that their race and ethnicity will be collected and will be used during analysis of study results.

A copy of the signed and dated ICF must be given to the subject. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the subject's medical record.

17.4. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., Protected Health Information authorization in North America).

Ethnicity data will be used during subgroup analysis of the safety, efficacy, and PK profile of the study treatment. Ethnic differences in drug absorption, distribution, metabolism and excretion have been described as well as differences in drug safety and efficacy in distinct ethnic groups. Multiple factors may contribute to observed variation in drug response during a clinical study. These observed differences may be due to intrinsic factors such as genetics and/or extrinsic factors such as diet, environmental exposure, and sociocultural issues that differ between ethnic groups. Subjects will be informed that their ethnicity will be collected and used during analysis of study results.

Study reports will be used for research purposes only. The subject will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Biogen, its partners and designees, ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

Biogen maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Biogen or its partners) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

Biogen will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Biogen or designee. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

During and/or after completion of the study, quality assurance officers named by Biogen or the regulatory authorities may wish to perform onsite audits or inspections. The Investigator will be expected to cooperate with any audit or inspection and to provide assistance and documentation (e.g., source data) as requested.

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor will visit the Investigator at regular intervals during the study and after the study has completed, as appropriate.

During these visits, eCRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contracts between the institution, Investigator, and Biogen.

18.5. Publications

Details are included in the clinical trial agreement for this study.

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including but not limited to study initiation, monitoring, management of SAE reports, and data management. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or enrolled, the IRT vendor will provide each study site with the necessary training, a user manual, and access rights to the system.

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on eCRFs by a web-based electronic data capture tool that is supported by a vendor and configured by Biogen or the CRO. With the exception of the corticosteroid diary, which will be a paper diary, all subject-reported outcomes will be captured in an electronic diary.

19.1.4. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by Biogen to analyze the hematology, blood chemistry, and urine samples collected for this study

19.1.5. Central Facility for Other Assessments

A central facility will be selected by Biogen to perform skin tape harvesting and skin biopsy assessments for this study. A central reader will be used to adjudicate the skin photography assessments.

19.2. Study Committees

19.2.1. Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) will be formed to review interim safety and efficacy data for this study. A charter will be written for the IDMC.

19.2.2. CLASI Assessment and Adjudication

For Part B of the study, an independent CLASI Assessment Adjudicator will confirm CLASI scoring at Screening for the purpose of study eligibility. The Adjudicator will review the photographs to determine if they meet CLASI criteria.

A charter for the establishment and operation of the CLASI assessment adjudication process will be provided by Biogen.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Section 17).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the regulatory authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator must notify Biogen of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Biogen will designate one or more of the participating Study Investigators as a signatory for the study report. This determination will be made by several factors, including but not limited to, the Investigator's experience and reputation in the studied indication; the Investigator's contribution to the study in terms of design, management, and/or subject enrollment; or by other factors determined to be relevant by Biogen.

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A 2-Part Phase 2 Randomized, Double-blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of BIIB059 in Subjects with Systemic Lupus Erythematosus and Active Skin Manifestations and in Subjects with Active Cutaneous Lupus Erythematosus with or without Systemic Manifestations " and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

APPENDIX A. DESCRIPTIONS OF EFFICACY INSTRUMENTS

Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)

The CLASI instrument was developed to specifically evaluate lupus skin manifestations. It differentiates and separately scores disease activity (CLASI-A) and skin damage (CLASI-D). The activity scale includes measurements of erythema, scale and hypertrophy, and mucous membrane disease, whereas the damage scale measures hyperpigmentation, atrophy, and scarring alopecia. Each part of the body is listed separately, from the scalp to the feet, in addition to sections focusing on mucous membrane involvement and alopecia. For the activity score, points are given for the presence of erythema, scale, mucous membrane lesions, recent hair loss, and inflammatory alopecia. For the damage score, points are given for the presence of dyspigmentation, scarring, and scarring alopecia. Total dyspigmentation scores are doubled when most of the dyspigmentation has been present for more than 1 year. Scores for each area are assigned based on the most severe lesion within the area of interest. Of note, affected body parts are weighted equally regardless of surface area and number of lesions present. Separate composite scores for activity and damage are calculated by simply summing the individual component scores. CLASI-A scores of 0-9, 10-20, and 21-70 represent disease severity of mild, moderate, and severe, respectively [Bonilla-Martinez 2008; Klein 2010].

A copy of the CLASI is provided in the Study Reference Guide.

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

The SLEDAI-2K is a reliable, valid, simple, 1-page activity index that measures disease activity and records features of active lupus as present or not [Gladman 2002]. It is a modification of the SLEDAI to reflect persistent, active disease in those descriptors that had previously only considered new or recurrent occurrences. The SLEDAI-2K has been validated against the SLEDAI, which has been shown to be reliable at different levels of disease activity [Gladman 1994].

The SLEDAI-2K uses a weighted checklist to assign a numeric score based on the presence or absence of 24 symptoms at the time of assessment or during the previous 28 days. Each symptom present is assigned between 1 and up to 8 points based on its usual clinical importance, yielding a total score that ranges from 0 points (no symptoms) to 105 points (presence of all defined symptoms). However, if scored correctly, it is rare for even the sickest patients to score more than 20 points. The assessor is also requested to assess the subject's symptoms using the visual analog scale (VAS) for the Physician's Global Assessment (PGA).

SLEDAI-2K assessments should be conducted by the same trained evaluator at each visit.

A copy of the SLEDAI-2K and glossary is provided in the Study Reference Guide.

[redacted]

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

- Change in SLEDAI instrument score of 3 points or more (but not to >12)
- New or worse discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus; nasopharyngeal ulcers; pleuritis; pericarditis; arthritis; or fever due to systemic lupus erythematosus (SLE)
- Increase in prednisone requirement, but not to >0.5 mg/kg/day
- Addition of NSAID or antimalarial medication for SLE activity
- ≥1.0 increase in PGA score, but not to >2.5

A severe flare is defined as any of the following:

- Change in SLEDAI instrument score to >12
- New or worse central nervous system SLE; vasculitis; nephritis; myositis; platelets <60,000/ml; or hemolytic anemia with hemoglobin <7 g/dL or decrease in hemoglobin >3 g/dL AND requiring: doubling prednisone dose, increase to >0.5 mg/kg/day or hospitalization
- Increase in prednisone dose to >0.5 mg/kg/day
- New requirement for cyclophosphamide, azathioprine, methotrexate, or mycophenolate for SLE activity
- Hospitalization for SLE activity
- Increase in PGA score to >2.5

British Isles Lupus Activity Group - 2004

The BILAG-2004 Disease Activity Index evaluates SLE activity in a number of organ systems, based on the principle of "physician's intention to treat" [Isenberg 2005]. The primary purpose of the BILAG in this study is to assess possible worsening in specific organ systems. Additional analyses of improvements in disease activity as assessed by the BILAG-2004 numeric scoring will also be performed [Yee 2010].

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

- BILAG A: Severe disease activity requiring systemic high-dose oral corticosteroids, intravenous pulse corticosteroids, systemic immunosuppressants, therapeutic high-dose anticoagulation in the presence of high-dose corticosteroids, or prednisone ≥20 mg/day. Note that in the context of a clinical trial protocol with medication restrictions and blinded study treatment, the term "requiring" is not taken literally but indicates that if all else were equal this would be the degree of treatment indicated. It is also understood that some patients respond differently to levels of medication than do others, so that in assessing patients with the BILAG, "intent- to- treat" really means that most patients with this degree of symptom would require this level of treatment, not necessarily the patient in question.
- BILAG B: Moderate disease activity requiring treatment with systemic low-dose oral glucocorticoids, intramuscular or intra-articular or soft tissue corticosteroid injection,

topical corticosteroid or immunosuppressants, or symptomatic therapy such as antimalarial medications or NSAIDs

- BILAG C: Mild disease
- BILAG D: System previously affected but now inactive
- BILAG E: System never involved

The BILAG-2004 is evaluated by scoring each item of a list of signs and symptoms as:

1. Improving
2. Same
3. Worse
4. New

0 Not present

(ND) Not done

For some items, appropriate responses may be:

- Y/N OR numeric values where indicated
- Y/N and confirm this is due to SLE activity

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

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

BILAG assessments should be conducted by a trained evaluator, with documentation of training.

A copy of the BILAG-2004 and glossary is provided in the Study Reference Guide.

Tender and Swollen Joint Counts

Joint involvement is a frequent manifestation in patients affected by SLE and occurs in up to 90% of patients at the onset or during the course of the disease [Ball and Bell 2012]. An active joint is defined as a joint with pain and signs of inflammation (e.g., tenderness, swelling or effusion). A 28-joint assessment will be performed. The joints to be assessed bilaterally include the shoulders, elbows, wrists (radiocarpal, carpal, and carpometacarpal bones are considered as a single unit), metacarpophalangeal (MCP) joints (MCP 1, 2, 3, 4, and 5), proximal interphalangeal (PIP) joints (PIP 1, 2, 3, 4 and 5), and the knees. Artificial and ankylosed or fused joints will be excluded from tenderness and swelling assessments.

A copy of the joint count form is provided in the Study Reference Guide.

Physician Global Assessment of SLE (VAS)

The PGA is used to quantify disease activity and is measured using an anchored VAS. The PGA asks the Investigator to assess the subject's current disease activity from a score of 0 (none) to 3 (severe), with the assessment made relative not to the subject's most severe state but the most severe state of SLE that might exist at study visits.

A copy of the PGA of SLE is provided in the Study Reference Guide.

[redacted]

[redacted]

APPENDIX B. TOPICAL CORTICOSTEROIDS NOT PERMITTED DURING THE STUDY

Topical Corticosteroids Not Permitted During the Study – Non-Exhaustive List

Potency	Generic Name and Strength
Super Potent (Class 1 United States classification)	Augmented Betamethasone Dipropionate 0.05%
	Clobetasol Propionate 0.05%
	Fluocinonide 0.1%
	Halobetasol Propionate 0.05%
Potent (Class 2 United States classification)	Amcinonide 0.1%
	Desoximetasone 0.25% Cream
	Desoximetasone 0.05% Gel
	Naricort 0.025% C
	Betamethasone valerate*
	Diflorasone Diacetate 0.05%
	Fluocinonide 0.05%
	Halcinonide 0.1%
	Mometasone Furoate 0.1%
	Triamcinolone Acetonide 0.5%
Upper-mid Strength (Class 3 United States classification)	Betamethasone Dipropionate 0.05%
	Betamethasone Valerate 0.1%
	Fluticasone Propionate 0.005%
	Diflorasone diacetate 0.05%
	Clobetasone butyrate*
Mid Strength (Class 4 United States classification)	Clocortolone Pivalate 0.1%
	Fluocinolone Acetonide*
	Flurandrenolide 0.05%
	Hydrocortisone Valerate 0.2%

Source: [Ference and Last 2009; Jacob and Steele 2006]
* See Table 6 for allowable strength

APPENDIX C. AMERICAN COLLEGE OF RHEUMATOLOGY REVISED CRITERIA FOR CLASSIFICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS

1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus

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

Criterion	Definition
	2. Leukopenia--< 4,000/mm³ on ≥ 2 occasions 1. *OR* 3. Lyphopenia--< 1,500/ mm³ on ≥ 2 occasions 1. *OR* 4. Thrombocytopenia--<100,000/ mm³ in the absence of offending drugs
10. Immunologic Disorder	1. Anti-DNA: antibody to native DNA in abnormal titer 1. *OR* 2. Anti-Sm: presence of antibody to Sm nuclear antigen 1. *OR* 3. Positive finding of antiphospholipid antibodies on: 1. 1. an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2. 2. a positive test result for lupus anticoagulant using a standard method, or 3. 3. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

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AMENDMENT SUMMARY

Biogen Protocol 230LE201

A 2-Part Phase 2 Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of BIIB059 in Subjects with Systemic Lupus Erythematosus and Active Skin Manifestations and in Subjects with Active Cutaneous Lupus Erythematosus with or without Systemic Manifestations

Version 4.0

Date: 08 February 2018

EUDRA CT Number: 2015-004359-32

Version 4.0 of the protocol has been prepared for this amendment, which supersedes Version 3.0.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol Version 3.0 is to correct errors that were inadvertently made in Table 1: Schedule of Activities for Part A

- Erroneous footnotes (footnote 10 and footnote 12, Version 3 numbering) and corresponding footnote indicators were deleted from Table 1. The remaining footnotes were renumbered accordingly.
- Footnote 13 (Version 3 numbering) was corrected to accurately reflect the instructions for Part A.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 4.2, Schedule of Activities, Table 1: Schedule of Activities Part A

Now reads: See Table 1 and table footnotes on the following pages.

Rationale: These changes were made to correct errors in the footnotes and footnote indicators of Table 1: Schedule of Activities Part A.

Table 1: Schedule of Activities Part A

	Screening Period	Treatment Period									Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ET**	**FU4**	**FU8**	**FU12**
Study Day		**1[3]**	**8 (±2D)**	**15[3] (±2D)**	**29[3] (±3D)**	**57[3] (±3D)**	**85[3] (±3D)**	**113[3] (±3D)**	**141[3] (±3D)**	**169 (±3D)**	**197 (±5D)**	**225 (±5D)**	**253 (±5D)**
Tests and Assessments[2,3]													
Informed Consent Form(s)	X												
Inclusion/Exclusion Criteria	X	X											
Randomization		X											
Demographic data	X												
SLE and other medical history	X												
Documentation of SLE by ACR Criteria	X												
12-lead ECG[4]	X									X			
Chest X-Ray[4,5] (if required by local regulation)	X												
Tuberculosis test[6]	X												
Serum virology RNA (HIV, hepatitis B and C)	X												
Urine drug screen	X												
Serum pregnancy test	X												

	Screening Period	Treatment Period									Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ET**	**FU4**	**FU8**	**FU12**
Study Day		**1**[3]	**8 (±2D)**	**15**[3] **(±2D)**	**29**[3] **(±3D)**	**57**[3] **(±3D)**	**85**[3] **(±3D)**	**113**[3] **(±3D)**	**141**[3] **(±3D)**	**169 (±3D)**	**197 (±5D)**	**225 (±5D)**	**253 (±5D)**
Tests and Assessments[2,3]													
Urine pregnancy test[7]		X		X	X	X	X	X	X	X	X	X	X
Physical examination, weight, height[8]	X	X		X	X	X	X	X	X	X	X		X
Vital signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]													
BILAG-2004	X	X			X	X	X	X	X	X			
CLASI~~[10]~~	X	X		X	X	X	X	X	X	X			X
[redacted]													
Physicians Global Assessment of SLE (VAS) ~~[11,12]~~ **[10]**	X	X		X	X	X	X	X	X	X			X
Skin photography of target lesion~~[13]~~**[11]**		X			X			X~~[14]~~ **[12]**					
Joint Count (28 joint assessment)	X	X		X	X	X	X	X	X	X			X

	Screening Period	Treatment Period									Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ET**	**FU4**	**FU8**	**FU12**
Study Day		**1**[3]	**8 (±2D)**	**15**[3] **(±2D)**	**29**[3] **(±3D)**	**57**[3] **(±3D)**	**85**[3] **(±3D)**	**113**[3] **(±3D)**	**141**[3] **(±3D)**	**169 (±3D)**	**197 (±5D)**	**225 (±5D)**	**253 (±5D)**
Tests and Assessments[2,3]													
Study treatment administration~~15~~ **13**		X		X	X	X	X	X	X				
Corticosteroid diary~~16~~ **14**		X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessment													
Hematology	X	X		X	X	X	X	X	X	X	X		X
Blood chemistry	X	X		X	X	X	X	X	X	X	X		X
Urinalysis (including microscopic examination)	X	X		X	X	X	X	X	X	X	X		X
Urine protein-creatinine Ratio (spot urine)	X	X		X	X	X	X	X	X	X	X		X
Direct Coombs Analysis	X	X			X	X	X	X	X	X			
Coagulation	X	X			X	X	X	X	X	X			
CD19+ B Cell count~~17~~ **15**	X												
Pharmacokinetics													
Serum BIIB059~~18~~ **16**		X	X		X		X	X		X	X		X
[redacted]													
[redacted]													

	Screening Period	Treatment Period									Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ET**	**FU4**	**FU8**	**FU12**
Study Day		**1**[3]	**8 (±2D)**	**15**[3] **(±2D)**	**29**[3] **(±3D)**	**57**[3] **(±3D)**	**85**[3] **(±3D)**	**113**[3] **(±3D)**	**141**[3] **(±3D)**	**169 (±3D)**	**197 (±5D)**	**225 (±5D)**	**253 (±5D)**
Tests and Assessments[2,3]													
[redacted]													

	Screening Period	Treatment Period									Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ET**	**FU4**	**FU8**	**FU12**
Study Day		**1**[3]	**8 (±2D)**	**15**[3] **(±2D)**	**29**[3] **(±3D)**	**57**[3] **(±3D)**	**85**[3] **(±3D)**	**113**[3] **(±3D)**	**141**[3] **(±3D)**	**169 (±3D)**	**197 (±5D)**	**225 (±5D)**	**253 (±5D)**
Tests and Assessments[2,3]													
[redacted]													
Safety													
Serum for vaccine-related immunoglobulin titers[~~22~~ **21**]		X								X			
Antibodies to BIIB059		X			X			X		X			X
Immunoglobulin (total, IgG, IgA, IgM)		X						X		X			
Concomitant medication/ procedures	Monitor and record from signing of informed consent through the end of the study												
Serious adverse events	Monitor and record from signing of informed consent through the end of the study												
Adverse events		Monitor and record from time of first dose through the end of the study											

Abbreviations: ACR=American College of Rheumatology; BILAG=British Isles Lupus Activity Group; CLASI=Cutaneous Lupus Disease Area and Severity Index; CLE=cutaneous lupus erythematosus; C=complement; CPK=creatine phosphokinase; CRP=C-reactive protein; D=day; DNA=deoxyribonucleic acid; dsDNA=double-stranded DNA; ECG=electrocardiogram; ESR=erythrocyte sedimentation rate; ET=early termination; FU=follow-up; h=hour(s); HIV=human immunodeficiency virus; Ig=immunoglobulin; [redacted]; RNA=ribonucleic acid; [redacted]; SLE=systemic lupus erythematosus; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; **TB=tuberculosis;** VAS=visual analog scale.

[1] Follow-up visit will be conducted 4, 8 and 12 weeks after the last Treatment Period Visit (Week 24 or ET).

[2] Assessments (e.g., CPK, ECG, etc.) may be performed as required to confirm SLEDAI-2K and BILAG findings.
[3] On each dosing day (Day 1, Day 15, Day 29, Day 57, Day 85, Day 113, and Day 141) all assessments should be performed prior to dosing.
[4] To be performed locally.
[4,5] Where mandated by local regulation, a chest X-ray will be obtained locally during the screening period, unless a previous chest X-ray or the documented results from a chest X-ray obtained within 12 weeks prior to screening are available. The chest X-ray or X-ray results will be reviewed by the Investigator (or designee) in order to exclude patients with active TB infection from entering the study.
[6] Testing to be performed locally. Indeterminate Quantiferon or T-SPOT tests may be repeated once and will be considered positive if retest results are positive or indeterminate. Subjects with documented BCG vaccination must perform a TB test at Screening and will be excluded if they exhibit skin induration ≥5 mm or a positive Quantiferon or positive or borderline T-SPOT (Elispot) test.
[7] To be performed locally.
[8] Height should ~~only~~ be measured **only** once; i.e., at the Day 1/baseline visit.
[9] Vital signs include seated arterial blood pressure, heart rate, and oral body temperature.
[10] ~~CLASI will be assessed by the Investigator or a trained designee at all assessments (Section 19.2.2). CLASI scores at Screening will be verified by an Independent CLASI Adjudicator to confirm eligibility.~~
[11][10] Assessments **results** should be reported electronically.
[12] ~~Only applicable for subjects with SLE.~~
[13][11] ~~For skin lesions with a CLASI A score greater than 0, photographs of each lesion and of the corresponding region with lesion will be obtained. Photographs will be evaluated by a central adjudicator to verify the CLASI A score assignment by the Investigator.~~ One lesion is to be selected at baseline as the target lesion (the most severe active CLE lesion is recommended). The ~~same~~ target lesion must be ~~photographed and~~ the same lesion used for tape harvesting ~~at each timepoint~~ and the same lesion over time**.**
[14][12] If the ET Visit occurs before Week 16, skin photography should be performed at the ET Visit.
[15][13] Following administration of study treatment, subjects should remain at the study center for 1 hour to be observed for the development of potential allergic or anaphylactic reactions.
[16][14] Subject paper diaries for recording corticosteroid use will be distributed on Day 1, reviewed with site staff at each study visit, and collected by the study site at the final study visit.
[17][15] Only for subjects with prior B cell directed therapies within 52 weeks of Screening; this test should be performed at a central laboratory.
[18][16] Pharmacokinetic evaluations will be conducted as follows: Study Day 1 (predose –1 h and post-dose 4 h ±1 h), Day 8 (any time during visit), Day 29 (predose –1 h and postdose 4 h ±1 h), Day 85 (predose –1 h and postdose 4 h±1 h), Day 113 (predose –1 h), and Day 169 (any time during visit). During the Follow-up Period, 1 sample will be collected on Days 197 and 253 (any time during the visit) **[**~~see~~ Table 3**].** The time and date of PK sample collection and BIIB059 dose should be recorded in the eCRF.

[redacted]

[22] Vaccine-related immunoglobulin titers for tetanus, diphtheria, and *Pneumococcus* will be collected.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and protocol date were updated throughout the protocol and synopsis.
- Minor typographical corrections and formatting improvements were made.

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AMENDMENT SUMMARY

Biogen Protocol 230LE201

A 2-Part Phase 2 Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of BIIB059 in Subjects with Systemic Lupus Erythematosus and Active Skin Manifestations and in Subjects with Active Cutaneous Lupus Erythematosus with or without Systemic Manifestations

Version 3.0

Date: 11 December 2017

EUDRA CT Number: 2015-004359-32 Version 3.0 of the protocol has been prepared for this amendment, which supersedes Version 2.0.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 230LE201is to inform the sites of the correct type of screening biopsy to be performed.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 4.3.5.1, Skin Biopsy for Confirming CLE Diagnosis

Now reads:

For subjects without historical biopsy data, diagnosis will be confirmed during Screening by skin biopsy that can be read at a local laboratory or the central laboratory, at the discretion of the Investigator. A ~~shave~~ **punch** biopsy will be performed for diagnostic purposes. Subjects with an available historical biopsy do not need a screening biopsy for diagnosis.

Rationale: Shave biopsy was replaced by punch biopsy because it is not standard clinical practice to perform a shave biopsy for diagnostic purposes in patients with lupus erythematosus. This change also affects Section 4.2, Table 2: Schedule of Activities Part B (footnotes #20 and #21).

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 1, Synopsis

The Synopsis was revised to reflect changes made throughout the protocol.

Section 4.2, Schedule of Activities (Table 1: Schedule of Activities Part A)

Change: The phrase "Where mandated by local regulation" was added within body of Table 1 and footnote #5.

Now reads:

	Screening Period	**Treatment Period**									**Follow-up Period**[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ET**	**FU4**	**FU8**	**FU12**
Study Day		**1**[3]	**8 (±2D)**	**15**[3] **(±2D)**	**29**[3] **(±3D)**	**57**[3] **(±3D)**	**85**[3] **(±3D)**	**113**[3] **(±3D)**	**141**[3] **(±3D)**	**169 (±3D)**	**197 (±5D)**	**225 (±5D)**	**253 (±5D)**
Tests and Assessments[2,3]													
Informed Consent Form(s)	X												
Inclusion/Exclusion Criteria	X	X											
Randomization		X											
Demographic data	X												
SLE and other medical history	X												
Documentation of SLE by ACR Criteria	X												
12-lead ECG[4]	X									X			

	Screening Period	Treatment Period									Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ET**	**FU4**	**FU8**	**FU12**
Study Day		**1[3]**	**8 (±2D)**	**15[3] (±2D)**	**29[3] (±3D)**	**57[3] (±3D)**	**85[3] (±3D)**	**113[3] (±3D)**	**141[3] (±3D)**	**169 (±3D)**	**197 (±5D)**	**225 (±5D)**	**253 (±5D)**
Tests and Assessments[2,3]													
Chest X-Ray[4,5] **(if required by local regulation)**	X												
Tuberculosis test[6]	X												
Serum virology RNA (HIV, hepatitis B and C)	X												
Urine drug screen	X												
Serum pregnancy test	X												
Urine pregnancy test[7]		X		X	X	X	X	X	X	X	X	X	X
Physical examination, weight, height[8]	X	X		X	X	X	X	X	X	X	X		X
Vital signs[9]	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]													
BILAG-2004	X	X			X	X	X	X	X	X			
CLASI[10]	X	X		X	X	X	X	X	X	X			X
[redacted]													

	Screening Period	Treatment Period									Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ET**	**FU4**	**FU8**	**FU12**
Study Day		**1[3]**	**8 (±2D)**	**15[3] (±2D)**	**29[3] (±3D)**	**57[3] (±3D)**	**85[3] (±3D)**	**113[3] (±3D)**	**141[3] (±3D)**	**169 (±3D)**	**197 (±5D)**	**225 (±5D)**	**253 (±5D)**
Tests and Assessments[2,3]													
[redacted]													
Physicians Global Assessment of SLE (VAS) [11,12]	X	X		X	X	X	X	X	X	X			X
Skin photography of target lesion[13]		X			X			X[14]					
Joint Count (28 joint assessment)	X	X		X	X	X	X	X	X	X			X
Study treatment administration[15]		X		X	X	X	X	X	X				
Corticosteroid diary[16]		X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessment													
Hematology	X	X		X	X	X	X	X	X	X	X		X
Blood chemistry	X	X		X	X	X	X	X	X	X	X		X
Urinalysis (including microscopic examination)	X	X		X	X	X	X	X	X	X	X		X
Urine protein-creatinine Ratio (spot urine)	X	X		X	X	X	X	X	X	X	X		X

	Screening Period	Treatment Period									Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ET**	**FU4**	**FU8**	**FU12**
Study Day		**1[3]**	**8 (±2D)**	**15[3] (±2D)**	**29[3] (±3D)**	**57[3] (±3D)**	**85[3] (±3D)**	**113[3] (±3D)**	**141[3] (±3D)**	**169 (±3D)**	**197 (±5D)**	**225 (±5D)**	**253 (±5D)**
Tests and Assessments[2,3]													
Direct Coombs Analysis	X	X			X	X	X	X	X	X			
Coagulation	X	X			X	X	X	X	X	X			
CD19+ B Cell count[17]	X												
Pharmacokinetics													
Serum BIIB059[18]		X	X		X		X	X		X	X		X
[redacted]													

	Screening Period	Treatment Period									Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ET**	**FU4**	**FU8**	**FU12**
Study Day		**1[3]**	**8 (±2D)**	**15[3] (±2D)**	**29[3] (±3D)**	**57[3] (±3D)**	**85[3] (±3D)**	**113[3] (±3D)**	**141[3] (±3D)**	**169 (±3D)**	**197 (±5D)**	**225 (±5D)**	**253 (±5D)**
Tests and Assessments[2,3]													
[redacted]													
Safety													
Serum for vaccine-related immunoglobulin titers[23]		X								X			
Antibodies to BIIB059		X			X			X		X			X
Immunoglobulin (total, IgG, IgA, IgM)		X						X		X			

	Screening Period	Treatment Period									Follow-up Period[1]		
Study Week	**Within 4 Weeks Prior to Randomization**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ET**	**FU4**	**FU8**	**FU12**
Study Day		**1[3]**	**8 (±2D)**	**15[3] (±2D)**	**29[3] (±3D)**	**57[3] (±3D)**	**85[3] (±3D)**	**113[3] (±3D)**	**141[3] (±3D)**	**169 (±3D)**	**197 (±5D)**	**225 (±5D)**	**253 (±5D)**
Tests and Assessments[2,3]													
Concomitant medication/ procedures	Monitor and record from signing of informed consent through the end of the study												
Serious adverse events	Monitor and record from signing of informed consent through the end of the study												
Adverse events		Monitor and record from time of first dose through the end of the study											

[5] ~~During the screening period~~ **Where mandated by local regulation**, a chest X-ray will be obtained locally **during the screening period**, unless a previous chest X-ray or the documented results from a chest X-ray obtained within 12 weeks prior to screening are available. The chest X-ray or X-ray results will be reviewed by the Investigator (or designee) in order to exclude patients with active TB infection from entering the study.

Rationale: For countries that require a chest X-ray for tuberculosis screening, a provision to obtain a chest X-ray was added to the protocol.

This change also affects Section 4.2, Schedule of Activities, Table 2: Schedule of Activities Part B and footnote #5.

Section 4.2, Schedule of Activities (Table 1: Schedule of Activities Part A)

Change: Pharmacokinetic (PK) evaluation timepoints were corrected for Day 85 and Day 113 in footnote #18.

Now reads:[18] Pharmacokinetic evaluations will be conducted as follows: Study Day 1 (predose –1 h and post-dose 4 h ±1 h), Day 8 (any time during visit), Day 29 (predose –1 h and postdose 4 h ±1 h), Day 85 (predose –1 h **and postdose 4 h±1 h**), Day 113 (predose –1 h ~~and postdose 4 h ±1 h~~), and Day 169 (any time during visit). During the Follow-up Period, 1 sample will be collected on Days 197 and 253 (any time during the visit). See Table 3. The time and date of PK sample collection and BIIB059 dose should be recorded in the eCRF.

Rationale: The PK evaluation timepoints were corrected to align with the PK sampling timepoints presented in Table 3 (Pharmacokinetic Assessments). The description of collection timepoints for Week 12 (Day 85) and Week 16 (Day 113) were unintentionally inverted according to the site communication letter on PK assessment timepoints.

Section 4.2, Schedule of Activities (Table 3, Pharmacokinetic Assessments)

Change: The Follow-Up period was changed to Day 197 and 253 (±5 d) for Part A and Days 141, 169, and 197 (±5 d) for Part B.

Now reads:

Table 3: Pharmacokinetic Assessments

Study Week	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**Follow-Up Period**
Study Day	1	8 (±2 d)	15 (±2 d)	29 (±3 d)	57 (±3 d)	85 (±3 d)	113 (±3 d)	141 (±3 d)	169 (±3 d)	Part A Day 197 ~~, 225 or~~ **and** 253 (±5 d) Part B Day 141, 169, ~~or~~**and** 197 (±5 d)
Part A										
PK Sampling Timepoint(s)	• Predose (–1 h) • Postdose (4 h ±1 h)	• Any time during visit		• Predose (–1 h) • Postdose (4 h ±1 h)		• Predose (–1 h) • Postdose (4 h ±1 h)	• Predose (–1 h)		• Any time during visit	• Any time during visit

Part B										
PK Sampling Timepoint(s)	• Predose (–1 h) • Postdose (4 h ±1 h)	• Any time during visit		• Predose (–1 h) • Postdose (4 h ±1 h)		• Predose (–1 h) • Postdose (4 h ±1 h)	• Any time during visit			• Any time during visit

Rationale: In Table 3, Follow-Up Period collection visits had been specified incorrectly. Collection visits were corrected to align with Table 1: Schedule of Activities Part A and Table 2: Schedule of Activities Part B.

Section 4.3.3, Joint Count Assessment (Part A Only)

Change: The language for joint count assessment was revised to indicate that the same joint assessor must perform the joint count assessment for the same subject at every visit.

Now reads:
~~Joint counts will be evaluated at all visits by a trained independent joint assessor.~~ **Joint counts will be evaluated at all visits by a trained independent joint assessor. The joint counts for an individual subject must be performed by the same joint assessor throughout the trial.**

Rationale: This change was made to ensure that investigational sites assign same joint assessor to the same subject at every visit. This practice is expected to prevent the occurrence of major protocol deviations.

Section 7.2.3, Follow-Up

Change: The language pertaining to follow-up visits for subjects who prematurely discontinue study treatment and/or who prematurely withdraw from the study was revised.

Now reads:
Subjects are to return to the study site for follow-up (FU) visits at 4, 8, and 12 weeks after the last Treatment Period visit (Week 24 or Early Termination [ET] Visit). Follow-up visits will be conducted at Week FU4 (Day 197), Week FU8 (Day 225) and Week FU12 (Day 253). The final study visit will be Week FU12. ~~Subjects who prematurely discontinue treatment during the double-blind treatment period should undergo ET Visit assessments and be encouraged to complete the Follow-up Period.~~

Subjects who prematurely discontinue study treatment during the Double blind Treatment Period should complete all study assessments for the Week 24/ET Visit as soon as possible, but within 4 weeks. Subjects who discontinue study treatment should also complete the study assessments for the Safety FU Visits at Week FU4, Week FU8, and Week FU12 after their ET Visit.

Subjects who are prematurely withdrawn from the study during the Double blind Treatment Period should complete all study assessments for the Week 24/ET Visit as soon as possible, but within 4 weeks. Withdrawn subjects should also be encouraged to complete the study assessments for the Safety FU Visits at Week FU4, Week FU8, and Week FU12 after their ET Visit. However, if the subject is unwilling or unable to attend the study FU Visits, or at minimum the ET Visit, and decides to withdraw consent, the reason for withdrawal will be documented and no further assessments will be obtained.

Rationale: This new text provides more detailed instructions to the sites regarding study activities for subjects who discontinue study treatment and/or who are prematurely withdrawn from the study.

This change also affects Section 4.2, Schedule of Activities, footnote #1.

Section 7.3.3, Follow-Up

Change: The language pertaining to follow-up visits for subjects who prematurely discontinue study treatment and/or who prematurely withdraw from the study was revised.

Now reads:

Subjects are to return to the study site for follow up visits on Week FU4 (Day 141), Week FU8 (Day 169), and Week FU12 (Day 197) after the last Treatment Period visit (Week 16 or ET Visit). The final study visit will be Week FU12. ~~Subjects who prematurely discontinue treatment during the double-blind Treatment Period should undergo ET visit assessments and be encouraged to complete the Follow-up Period.~~

Subjects who prematurely discontinue study treatment during the Double blind Treatment Period should complete all study assessments for the Week 16/ET Visit as soon as possible, but within 4 weeks. Subjects who discontinue study treatment should also complete the study assessments for the Safety FU Visits at Week FU4, Week FU8, and Week FU12 after their ET Visit.

Subjects who are prematurely withdrawn from the study during the Double blind Treatment Period should complete all study assessments for the Week 16/ET Visit as soon as possible, but within 4 weeks. Withdrawn subjects should be encouraged to complete the study assessments for the Safety FU Visits at Week FU4, Week FU8, and Week FU12 after their ET Visit. However, if the subject is unwilling or unable to attend the study FU Visits, or at minimum the ET Visit, and decides to withdraw consent, the reason for withdrawal will be documented and no further assessments will be obtained.

Rationale: This new text provides more detailed instructions to sites regarding study activities for subjects who discontinue study treatment and/or who are prematurely withdrawn from the study.

This change also affects Section 4.2, Schedule of Activities, footnote #1.

Section 8.2.1, Exclusion Criteria (Parts A and B)

Change: Exclusion criterion #7, regarding hepatitis C virus (HCV), was revised.

Now reads:

7. ~~Current active hepatitis C virus (HCV) infection, determined as HCV RNA above the limit of detection.~~ **Current active hepatitis C virus (HCV) infection, determined as HCV RNA above the limit of detection, in subjects with positive HCV antibody titer.**

Rationale: This exclusion criterion was revised to indicate that subjects must have a positive HCV antibody titer in order to confirm the diagnosis of current active HCV infection.

Section 8.2.1, Exclusion Criteria (Parts A and B), Medical History

Change: A sentence was added to exclusion criterion #20 clarifying specific autoimmune diseases that may confound the evaluation of the effect of the investigational product (IP).

Now reads:

20. History of any clinically significant cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric and renal, or other major disease, as determined by the Investigator. **Specifically, a diagnosis of any other systemic autoimmune disease other than secondary Sjögren's syndrome, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), dermatopolymiositis (DM), systemic sclerosis (scleroderma), etc. which may confound the evaluation of the effect of IP.**

Rationale: The added language to this exclusion criterion is intended to prevent study Investigators from excluding subjects who were diagnosed with secondary Sjögren's syndrome (sicca syndrome), which is frequent and commonly allowed in clinical trials for SLE.

Section 8.2.1, Exclusion Criteria (Parts A and B), Laboratory abnormalities

Change: In exclusion criterion 35, the unit of measure for neutrophils count was changed from L to µL**.**

Now reads:

35. Hemoglobin <5.5 mmol/L [9 g/dL], neutrophils <1.5 x 10^3/~~L~~**µL**, platelets <75 x 10^9/L at Screening.

Rationale: The operating laboratories at investigational sites provide results for neutrophils count equivalent to 10^3/ µL. The protocol incorrectly showed the unit for neutrophils as 10^3/L;

this change corrects the error. This correction will help investigational sites report clean data for neutrophil counts.

Section 10.1, Discontinuation of Study Treatment

Change: The language for discontinuation of study treatment was revised.

Now reads: A subject *must* permanently discontinue study treatment for any of the following reasons:

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.4.1.
- The subject withdraws consent to continue study treatment.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- The subject experiences a medical emergency that necessitates unblinding of the subject's treatment assignment.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator for medical reasons.

The reason for discontinuation of study treatment must be recorded in the subject's electronic case report form (eCRF).

Subjects who prematurely discontinue study treatment during the Double blind Treatment Period should complete all study assessments for the ET Visit as soon as possible, but within 4 weeks. Subjects who discontinue study treatment should also complete the study assessments for the Safety FU Visits at 4, 8, and 12 weeks after the ET Visit. ~~protocol required tests and assessments during the follow-up visits (Week 4, 8, and 12 Follow-Up Visits)). In the event that a subject withdraws from the study prematurely, at minimum, an Early Termination Visit should be performed as soon as possible, to be followed by Follow-up Visits at 4, 8, and 12 weeks after last visit; all Early Termination assessments listed in the study schedule should be performed at this Early Termination visit.~~

Rationale: This new text provides more detailed instructions to the sites regarding study activities for subjects who discontinue study treatment.

Section 10.2, Withdrawal of Subjects From Study

Change: A sentence from Section 10.1 (Discontinuation of Study Treatment) was moved to Section 10.2.

Now reads: Subjects must be withdrawn from the study for any one of the following reasons:

- The subject withdraws consent.

- The subject enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.
- The subject is unwilling or unable to comply with the protocol.

Subjects who are prematurely withdrawn from the study during the Double-blind Treatment Period should complete all study assessments for the ET Visit as soon as possible, but within 4 weeks. Withdrawn subjects should be encouraged to complete the study assessments for the Safety FU Visits at 4, 8, and 12 weeks after the ET Visit. However, if the subject is unwilling or unable to attend the study FU Visits, or at minimum the ET Visit, and decides to withdraw consent, the reason for withdrawal will be documented and no further assessments will be obtained.

The reason for the subject's withdrawal from the study must be recorded in the subject's eCRF. The level of consent withdrawal (e.g., whether samples collected but not yet analyzed can still be used/analyzed, and so on) should also be recorded in the eCRF.

Rationale: The sentence describing visits and assessments to be performed for subjects who withdraw from the study prematurely was mistakenly placed in Section 10.1 (Discontinuation of Study Treatment), which applies only to subjects who discontinue the study treatment. This change more appropriately places the information in Section 10.2.

Appendix A: Description of Efficacy Instruments, [redacted]

Change: [redacted]

Now reads: [redacted]

Rationale: [redacted]

Appendix A: Description of Efficacy Instruments, [redacted]

[redacted]

[redacted]

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- Time periods or timepoints expressed in months were converted to weeks to maintain consistency throughout the protocol.
- The wording “protocol version 2” was replaced with “protocol version 2 or subsequent versions” wherever applicable.
- Typographical and formatting errors were corrected.

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AMENDMENT SUMMARY

Biogen Protocol 230LE201

A 2-Part Phase 2 Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of BIIB059 in Subjects with Systemic Lupus Erythematosus and Active Skin Manifestations and in Subjects with Active Cutaneous Lupus Erythematosus with or without Systemic Manifestations.

Version 2

Date: 16 May 2017

EUDRA CT Number: 2015-004359-32

Version 2 of the protocol has been prepared for this amendment, which supersedes Version 1.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 230LE201 is to modify the overall design of the 2-part study (Part A in subjects with systemic lupus erythematosus [SLE] with active skin manifestations, and Part B in subjects with cutaneous lupus erythematosus [CLE] with or without systemic manifestations). The study design changes take into account Biogen's initial experience to more successfully enroll subjects into Part B and are intended to increase the focus of the study on CLE, which is the lead indication for BIIB059.

Part A was initially designed as a dose-ranging study of the effects of BIIB059 on the skin manifestations of SLE measured by the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI). In the amended protocol, Part A has been modified to evaluate the effects of a single dosing regimen of BIIB059 on the joint and skin manifestations of SLE. The change was made because joint symptoms are a common systemic component of SLE that has been shown to improve in the first 6 months of treatment, based on recent Phase 2 comparator data. With this change, Part A of the study now is a proof-of-concept study to evaluate whether BIIB059 works beyond the skin in SLE. Key changes to Part A are as follows:

- Of the 3 BIIB059 dosing regimens in the original protocol (50, 150, and 450 mg subcutaneously [SC] every 4 weeks [Q4W]), the 450 mg Q4W regimen will continue to be evaluated, while the 50 mg Q4W and 150 mg Q4W regimens will be dropped. The 450 mg Q4W regimen, with an additional loading dose at Week 2, was maintained based on Phase 1 safety, pharmacokinetic (PK), PK-blood dendritic cell antigen-2 (BDCA2) internalization relationship, and extrapolated inhibitory potency (concentration resulting in 90% inhibition of response [IC_{90}]) of interferon-alpha (IFN-α) production by plasmacytoid dendritic cells). The Treatment Period remains 24 weeks.
- Skin-related criteria for study eligibility were made less stringent. Per the original protocol, subjects in Part A were required to have a minimum CLASI-Activity (CLASI-A) score of ≥8. The CLASI requirement proved challenging for enrollment, so a specific CLASI threshold will no longer be required for Part A (but will still be required for Part B). Instead, subjects in Part A will be required to have some sign of active skin disease, as defined by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)-2K with no CLASI restriction. A requirement for skin involvement was maintained because data suggest that BIIB059 has its primary effect in the skin. Joint-related criteria for study eligibility were also added.
- The primary endpoint was modified from the Week 12 percent change from baseline in CLASI-A score to the Week 24 change from baseline in active joint count (28-joint assessment), in line with the focus of Part A on joint manifestations instead of skin manifestations of SLE. This primary endpoint was selected because joint count is considered a reliable indicator of SLE disease activity, based on the medical literature, other clinical trials, and discussions with key opinion leaders, indicating that a high proportion of SLE patients have joint involvement.
- The effect of BIIB059 on skin manifestations in patients with an SLE diagnosis (fulfilling 4 of 11 American College of Rheumatology [ACR] criteria) will be evaluated as secondary endpoints. The skin-related secondary endpoints were changed to reflect

the removal of a minimum CLASI score of ≥8 for eligibility. Since a minimum CLASI score is no longer required in Part A, the CLASI-50 and ≥4-point reduction endpoints will only be evaluable for subjects who have a baseline CLASI score of ≥4.

Part B was initially designed as a single-dose study of the effects of BIIB059 in CLE. In the amended protocol, Part B has been modified to be a dose-ranging study of BIIB059 in CLE. A larger number of subjects will be enrolled into Part B (130 instead of 30 subjects). The larger sample size and addition of a dose-ranging evaluation will allow for a more thorough evaluation of the activity of BIIB059 in CLE observed in the Phase 1 study (230LE101) and to identify an efficacious dose for CLE. Key changes to Part B are as follows:

- BIIB059 dosing regimens of 50, 150, and 450 mg SC Q4W, with an additional loading dose at Week 2, were selected based on the results of the completed Phase 1 study (230LE101) and on a population PK model developed using Phase 1 data.
- The Treatment Period was extended from 12 weeks to 16 weeks to better characterize the effects of BIIB059 in CLE, including the CLASI-A response, because comparator data suggest that the CLASI response does not plateau until after 16 weeks.
- The primary endpoint was modified from the percent change at Week 12 from baseline in CLASI-A score to the percent change at Week 16 from baseline in CLASI-A score to reflect the longer treatment period. The skin-related secondary endpoints will be evaluated at both Week 12 and Week 16.
- The amended protocol specifies a larger planned sample size for Part B. A revised sample size of 100 subjects will provide approximately 90% power to detect a dose-response relationship in the percent change at Week 16 from baseline in CLASI-A score.

An interim analysis (IA) was planned in the original protocol to occur approximately 12 weeks after 75% of subjects had been randomized into Part A. In the amended protocol, the IA for futility of Part B and possible expansion of Part A will be performed. The IA will be performed after approximately 45% of Part B subjects under protocol Version 2 have completed their Week 12 Treatment Period visit. At the time of the IA, it is estimated that over 50% of subjects in Part A enrolled under Version 1 of the protocol will have completed their Week 12 Treatment Period visit. Following the IA, up to an additional 70 subjects may be enrolled in Part A and BIIB059 dose may be adjusted. The additional subjects in Part A may be enrolled based on a more inclusive criteria to include an expanded SLE population. Details are provided in Section 16.7 of the protocol.

Key sections of the protocol that are affected by the above changes are presented in this section. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 5.5, Rationale for Dosing Regimen

Now reads:

5.5.1 Part A

~~A primary objective of this study is to evaluate the dose-response relationship of BIIB059 at 3 different dose levels given SC Q4W with an additional loading dose at Week 2. Dosing~~

~~regimens were selected based on emerging~~ **Single IV as well as multiple SC doses of BIIB059 up to and including 20 mg/kg and 300 mg, respectively, in healthy volunteers have demonstrated acceptable tolerability in the Phase 1 Study (230LE101). In general, BIIB059 serum concentrations were slightly lower in subjects with SLE than in healthy volunteers following dosing with BIIB059 50 mg SC (single and multiple dose administration). Additionally, the median percent change from baseline in BDCA2 on pDC surfaces was equivalent between SLE and healthy subjects following SC doses of 50 mg.**

Single doses of 450 mg, administered SC every 4 weeks (Q4W) with an additional dose at Week 2 will be used in Part A. The dosing regimen was selected based on Phase 1 safety, PK, PK-BDCA2 internalization relationship and extrapolated inhibitory potency (concentration resulting in 90% inhibition of response [IC_{90}]) of pDC IFN-α production [Pellerin 2015]. The **BIIB059 fixed** dose of 450 mg SC **every 4 weeks** (Q4W) **with an additional dose at Week 2** was selected to achieve C_{min} levels similar to 3-fold of the calculated IC_{90} for IFN-α inhibition. Furthermore, this dose regimen with an additional dose of 450 mg at Week 2 and a bioavailability (F) of 0.45 is expected to result in cumulative exposure **comparable to that achieved by the single dose of 20 mg/kg IV for a 65-kg person, the highest dose tested in healthy volunteers.**

~~Single IV doses of BIIB059 up to and including 20 mg/kg in healthy have demonstrated acceptable tolerability to date in Part 1 of the Phase 1 SAD study (230LE101). BDCA2 target engagement, as measured by BDCA2 internalization and reappearance, was observed in a dose-dependent manner across the dose range of 0.3 to 20 mg/kg. EC_{90} values for BDCA2 internalization were derived from population-based PK and PD modeling with the mean value of 1.5 µg/mL. IC_{90} for IFNα inhibition was estimated from in vitro to in vivo extrapolation of BDCA2 internalization and IFNα inhibition[Pellerin 2015].~~

~~BIIB059 fixed doses of 50, 150 and 450 mg SC Q4W with an additional dose at Week 2 were chosen and are supported by the following:~~

- ~~The low dose of 50 mg SC Q4W was chosen to maintain BDCA2 internalization for the majority of the dosing interval~~
- ~~The middle dose of 150 mg SC Q4W was selected to achieve minimum observed concentration (C_{min}) levels similar to the calculated IC_{90} for IFNα~~
- ~~The top dose of 450 mg SC Q4W was selected to achieve C_{min} levels similar to 3-fold of the calculated IC_{90} for IFNα inhibition. Furthermore, this dose regimen with an additional dose of 450 mg at Week 2 and a bioavailability (F) of 0.45 is expected to result in cumulative exposure over 3 months comparable to that achieved by the single dose of 20 mg/kg IV for a 65-kg person, the highest dose tested in healthy volunteers~~

~~To ensure sufficient drug exposure and concentration levels above the target steady-state values within 1 month following SC administration, an SC loading dose on Week 2 (Day 15) will be included.~~

~~The emerging PK data from the SAD study using weight-adjusted dosing show that body weight is not an influential covariate for BIIB059 exposure. Further, population PK simulations showed that both weight-adjusted dosing and fixed dosing result in comparable BIIB059 exposure. Fixed dose regimens, therefore, are proposed for the Phase 2 study. The proposed doses and/or dosing regimen may be modified based on additional PK and PD data emerging from subjects with SLE (20 mg/kg IV) and healthy volunteers (multiple doses SC) in the ongoing Phase 1 study (230LE101).~~

5.5.2 Part B

~~A single high dose of 450 mg SC Q4W and a loading dose at Week 2 will be used in Part B. This approach is based on PK simulations using data from the ongoing Phase 1 study with both SC and IV Q2W regimens, and the expectation that the 450 mg dose level will have adequate target coverage to suppress pDC function, including the production of type I IFN, over the 12 weeks preceding the primary endpoint.~~

The dosing regimen was selected based on the Phase 1 safety, PK, PK-BDCA2 internalization relationship, and extrapolated inhibitory potency (concentration resulting in 90% inhibition of response [IC_{90}]) of pDC IFN-α production [Pellerin 2015]. BIIB059 fixed doses of 50, 150 and 450 mg SC Q4W, with an additional loading dose at Week 2, were selected for the Phase 2 study because simulations conducted, based upon the population PK model developed using the Phase 1 data, predicted that:

- **At the low dose of 50 mg SC Q4W is expected to achieve plasma concentrations sufficient to maintain 90% BDCA2 internalization for the majority of the dosing interval.**
- **At the middle dose of 150 mg SC Q4W is expected to achieve plasma concentrations similar to or in excess of the calculated IC90 for IFNα for the majority of the dosing interval.**
- **At the top dose of 450 mg SC Q4W is expected to achieve C_{min} levels similar to 3-fold of the calculated IC90 for IFN-α inhibition.**

The selected doses are considered safe and tolerable, based upon the results of Phase 1 study. The dosing regimen of 450 mg SC Q4W, with an additional dose of 450 mg at Week 2 and a bioavailability (F) of 0.45, is expected to result in cumulative exposure over 3 months comparable to that achieved by the single dose of 20 mg/kg IV for a 65-kg person, the highest dose tested in healthy volunteers**.**

Section 6, Study Objectives and Endpoints (Primary)

Now reads:

Primary Objective

To evaluate the efficacy of BIIB059 in ~~skin~~ reducing disease activity in subjects with SLE **with active cutaneous manifestations and joint involvement** (Part A), and in subjects with active

CLE (SCLE or chronic CLE, including DLE) with or without systemic manifestations (Part B)**.** ~~and to investigate the dose-response relationship in subjects with active SLE and skin manifestations (Part A only)~~

Primary Endpoint

~~Week 12 percent change from baseline in CLASI-A score~~

Part A:

Change in active joint count (28-joint assessment) from Baseline to Week 24; the active joint count is defined as the sum of tender and swollen joint counts.

Part B:

Percent change ~~from baseline~~ in CLASI-A score **from Baseline to Week ~~12~~16**

Section 6, Study Objectives and Endpoints (Secondary Endpoints, Skin-related, Parts A and B)

Now reads:

- CLASI-50 ~~response~~, defined as a 50% improvement from baseline in CLASI-A score at **Week 24 (Part A**) and **Weeks 12 and 16 (Part B**)

Percent change in CLASI-A score from Baseline to Weeks 16 and 24 (Part A) and Week 12 (Part B)

- **A ≥4-point reduction in CLASI-A score relative to baseline at Week 24 (Part A) and at Weeks 12 and 16 (Part B)**

Section 6, Study Objectives and Endpoints (Secondary Endpoints, SLE-disease activity related (Part A only)

Now reads:

- ~~Composite endpoint of SRI-4 at Week 24 compared with baseline, with concomitant oral corticosteroid dosage ≤ 10 mg/day and ≤ Day 1, and stable or decreased oral corticosteroid dose between Weeks 12 and 24.~~

  ~~Composite endpoint SRI-4 is defined as:~~

  - ~~A reduction from baseline of ≥ 4 points in SLEDAI-2K score AND~~
  - ~~No new organ system affected as defined by no new BILAG-2004 A or ≤ 2B AND~~
  - ~~No worsening from baseline in subject's lupus disease activity defined by ≤ 0.3 point increase in PGA(VAS) AND~~

~~No protocol-prohibited medication/treatment~~

- **Proportion of subjects with a composite response, defined as:**
  - **SLE Responder Index (SRI) of ≥4 (SRI-4) at Week 24, where SRI-4 is defined as:**
    - **A reduction from baseline of ≥4 points in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) and**
    - **No new organ system affected, as defined by no new BILAG-2004 A and no more than one new BILAG-2004 B and**
    - **No worsening from baseline in subject's lupus disease activity defined by <0.3 point increase in PGA (VAS)**
  - **No protocol-prohibited medication or treatment.**
  - **Concomitant corticosteroid dosage at Week 24 to be ≤10 mg/day**
  - **Concomitant corticosteroid dosage at Week 24 to be ≤Day 1 corticosteroid dosage**
  - **No increase in corticosteroid dose between Weeks 17 and 24**

- **Change from baseline to Week 24 in SLEDAI-2K score**
- **Proportion of subjects with no new organ system affected, as defined by no new BILAG-2004 A and no more than one new BILAG-2004 B from baseline to Week 24**
- **Change from baseline to Week 24 in PGA VAS score**

Section 7.1, Study Overview

Now reads:

~~This is a 2-part randomized, double-blind, placebo-controlled, multicenter Phase 2 trial designed to evaluate the efficacy and safety of BIIB059 in subjects with SLE with skin manifestations (Part A) or active CLE, defined as discoid or subacute subtypes, with or without SLE (Part B). The study will be conducted at approximately 95 centers in the United States, Europe, Latin/South America and Asia.~~

~~In Part A, subjects will be randomly assigned to 1 of 4 treatment groups in a 1:1:1:1 ratio and receive either fixed doses of BIIB059 (50, 150 or 450 mg) or placebo subcutaneously Q4W for 24 weeks with a loading dose at Week 2, for a total of 7 doses (Figure 1). Randomization will be stratified by baseline CLASI-A score (≤ 10, >10) and prior oral corticosteroid usage (≤ 10 mg/d, >10 mg/d). Approximately 100 subjects are planned to be randomized (25 per treatment group). An interim analysis is planned to occur approximately 12 weeks after 75% of subjects are randomized. Following review of the interim analysis data, up to 40 additional subjects in each group (up to a total of approximately 260 subjects) may be enrolled based on pre-defined decision criteria. See Section 16.7 for details.~~

~~In Part B, 30 subjects will be randomly assigned to 1 of 2 treatment groups in a 2:1 ratio (20 subjects to BIIB059, 10 subjects to placebo) and receive either a fixed dose of BIIB059 (450 mg) or placebo SC Q4W for 12 weeks with a loading dose at Week 2, for a total of 4 doses.~~

~~(Figure 2). Randomization will be stratified by CLASI-A score (≤ 10, >10) and SLE (presence, absence). Individual subjects may participate in EITHER Part A or Part B.~~

This is a 2-part randomized, double-blind, **parallel-group,** placebo-controlled, multicenter Phase 2 trial designed to evaluate the efficacy and safety of BIIB059 in subjects with SLE with **active** skin manifestations **and joint involvement** (Part A) or active CLE, defined as **SCLE** or **chronic CLE including DLE**, with or without SLE (Part B). The study will be conducted at approximately **130** centers in the United States, Europe, Latin~~/South~~ America, and Asia.

Study treatment will begin following a 28-day Screening period.

In Part A, subjects will be randomly assigned to 1 of **2** treatment groups in a **1:1** ratio and receive either BIIB059 (450 mg) or placebo subcutaneously **every 4 weeks (**Q4W) for 24 weeks, with **an additional** dose at Week 2, for a total of 7 doses **(Figure 1)**. **The maximum number of subjects in Part A is approximately 190 subjects. Of these 190 subjects, approximately 100 subjects will be enrolled under protocol version 2. If the study is not stopped for futility at the interim analysis, then up to 70 additional subjects may be added (up to a total of approximately 170 subjects under protocol version 2). Subjects enrolled under protocol version 1 will remain on their original treatment assignment (up to a total of approximately 20 subjects) and not be re-consented under protocol version 2. Randomization will be stratified by oral corticosteroid usage (≤10 mg vs >10 mg) and by geographic region (United States vs. Asia vs. Latin America and Europe).**

In Part B**, approximately 130** subjects will be **randomized; of these, approximately 100 subjects will be enrolled under protocol version 2. Subjects enrolled under protocol version 1 will remain on their original treatment assignment and may be re-consented under protocol version 2 unless they have completed the Week 12/Early Termination Visit. Subjects enrolled in protocol version 2 will be** randomly assigned to 1 of **4** treatment groups in a **1:1:1**:1 ratio **with approximately 25** subjects **per treatment arm** and receive either a fixed dose of BIIB059 (**50 mg, 150 mg, or** 450 mg) or placebo SC **every 4** weeks **(Q4W) for 16 weeks** with **an additional** dose at Week 2, for a total of **5** doses (Figure 5). Randomization will be stratified by CLASI-A score (≤10 **vs** >10) and **DLE** (presence, absence)**.**

An IA for futility of Part B and possible expansion of Part A will be performed. The IA will be performed after approximately 45% of Part B subjects under protocol version 2 have completed their Week 12 Treatment Visit. At the time of the IA, it is estimated that over 50% of subjects in Part A will have completed their Week 12 treatment visit. Following the IA, up to an additional 70 subjects may be enrolled in Part A and BIIB059 dose may by adjusted. The additional subjects in Part A may be enrolled based on a more inclusive criteria to include an expanded SLE population. Details are provided in Section 16.7.

Section 8.1.2, Inclusion Criteria (Part A Specific)

Now reads:

- Diagnosis of SLE fulfilling at least 4 out of 11 1997 revised ACR classification criteria for SLE **(Appendix C),** with a diagnosis made ≥24 weeks prior to signing the informed consent form (ICF).
- Positive antinuclear antibody test at Screening (central laboratory titer ≥1:80) and/or elevated anti-double-stranded DNA (≥30 IU/mL).
- **At least one sign of active skin disease, including acute, subacute, and/or chronic cutaneous lupus (e.g., discoid lupus erythematosus), with skin activity defined by SLEDAI-2K**
- **Must have at least 4 tender joints based on assessment of 28 joints as described in Section 4.3.3.**
- **Must have at least 4 swollen joints based on assessment of 28 joints as described in Section 4.3.3, with at least 4 occurring in the PIP, MCP, or wrist joints. Note: A joint that is both tender and swollen will be included in both categories (counts as 1 tender and 1 swollen).**
- **To allow for accurate assessment of joint tenderness and swelling, subjects who may be taking NSAIDs or other analgesics including narcotics or medical marijuana must agree not to take a dose of these medications within 12 hours prior to the joint assessment visits.**
- ~~CLASI-A ≥ 8 at Screening and Randomization.~~
- ~~SLEDAI-2K ≥ 4 at Screening and Randomization (excluding fever).~~

Section 8.1.3, Inclusion Criteria (Part B Specific)

Now reads:

- Must have diagnosis of CLE **that has been histologically confirmed (in the past or at Screening),** with or without systemic LE **manifestations. The histological diagnosis confirmation** should be documented at Screening. For subjects without historical biopsy data, a skin biopsy must be performed at Screening to confirm CLE diagnosis prior to **randomization. All subjects must also** have **active skin manifestations that fulfill the following:**
  - **Subacute CLE with a CLASI-A erythema score of ≥2**

    and/or
  - **Chronic CLE, including DLE, with** at least 1 active **CCLE** lesion with a minimum CLASI-**A erythema score ≥2 and in addition** CLASI-D scarring ≥1
- **CLASI-A ≥8 at Screening and randomization**
- Must have active CLE despite an adequate trial of conventional therapies (defined as either topical corticosteroids or an antimalarial agent used for at least **12 weeks prior to Screening) OR previously documented failure to respond to these agents when used**

for at least 12 weeks OR the requirement to discontinue these agents due to side effects or poor tolerability.

Section 8.2.1, Exclusion Criteria (Parts A and B), Previous Therapies

Now reads:

1. ~~Concomitant and~~ Previous Therapies

2. **23.** Use of IV, intramuscular (IM), or intra-articular (Part A only) corticosteroids within 12 weeks prior to randomization.

~~Use of high potency topical and/or intralesional corticosteroid within 1 month prior to Screening and during the study.~~

3. **24.** Use of high-potency topical corticosteroid and/or **topical agents (immunosuppressant) for skin lesions within 7 days prior to randomization.**

4. **25. Use of high-potency** intralesional corticosteroid within **4 weeks** prior to **randomization.**

5. **26. Part A subjects who are receiving systemic corticosteroid treatment at a dose exceeding 20 mg/day prednisone (or its equivalent), or if any dose of prednisone (or its equivalent) has not been stable for ≥4 weeks prior to randomization.**

6. **27. Part B subjects who are receiving systemic corticosteroid treatment at a dose exceeding 15 mg/day of prednisone (or its equivalent), or if any dose of prednisone (or its equivalent) has not been stable for ≥4 weeks prior to randomization.**

~~Use of thalidomide or lenalidomide within 2 months of Screening and during the study.~~

7. **28.** Use of thalidomide or lenalidomide**, IV or SC immunoglobulin, or plasmapheresis** within **12 weeks** of **randomization.**

~~Use of cyclosporine, tacrolimus, pierolimus, sirolimus, imiquimod, IV immunoglobulin, IV and oral cyclophosphamide and plasmapheresis within 3 months of Screening and during the study.~~

29. Use of tacrolimus, pimecrolimus, and sirolimus **within 4 weeks prior to randomization**.

~~Use of abatacept, belimumab, tocilizumab or tumor necrosis factor (TNF) inhibitors within 3 months or 5 half-lives, whichever is longer, before Screening and during the study.~~

8. **30.** Use of **oral or parenteral** rituximab, ~~atacicept~~, ocrelizumab, or other B cell-directed biologic therapies within **24 weeks prior to randomization**. Subjects with prior B cell-directed therapies within 12 months of Screening will be excluded if total CD19 B cell level is <25 cells/µL as measured at Screening **at the central laboratory**.

31 Use of cyclophosphamide, cyclosporine, mixoribine, atacicept, abatacept, belimumab, tocilizumab, or tumor necrosis factor (TNF) inhibitors within 12 weeks or 5 half-lives (whichever is longer) prior to randomization.

9. ~~Initiation of disease-modifying antirheumatic agents or immunosuppressive treatments with the exception of those listed in exclusion criteria 31, within 3 months of Screening and during the study.~~
10. **32.** Use of immunosuppressive or disease-modifying treatments for SLE **or CLE (via an oral, IV, or SC route)** that were initiated less than **12 weeks** prior to **randomization**, have not been at a stable dose for at least **4 weeks** prior to randomization, or have been taken **during the last 12 weeks** at doses above the prescribed maximum listed here **(medication list includes, but is not limited to the following): antimalarial medications** (hydroxychloroquine **up to 400** mg/day, quinacrine 100 mg/day maximum, chloroquine **250** mg/day), dapsone 150 mg/day, methotrexate **25** mg/week, azathioprine 200 mg/day, 6-mercaptopurine **100** mg/day, and mycophenolate mofetil (MMF) **3** g/day or mycophenolate sodium (MPS) **2160** mg/day.
11. **33.** Immunizations with live or live-attenuated vaccines within **4 weeks** before Screening and throughout the study and for **16 weeks** after the last dose of study treatment.
12. ~~Allergy shots or completion of desensitization therapy within 1 month prior to Screening.~~
13.

Section 9.1, Screening and Registration

Now reads:

9.1 Screening and ~~Enrollment~~ Registration

Subjects (or their legally authorized representative [e.g., parent or legal guardian], where applicable) must provide informed consent before any screening tests are performed (see Section 17.3). When a subject signs the ICF, that subject is considered to be enrolled in the study. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log.

~~A subject with a CLASI-A score of > 4 but < 8 and otherwise not meeting any other exclusion criteria may be rescreened on CLASI-A alone within 3 months to determine study eligibility or undergo full rescreening if beyond 3 months.~~

For subjects entering Part A, screening **tender and swollen** joint ~~scores~~**counts** will be ~~evaluated~~**performed by an independent joint assessor at each site prior to study entry.**

For subjects entering Part B, screening CLASI scores will be verified by an independent CLASI Adjudicator (Section 19.2.2) prior to study entry.

Subjects will be registered at the Screening Visit; **as part of study screening, potential subjects will have the study risks and benefits explained to them, the associated ICF reviewed with them, and all their questions answered**.

If a subject initially fails any of the screening criteria and is deemed as a screen failure by the end of the initial 28-day screening period, they will be allowed to be rescreened one time at the discretion of the Investigator. Upon rescreening, and in consultation with the Medical Monitor, subjects should repeat the Screening assessments and receive a new Screening Number.

Section 11.1, Study Treatment Regimen

Part A

~~Subjects will be randomized in a 1:1:1:1 ratio to 1 of the following 4 treatment groups:~~

- ~~BIIB059 50 mg~~
- ~~BIIB059 150 mg~~
- ~~BIIB059 450 mg~~
- ~~Placebo~~

~~Dose regimen: Q4W SC, with a loading dose at Week 2, for a total of 7 doses.~~

Subjects will be randomized in a **1:1** ratio to 1 of the following **2** treatment groups:

- **BIIB059 450 mg**
- **Placebo**

Dose regimen**: every 4 weeks (**Q4W**)** SC, with **an additional** dose at Week 2, for a total of **7 doses.**

Part B

~~Subjects will be randomized in a 1:1 ratio to 1 of the following 2 treatment groups:~~

- ~~BIIB059 450 mg~~
- ~~Placebo~~

~~Dose regimen: Q4W SC, with a loading dose at Week 2, for a total of 4 doses~~.

Subjects will be randomized in a **1:1:1:1** ratio to 1 of the following **4** treatment groups:

- **BIIB059 50 mg**
- **BIIB059 150 mg**
- **BIIB059 450 mg**
- **Placebo**

Dose regimen: every 4 weeks SC (Q4W), with an additional dose at Week 2, for a total of 5 doses.

Section 16.1.2.1, Analysis of the Primary Endpoint

Now reads:

Part A:

~~The primary analysis of the primary endpoint is a test of dose-response, using the Multiple Comparison Procedure – Modelling (MCP-Mod) methodology[Bretz 2005].~~

~~Three monotonic dose-response trends will be tested using the appropriate contrasts as determined by the MCP-Mod methodology in an analysis of covariance (~~**~~ANCOVA~~A Mixed Effect Model Repeat Measurement (MMRM)** model ~~such that the overall Type 1 error rate for these 3 resulting p-values is controlled at 0.10 (2-sided testing). Additional information~~ will be ~~provided in~~**used as** the ~~SAP.~~

~~The ANCOVA model will have Week 12 percent~~**primary method to analyze** change from baseline ~~score~~ in ~~CLASI-A score as~~ the ~~dependent variable,~~**active joint count using** treatment ~~(50 mg, 150 mg, 450 mg, and placebo),~~**group, study visit,** prior oral corticosteroid usage, ~~season of enrollment and smoking status as~~**region, and study visit-by-treatment interaction as fixed effect** factors and baseline ~~SLEDAI-2K and CLASI-A scores~~**active joint count** as ~~covariates.~~

~~In addition, the following analyses of the~~**covariate. The** primary ~~endpoint will be performed:~~

~~Pairwise~~**treatment** comparison ~~of each BIIB059 treatment group versus placebo, based~~**will be the difference between the 450 mg dose and placebo at the end of the Week 24** on the ~~ANCOVA model.~~**change from baseline in active joint count.**

~~Sensitivity~~**In addition, sensitivity** analysis based on the ~~ANCOVA~~**MMRM** model, with missing values imputed **will also be performed** (imputation methods **are** defined in the SAP).

Due to the impact of corticosteroid and rescue medication use on ~~CLASI-A scores~~**active joint count**, if a subject has an increase from baseline in corticosteroid use after Week 4 (excluding allowed corticosteroid use as described in Section 11.4.1.1.2) or uses any SLE rescue medication (as described in Section 11.4.1.1.1) during the **24-week treatment period** of the study, the subject will be a treatment failure. The subject's ~~CLASI-A scores~~**joint count** after the increased corticosteroid use or after SLE rescue medication will not be included in the primary analysis. For subjects who are treatment failures prior to the Week ~~12~~24 assessment of ~~CLASI-A score~~**joint count,** a ~~last~~**worst** observation carried forward (~~LOCF~~**WOCF**) method will be applied using the patient's last post-baseline ~~CLASI-A score~~**joint count** prior to treatment failure. ~~Additional~~ **In addition, if a subject deviates from the planned tapering schedule (Table 7), they might be considered as a treatment failure depending on the severity and timing of deviation. Additional** details will be provided in the SAP.

Part B:

~~The primary analysis of the primary endpoint is~~**An MMRM model will be used to analyze the percent change from baseline in CLASI-A score using treatment group, study visit, study visit-by-treatment interaction, DLE (presence or absence), and SLE (presence or absence) as fixed effect factors and baseline CLASI-A scores as a covariate.**

The primary analysis of the primary endpoint is a test of dose-response, using the Multiple Comparison Procedure – Modelling (MCP-Mod) methodology [Bretz 2005].

Five dose-response trends will be tested using the appropriate contrasts, as determined by the MCP-Mod methodology, on the treatment effects obtained from the MMRM model . Additional information will be provided in the SAP.

[redacted]

~~The credible interval will be derived from an ANCOVA model with Week 12 percent change from baseline score in CLASI-A score as the dependent variable, treatment (BIIB059 450 mg, placebo), SLE (presence, absence), season of enrollment and smoking status as factors, and baseline CLASI-A score as a covariate.~~

~~In addition, the~~**The** following analyses of the primary endpoint will **also** be performed:

- ~~Comparison~~**Pairwise comparison** of ~~the~~**each** BIIB059 treatment group versus placebo, based on the ~~ANCOVA model (not using the Bayesian methodology).~~**MMRM model.**
- Sensitivity analysis based on the ~~ANCOVA~~**MMRM** model, with missing values imputed (imputation methods defined in the SAP).

Due to the impact of corticosteroid use on CLASI-A scores, if a subject has an increase from ~~screening~~**Screening** in corticosteroid use, the subject's CLASI-A scores after the **increased** corticosteroid use will not be included in the primary analysis. The missing data handling methodology will follow the methods described for Part A. For subjects in Part B with a diagnosis of SLE in addition to CLE, please refer to Section 11.4.1.1.1 Additional details will be provided in the SAP.

Section 11.4.1.1.1. Additional details will be provided in the SAP.

Section 16.7, Interim Analyses

Now reads:

Part A~~:~~

~~An interim analysis is planned~~ **and B:**

An IA for futility of Part B and possible expansion of Part A will be performed**. The IA will be performed after** approximately ~~12 weeks after 75~~**45%** of **Part B** subjects **under protocol version 2** have ~~been randomized.~~**completed their Week 12 Treatment Visit. At the time of the IA, it is estimated that over 50% of subjects in Part A will have completed their Week 12 treatment visit.** Following ~~unblinded independent analysis of the interim analysis dataset, Biogen may expand enrollment in Part A with~~**the IA,** up to ~~40~~**70** additional subjects ~~per group.~~**maybe enrolled in part A and BIIB059 dose may by adjusted.** At the interim analysis, unblinded ~~patient~~**subject** baseline characteristics (eg, **Joint Count,** SLEDAI-2K) will be assessed. The randomization stratification factors will be reevaluated in the expanded enrollment to achieve balance between treatment groups. The ~~objective~~**3 objectives** for adding additional subjects ~~at~~**to Part A after** the interim analysis ~~to Part A is~~**are to: 1) potentially include an expanded SLE patient population based on a more inclusive criteria, 2) potentially adjust the dose of BIIB059 and, 3)** to provide greater precision for the Week 24 endpoints, including the SRI-4. ~~The details of the interim analysis plan will be specified in the SAP.~~ Unblinded tables, listings, or graphs (TLGs) will be generated by independent personnel (internal or external) not involved in the conduct of the study. ~~Unblinded TLGs~~**The IA will be performed by independent personnel (internal** and/or ~~data will~~**external)** not ~~be shared with subjects, investigators, or the study team members directly~~ involved in the conduct of the study~~, prior to unblinding the study for final analysis or stopping for futility.~~. At the discretion of Biogen, unblinded TLGs and/or data may be shared with ~~sponsor~~**Sponsor** personnel who are not directly involved in the conduct of the study. **Additional information will be provided in an unblinding plan. Details of the data to be used for the interim analysis and the analyses planned for futility and possible expansion will be provided in the SAP.**

~~Details on data to be used for the interim analysis and the analyses planned will be provided in the SAP.~~

~~**Part B:**~~

~~No interim analysis is planned.~~

Section 16.8, Sample Size Considerations

Now reads (no strikethrough text is provided):

Part A:

The sample size for Part A is 100 subjects, **randomized** in a 1:1 ratio, **with 50** subjects **allocated t**o each treatment group. This sample size **will provide** approximately 71% power to detect a **statistically significant difference i**n the Week **24 absolute** change from baseline **active joint count,** assuming a standard deviation of **6,** a maximal difference of BIIB059 over placebo of **2.5,** a 20% drop out rate**, and a 2-sided testing at the 0.2 level significance.** Additional information will be provided in the **Statistical Analysis Plan (S**AP**).** If the study is not stopped for futility at the interim analysis (details in Section **16.7),** then up to **70** additional subjects may be added to

Part A. If an additional **70** subjects are added, the power will increase to **approximately 87**% at Week **24.**

Part B:

The planned sample size for Part B is **100** subjects, **randomized** in a **1:1:**1**:1** ratio**, with 25** subjects **per dosage arm of** BIIB059 **(50 mg, 150 mg, a**nd **450 mg) and** placebo. **This sample size will provide approximately 90% power to detect a dose-response relationship in the Week 16 percent change from baseline score in CLASI-A score, assuming a standard deviation of 30, a maximal difference of BIIB059 over placebo of 27.5%, and a 20% drop out rate. Five different dose-response relationships will be tested at the 2-sided 10% significance level with the MCP-Mod method being used to control for multiplicity [Bretz 2005].**

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 3, Synopsis

The Synopsis was revised to reflect changes made throughout the protocol.

Section 4.2, Schedule of Activities,Table 1 (Part A) and Table 2 (Part B) [Skin Photography]

Change: The whole-body skin photography requirement was removed from Part A; instead, a photograph of the target lesion only will be taken at the time of tape harvesting (Weeks 0, 4, and 16). No adjudication of the target lesion photography will be necessary in Part A. Footnote 10 below Table 1 provides additional details and requirements.

In Part B, whole-body photography was replaced by photography of each part of the body with skin involvement where a CLASI-A and/or CLASI-D score is present (including but not limited to the target lesions, biopsy lesions, head, and so on). The photographs taken at Screening will be evaluated by a central adjudicator to verify the CLASI-A score assignment by the Investigator and confirm eligibility. Also, the number of skin photography assessments was reduced from 6 (at Screening, baseline, and Weeks 2, 4, 8, and 12) to 4 (at Screening and Weeks 0, 4, and 16). Footnote 12 below Table 2 provides additional details and requirements.

Now reads:

(See Table 1, Schedule of Activities Part A, and Table 2, Schedule of Activities Part B, in the protocol.)

Rationale: Skin photography is a general enrollment barrier in subjects with skin rash. In order to facilitate subject enrollment, the necessity of this tool was reassessed across the study. In Part A, whole-body photography (and the associated adjudication process) proved unnecessary due to the change in outcome measure for the primary endpoint (from CLASI-A to joint count).

In Part B, the procedure was streamlined to include only affected skin areas based on CLASI-A and/or CLASI-D. The frequency was also reduced to focus on the most significant timepoints.

This change also affects Section 4.3.4, Additional Information – Skin Photography.

Section 4.2, Schedule of Assessments, (Table 1 (Part A) and Table 2 (Part B)

Change: The timing, frequency, and/or associated guidance for several study assessments were revised as follows:

- The following footnote was added to the "Tests and Assessments" column in Table 1 and Table 2: "[2]**Assessments (e.g., CPK, ECG, etc.) may be performed as required to confirm SLEDAI-2K and BILAG findings**" **("and BILAG findings"** Table 1 only**).**

- The chest X-ray was removed as a requirement for both Part A and Part B, and a footnote on tuberculosis testing was added to Table 1 and Table 2: "[5]**Testing to be performed locally. Indeterminate Quantiferon or T-SPOT tests may be repeated once and will be considered positive if retest results are positive or indeterminate. Subjects with documented BCG vaccination must perform a TB test at Screening and will be excluded if they exhibit skin induration ≥5 mm or a positive Quantiferon or positive or borderline T-SPOT (Elispot) test.**" For further information, see the change to exclusion criterion 16 (Section 8.2) below.
- Urine Pregnancy Test: An assessment was added at Week 2.
- A footnote was added to the Physical Examination, Weight, and Height assessment in Table 1 and Table 2: "[7]**Height should be measured only once; i.e., at the Day 1/baseline visit.**"
- For the Vital Signs assessment, it was clarified in footnote 8 to Table 1 and Table 2 that oral body temperature should be measured.
- [redacted]
- Joint count assessments were added to Table 1 at Screening and Weeks 2, 4, 8, 16, 20, and FU12. See detailed explanations in this document under Primary Reason for Amendment and Section 8.1.2, Inclusion Criteria (Part A Specific).
- The timing of PK assessments was revised in Table 1 and Table 2. In Table 1, assessments were removed at Weeks 2, 8, 20, and FU8. In Table 2, assessments were removed at Weeks 2 and 8. Also, a separate table on PK assessments (Table 3) was added to specify when PK assessments should be done during each visit. The frequency of [redacted], complement, skin RNA tape harvesting, [redacted], and blood RNA [Paxgene]) was reduced in Table 1 and Table 2.
- The following footnote was added to Table 1 (footnote 15) and Table 2 (footnote 17) to provide more guidance on performing the ESR: [redacted]
- A footnote on which vaccine-related immunoglobulin titers will be collected in Part A was added to Table 1: "[19]**Vaccine-related immunoglobulin titers for tetanus, diphtheria, and *Pneumococcus* will be collected.**"
- An electronic diary review of subject-reported questionnaires was added to Table 1 and Table 2.
- The timing of CLASI assessments in Part B was revised (assessments were removed at Week 2). Additional guidance on CLASI assessment and adjudication was provided in the footnote: "[9]**CLASI will be assessed by the Investigator or a trained designee at all**

assessments (Section 19.2.2). CLASI scores at Screening will be verified by an Independent CLASI Adjudicator to confirm eligibility."

- [redacted]
- [redacted]
- The skin biopsy for confirmation of CLE diagnosis and the optional skin biopsy for biomarkers were separated into 2 different assessments in Table 2.
- The vaccine status assessment was removed from Table 2.

Rationale: The timing and guidance provided on all study assessments was re-evaluated and, in some cases, revised in order to align with study design changes, ease patient burden, mitigate enrollment barriers, and provide clearer guidance on study assessments.

[redacted])

Change: [redacted]

Now reads:

Additional Objectives

[redacted]

Additional Endpoints

- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

[redacted].

Section 8.2.1, Exclusion Criteria (Tuberculosis)

Change: The criterion related to tuberculosis history (now exclusion criterion 16) was revised to exclude any subjects who tested positive for tuberculosis, including subjects who are undergoing current treatment.

Now reads:

- History of or current diagnosis of active tuberculosis (TB), or untreated latent TB infection (LTBI), determined by a TB skin test with purified protein derivative as evidenced by induration ≥5 mm or a positive Quantiferon, positive or borderline T-SPOT (Elispot) test performed locally, either at Screening or documented with results within **12 weeks** of the Screening Visit. ~~If the subject is undergoing current treatment for LTBI, they must have received at least 4 continuous weeks of an appropriate LTBI treatment prior to Screening without evidence of re-exposure.~~ Subjects who have previously completed appropriate and documented LTBI treatment ~~or who are undergoing current treatment for LTBI~~ will not be required to be tested. ~~If receiving LTBI treatment at Screening, the subject will be expected to complete an appropriate LTBI treatment regimen to remain in the trial.~~ **Subjects** must have received **complete** LTBI treatment prior to Screening without evidence of re-exposure **prior** to **entering the study**.
  - Subject with current household contacts with active TB will also be excluded unless the subject is being treated and there is evidence that household contacts are being treated
  - Indeterminate Quantiferon or T-SPOT tests may be repeated once, and will be considered positive if retest results are positive or indeterminate. **Subjects with documented BCG vaccination must perform a TB test at Screening and will be excluded if skin induration ≥5 mm or a positive Quantiferon or positive or borderline T-SPOT (Elispot) test.**

Rationale: This change was made to support the removal of the chest X-ray assessment from the schedule of activities for both Part A and Part B.

Investigators have indicated that performing the chest X-ray for all subjects as a screening tool for tuberculosis is unnecessary since tuberculosis is infrequently seen and subjects considered the chest X-ray burdensome. Furthermore, chest X-rays may not be permitted in some regions due to local regulations. However, in order to address the risk of enrolling a subject with active

tuberculosis in the absence of chest X-ray verification, the tuberculosis exclusion criterion was revise to exclude any subjects being treated for a latent tuberculosis infection as these subjects were previously allowed to participate.

This change also affects Section 4.2, Schedule of Activities, Table 1 (Part A) and Table 2 (Part B).

Section 8.2.1, Exclusion Criteria (IV, IM, intra-articular, and high-potency topical corticosteroid use prior to the study)

Change: In the original protocol, high-potency topical steroids were not allowed within 1 month prior to Screening and for the duration of Part B. In the amended protocol, more specific prerandomization guidance has been added on when IV, IM, intra-articular, and high-potency topical corticosteroids are allowed.

Now reads:

(New exclusion criterion 23)

23. Use of IV, intramuscular (IM), or intra-articular corticosteroids within 12 weeks prior to randomization.

(Revised exclusion criterion 24)

24. Use of high-potency topical **corticosteroid and/or topical agents (immunosuppressant) for skin lesions within 7 days prior to randomization.**

(Revised exclusion criterion 25)

25. **Use of high-potency** intralesional corticosteroid within **4 weeks** prior to **randomization**.

25.

Rationale: The revised criterion will allow greater precision and improve clarity in selecting for steroid use in Part B; the same rule will apply for target lesions in Part A. The criteria pertaining to low- and medium-potency topical steroids are unchanged in the amended protocol.

This change also affects Section 11.4.1.1.2.1, Topical and Intralesional Corticosteroids.

Section 8.2.1, Exclusion Criteria (General)

Change: Several exclusion criteria were modified, as follows:

Now reads:

26. 1. Current enrollment or a plan to enroll in any interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered. **A washout period of at least 3 months or** 5 half-lives **(whichever is longer) is required** prior to **randomization**. Participation in observational registries is allowed.

27. **2. For subjects who previously received an investigational or approved treatment that blocks IFN-α, a washout period of 6 months is required prior to randomization.**

3. For subjects who previously received BIIB059 in the phase 1 study, a washout period of 6 months is required prior to randomization in the present study. Subjects who discontinued previous BIIB059 study participation due to AEs are not eligible.

7. Current active hepatitis C virus **(HCV) infection, determined as HCV RNA above the limit of detection**.

8. Positive test result at Screening for hepatitis B virus (**HBV;** defined as positive for **either** hepatitis B surface antigen **or** hepatitis B core antibody).

~~12. Systemic comorbidities requiring systemic corticosteroid therapy (e.g. asthma or inflammatory bowel disease); systemic therapy is defined as treatment given orally, rectally, or by any injectable route of administration. (Comorbidities that require corticosteroid use administered by other routes, including inhaled, ophthalmic, otic, and intranasal, are allowed).~~

~~16. Active clinically significant viral, bacterial, or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral anti-infectives within 4 weeks of or during Screening, or completion of oral anti-infectives within 2 weeks before or during Screening. Vaginal candidiasis, onychomycosis, and genital or oral herpes simplex virus considered by the Investigator to be sufficiently controlled will not be exclusionary.~~

~~20. History of severe allergic or anaphylactic reactions.~~

19. History of, or ongoing, malignant disease, including solid tumors and hematologic malignancies with the exception of basal cell carcinomas and squamous cell carcinomas **and carcinoma in situ of the cervix** that have been completely excised and considered cured **>2** years prior to Screening.

24. Female subjects who are pregnant, currently **lactating, have stopped lactating in the past 12 weeks**, or are planning to become pregnant during the study and for 4 months after the last dose of study treatment.

26. Part A subjects who are receiving systemic corticosteroid treatment at a dose exceeding 20 mg/day prednisone (or its equivalent), or if any dose of prednisone (or its equivalent) has not been stable for ≥4 weeks prior to randomization.

27. Part B subjects who are receiving systemic corticosteroid treatment at a dose exceeding 15 mg/day of prednisone (or its equivalent), or if any dose of prednisone (or its equivalent) has not been stable for ≥4 weeks prior to randomization.

28. **37. Any abnormal laboratory test result at Screening that is considered clinically significant and unrelated to the underlying disease (SLE/CLE), as determined by the Investigator and would preclude the subject from participating in the study. Clinical laboratory tests may be repeated one time, at the discretion of the Investigator, if there are questionable results, or if abnormalities are felt to be due to inherent variability of the test procedure.** ~~A nonclinically significant out-of-range laboratory value would not be considered exclusionary.~~

~~8.2.2 Exclusion Criteria (Part A Specific)~~

1. ~~For subjects who have initiated systemic corticosteroids, a dose of prednisone exceeding 20 mg/day (or its equivalent) or if the dose has not been stable for ≥ 1 month prior to Randomization.~~ (replaced with criterion 26 above)

~~8.2.3 Exclusion Criteria (Part B Specific)~~

1. ~~For subjects who have initiated systemic corticosteroids, a dose of prednisone exceeding 15 mg/day (or its equivalent) or if the dose has not been stable for ≥ 1 month prior to Randomization.~~ (replaced with criterion 27 above)

29.

Rationale: The study exclusion criteria were generally simplified to increase study enrollment and, in some cases, made more stringent to ensure a more controlled analysis population.

Section 9.1, Screening and Registration

Change: The title of Section 9.1 was changed from "Screening and Enrollment" to "Screening and Registration" to better reflect the content of the section. (Information about randomization was placed in a new section, Section 9.2, Randomization of Subjects.) Text was added to describe the role of the independent joint assessor (Part A) and the independent CLASI Adjudicator (Part B) at Screening. A description of rescreening criteria was added.

Now reads:

Subjects (or their legally authorized representative [e.g., parent or legal guardian], where applicable) must provide informed consent before any screening tests are performed (see Section 17.3). When a subject signs the ICF, that subject is considered to be enrolled in the study. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log.

For subjects entering Part A, screening tender and swollen joint counts will be performed by an independent joint assessor at each site prior to study entry.

For subjects entering Part B, screening CLASI scores will be verified by an independent CLASI Adjudicator (Section 19.2.2) prior to study entry.

Subjects will be registered at the Screening Visit**; as part of study screening, potential subjects will have the study risks and benefits explained to them, the associated ICF reviewed with them,** and **all their questions answered.**

If a subject initially fails any of the screening criteria and is deemed as a screen failure by the end of the initial 28-day screening period, they will be allowed to be rescreened one time at the discretion of the Investigator. Upon rescreening, and in consultation with the Medical Monitor, subjects should repeat the screening assessments and receive a new Screening Number.

Rationale: The revision provides information about the roles of independent central review of key tests for eligibility. The revision also provides clarification of the circumstance under which a subject can be rescreened for study entry.

Section 9.3, Blinding Procedures

Change: Text to clarify study unblinding was added.

Now reads:

[redacted] Efforts will be made to ensure that no members of the team involved in study conduct will be unblinded. **Unblinding is permitted only in the case of a medical emergency or serious medical condition, when knowledge of the study treatment is essential for the immediate clinical management or welfare of the study subject, as judged by the Investigator. Details of unblinding will be provided in the Study Reference Manual.**

A team of Biogen personnel, independent of the study team, will be set up to conduct the unblinded interim analyses as discussed in Section 16.7.

Rationale: The revision provides further information about study unblinding directly in the protocol instead of a separate unblinding plan, as indicated in the original protocol.

Section 10.1, Discontinuation of Study Treatment

Change: More detailed guidance on early study termination was added.

Now reads:

Subjects who discontinue treatment **are allowed to** remain in the study and will be encouraged to continue protocol-required tests and assessments during the follow-up visits **(Week 4, 8, and 12 Follow-Up Visits). In the event that a subject withdraws from the study prematurely, at minimum, an Early Termination visit should be performed as soon as possible, to be followed by follow-up visits at 4, 8, and 12 weeks after last visit; all Early Termination assessments listed in the study schedule should be performed at this Early Termination visit.**

Rationale: The revision provides further information about early termination, including the desired visit window and guidance on assessments to be performed at study end.

Section 11.2, Study Treatment Precautions

Change: In the original protocol, there was no specific guidance on monitoring subjects immediately after study treatment administration. In the amended protocol, subjects will be asked to remain at the study center for 1 hour after study treatment administration for observation. A description of the process for handling missed doses of study treatment was also

added to this section, and the section title was changed from "Modification of Dose and/or Treatment" to "Study Treatment Precautions."

Now reads:

Following administration of study treatment, subjects should remain at the study center for 1 hour to monitor for the development of potential allergic or anaphylactic reactions.

Epinephrine for subcutaneous injection, diphenhydramine (or equivalent) for IV injection, and any other medications and resuscitation equipment for the emergency management of anaphylactic reactions must be available in the room where the infusion is being performed.

BIIB059 or placebo should be administered within the stated window of the scheduled visit (+/ 2 or 3 days; see Table 2 and Table 3). If a subject misses a planned dose (i.e., outside of the 2 or 3 day window), the missed dose should be administered as soon as possible, and no later than 5 days after the last day of the planned window. If the Week 2 dose (the second dose to be administered in the study) can't be given within the planned window, the missed dose should be skipped and the subject should receive the next scheduled dose as per protocol.

Rationale: This change was made because BIIB059 is a monoclonal antibody and, as with all monoclonal antibodies, has the potential to be immunogenic and trigger an allergic reaction. Therefore, a period of observation after administration is appropriate. If a severe allergic reaction occurs, the study treatment must be discontinued immediately and the subject must be immediately treated appropriately. Most severe acute allergic or anaphylactic reactions happen within 60 minutes after administration; therefore, observation for this time period is in the interest of subject safety.

This change also affects Sections 4.2, Schedule of Activities (Parts A and B); 7.2.2, Overall Study Duration and Follow-up (Part A) – Treatment; 7.3.2, Overall Study Duration and Follow-up (Part B) – Treatment; and 12, Study Treatment Management.

The detailed description of the process for handling missed doses of study treatment was added to improve clarity on this issue and to help ensure safety; i.e., so subjects do not receive study treatment dosing <2 weeks apart.

Section 11.4.1.1.2.2, Part A Specific Instructions – Oral Corticosteroids

Change: In the original version of the protocol, a prescribed corticosteroid tapering regimen was recommended for all subjects in Part A after 4 weeks of study treatment. The tapering schedule allowed 1 rescue either during the first 4 weeks OR between Weeks 13 and 16. Subjects who could not fulfill the tapering scheme, based on Investigator judgment, could remain in the study and receive immunosuppressive treatment as required.

In the amended protocol, the corticosteroid tapering regimen will be mandatory for all subjects in Part A. The prescribed tapering regimen has also been revised and is now more aggressive. During the tapering schedule, rescue oral corticosteroid dosing is allowed up to 2 times for any one subject at specified periods; i.e., during the first 4 weeks of treatment, between Weeks 5 and

7 (inclusive), and between Weeks 9 and 11 (inclusive). Subjects are allowed to revert to the previous dose level once and for only 1 week. Subjects who cannot fulfill the tapering scheme will be considered treatment failures and will be allowed to receive standard of care treatment. Subjects who are treatment failures will be allowed to continue to receive the investigational product and to complete the study, at the discretion of the Investigator.

Now reads:

Eligible subjects will have active SLE with **joint and** skin manifestations at **Screening and randomization. Subjects may be treated with SLE background SoC therapies as per exclusion criterion #31, and if taking corticosteroids, must have been on stable dosage for at least 4 weeks prior to randomization. Subjects who are not receiving corticosteroids at Screening or baseline are permitted to participate in the study.**

Doses of corticosteroid must remain stable during **S**creening and during the first 4 weeks after the first **dose** of study treatment (i.e. until Day 28). **The tapering schedule should begin 4 weeks (Week 5; Days 29 to 35) after the first dose of study treatment.** The tapering regimen **is intended** to reduce the daily **dose of** prednisone **(or** equivalent) to 10 mg/day or lower by Week **12** (Day **85**) of the study as outlined in Table 1.

If a subject deviates from the planned tapering schedule (Table 7), they might be considered a treatment failure (See Section 16.1.2.1). Subjects are allowed to continue to receive the investigational product (IP) and to complete the study, at the discretion of the Investigator.

Subjects achieving the Week **12** dose of 10 mg **of prednisone (or equivalent**) or lower may remain on this dose or continue to taper between Week 13 and Week 16 at the discretion of the Investigator. **The dose of prednisone (or equivalent) will remain stable (at the Week 16 dose) between Week 17 and Week 24**.

***Screening*:**

Subjects who are receiving corticosteroids must receive a stable dose throughout the Screening period; no initiation**,** increase**, or decrease** of corticosteroid **dose is permitted**.

The maximum **daily dose of corticosteroid allowed is 2**0 mg **prednisone (or equivalent).**

Treatment period:

Oral corticosteroid dose tapering (as **described in** Table 1 **) is mandatory** within the rules for dose changes outlined below.

Briefly, oral corticosteroids dosing guidelines are as follow:

- Stable corticosteroid dose from Day 1 to Week 4 (Day 1 to Day 28),
- Decrease in corticosteroid dose from baseline between Week 5 and Week **11** (Days 29 to **78),**
- Stable corticosteroid dose at Week 12 (Days **79** to **85**)

- **Stable Week 12** corticosteroid dose **or decrease by 2.5 mg b**etween Week 13 and Week 16 (Day **86** to **113**),
- Stable corticosteroid dose **(at ~~a minimum of~~ Week 12 dose) b**etween Week 17 and Week 24 (Days **114** to 169)

Between **Day 1 to Week 4 the corticosteroid dose can be increased to a maximum of 10 mg/day above Day 1 dosage, but must return to Day 1 level within 7 days (Rescue 1). Between Week 5 and Week 7 (Rescue 2), OR between Week 9 and Week 11 (Rescue 3), the** corticosteroid dose **can be increased to the previous dosage level for up to 1 week before resuming the tapering schedule. Only two rescues out of the three described above are allowed, at the discretion of the Investigator.**

Overall, TWO corticosteroid rescues are allowed:

- **Rescue 1 and Rescue 2; OR**
- **Rescue 1 and Rescue 3; OR**
- **Rescue 2 and Rescue 3.**

Any **other** increase in corticosteroid dose **may be considered** a treatment failure **and/or protocol deviation (depending on the timing or severity of the deviation) for the** analysis (see Section 0). Subjects **who cannot fulfill the corticosteroid tapering schedule should** still complete the study **and remain on IP. Corticosteroid dose should be recorded in the subject diary (Section 11.4.1.1.2.4).**

Day 1 to Week 4:

Stable dosage at Day 1 dose level, 1 oral corticosteroid rescue **(Rescue 1)** for SLE activity **is** allowed up to a dose no higher than 10 mg above the baseline level (maximum of 30 mg/day), but **the dose** must return to baseline (Day 1) level within 7 days. A dose increase is strongly recommended to be avoided within 1 week of a planned study visit.

Week 5 to Week 7:

Decrease as per **the** tapering schedule. One oral corticosteroid rescue **(Rescue 2)** for SLE activity **is** allowed up to a dose no higher than **the previous dosage** level, but **the dose** must be returned to **the** last oral corticosteroid dosage prior to rescue level within 7 days. A dose increase is **not permitted** within 1 week of a planned study visit.

Week 8:

Decrease as per tapering schedule. **No increases** are allowed.

Week 9 to Week 11:

Decrease as per tapering schedule. **One** oral corticosteroid rescue **(Rescue 3)** for SLE activity is allowed up to a dose **no higher than** the **previous** dosage **level, but the dose** must be returned

to **last oral corticosteroid dosage prior to rescue level** within 7 days. **A dose increase not permitted within 1 week of a planned study visit.**

Week 12:

No increase or decrease allowed.

Week 13 to Week 16:

Stable dosage or decrease as per the tapering schedule (no increase is allowed). The corticosteroid dose must always be ≤Week 12 dose.

Week 17 to Week 24:

Stable dosage at Week 16 dosage, no increases or decreases are allowed.

Table 1: Oral Corticosteroid Tapering Schedule

Table 2: ~~Suggested corticosteroid~~Oral Corticosteroid Tapering Schedule

Allowable OCS Rescue Dosing[1]	**Timing by Weeks (Days)**	**~~Corticosteroid~~OCS Starting Dose Prior to Tapering (mg/day)**							
		20 mg	**17.5 mg**	**15 mg**	**12.5 mg**	**10 mg**	**7.5 mg**	**5 mg**	**2.5 ~~–~~ ~~<~~to <5 mg**
Rescue 1	Week 1-4[2] **(Day 1 to 28)**	Stable 1 OCS rescue for SLE activity allowed up to maximum 10mg/day above Day 1 dosage, but must return to Day 1 level within 7 days							
Rescue 2	**Week 5[3] (Day 29 to 35)**	17.5	15	12.5	10	7.5	~~7.~~5	**5 or 2.**5	2.5 ~~–~~ ~~<~~**to <5**
	Week 6[3] **(Day 36 to 43)**	17.5	15	12.5	10	7.5	~~7.~~5	5 **or 2.5**	2.5 ~~–~~ ~~<~~**to** <5
	Week 7[3] **(Day 44 to 50)**	15	12.5	~~10~~**12.5**	10~~ or 7.5~~	7.5	~~7.5 or 5~~	5 or 2.5	2.5~~ – < 5~~
	Week 8 **(Days 51 to 57)**	~~12.5~~**15**	12.5	10	~~10 or~~ 7.5	7.5	~~7.5 or 5~~	5 or 2.5	~~0 or~~ 2.5~~ – < 5~~
Rescue 3	Week 9[3] **(Days 58 to 64)**	12.5	10	10~~ or 7.5~~	7.5	~~7.~~5~~ or 5~~	~~7~~2.5~~ or 5*~~	~~5 or~~ 2.5	0 ~~or~~**to** 2.5~~ < 5~~
	Week 10[3] (Days 65 to 71)	**12.5**	**10**	**10**	**7.5**	**5**	**2.5**	**2.5**	**0 to 2.5**

Allowable OCS Rescue Dosing[1]	**Timing by Weeks (Days)**	**~~Corticosteroid~~OCS Starting Dose Prior to Tapering (mg/day)**							
		20 mg	**17.5 mg**	**15 mg**	**12.5 mg**	**10 mg**	**7.5 mg**	**5 mg**	**2.5 ~~–~~ ~~<~~to <5 mg**
	Week 11[3] **(Days 72 to 78)**	10	~~10 or~~ 7.5	7.5~~ or 5~~	~~7.~~5 ~~or 5~~	~~7~~**2**.5 ~~or~~ **to** <5	~~5 or~~ 2.5	2.5	0 ~~or~~**to** 2.5~~–~~ ~~< 5~~
	Week ~~11–~~12 **(Days 79 to 85)**	~~Stable at Week 10 dose~~**10**	7.5	7.5	5	2.5 to <5	2.5	2.5	0 to 2.5
	Week 13-16 **(Days 86 to 113)**	Stable ~~or Decrease by 2.5 mg as tolerated.~~ ~~1 OCS rescue for SLE activity allowed up to Day 1 corticosteroid~~ **at Week 12** dose ~~(maximum 20 mg/day), however must be returned to week 12 level within 7 days.~~**or decrease**							
	Week 17-24 **(Days 114 to 169)**	Stable at Week 16 dose							

Abbreviations: OCS = oral corticosteroids; SLE = systemic lupus erythematosus.

[1] Two rescues are allowed out of the three described.

[2] Between Week 1 and 4 (Rescue 1). Once a dose is reduced it ~~can be maintained stable but~~ **must** not **be** re-increased, with the exception of the 1 time rescue.

[3]Between Week 5 and Week 7 (Rescue 2) and between Week ~~1 and 4~~**9 and 11(Rescue 3), the dose can be increased to the previous dose level for up to 1 week before restarting the tapering schedule**.

~~[2]One oral corticosteroid rescue for SLE activity allowed up to a dose no higher than baseline level, but must be returned to last OCS dosage prior to rescue level within 7 days~~

Rationale: A lower therapeutic level of corticosteroid (or complete washout) will lower the responder rate in the placebo group.

This change also affects Sections 6, Study Objectives and Endpoints; 11.4.1.1.1.1, Background Therapy for Lupus - Systemic Lupus Erythematosus; 11.4.1.3, Rescue Medication Usage Guidelines During the Treatment Period; and 11.4.1.4, Rescue Medication Usage Guidelines During the Safety Follow-up Period.

Section 19.2.2, CLASI Assessment and Adjudication

Change: Reference to the BILAG Assessment and Adjudication Committee was removed. Reference to the CLASI Assessment Adjudicator was added.

Now reads:

~~**BILAG Assessment and Adjudication Committee**~~

~~Variability of BILAG data due to reporting issues will be monitored with an ongoing review of the data.~~

~~An independent BILAG Assessment and Adjudication Committee may be convened to confirm the individual attribution of BILAG scoring. The Adjudication Committee will review the assessments reported by the Investigators to determine if the assessments meet BILAG criteria. Information reviewed may include laboratory, pathology and/or imaging data (e.g., photographic), physical descriptions, and any other data deemed relevant. The committee will be masked to assigned study treatment to ensure the unbiased assessment of clinical outcome. A charter for the establishment and operation of the independent BILAG Assessment and Adjudication Committee will be provided.~~

For Part B of the study, an independent CLASI Assessment Adjudicator will confirm CLASI scoring at Screening for the purpose of study eligibility. The Adjudicator will review the photograph to determine if they meet CLASI criteria.

A charter for the establishment and operation of the CLASI assessment adjudication process will be provided by Biogen.

Rationale: No BILAG Assessment and Adjudication Committee is planned for this study.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol:

- The version number and date were updated throughout the protocol.
- Section 2, List of Abbreviations, was updated.
- Text was modified throughout the protocol to further clarify guidance and instructions. Typographical errors and formatting were corrected.
- The definition of washout periods for allowed medications was changed from number of months to "half-lives," where appropriate.
- Throughout the protocol, the units for maximum dose of allowed medications was changed from mg/kg/day to a fixed dose/day.
- Section 11.4.1.1, Allowed Concomitant Therapy: A statement was added to define the term "stable" as applies to corticosteroid dosing.
- Section 11.4.1.1.1.1, Systemic Lupus Erythematosus: The routes of administration (IV, SC, or oral) were specified for the standard of care (SoC) therapy that subjects with SLE can receive during the trial. Also, dapsone (up to 150 mg/day) was added to the list of allowed SoC medications.
- Section 11.4.1.1.2.3, Part B Specific Instructions – Oral Corticosteroids: An explicit statement was added to state that no corticosteroid tapering schedule was required for subjects in Part B and that no increase beyond 15 mg/day was permitted.
- Section 11.4.1.1.3.1, Nonsteroidal Anti-Inflammatory Treatments (NSAIDs): Ibuprofen and naproxen were added to the list of examples of NSAIDs; the original protocol listed only aspirin as an example.
- Section 11.4.1.1.3.2, Acetaminophen: The maximum allowed dose of acetaminophen or pain medications with acetaminophen was specified to be 3 g/day.
- Section 11.4.2, Concomitant Procedures: In the original protocol, allergy desensitization treatment was not permitted in the study. In the amended protocol, subjects are allowed to participate in allergy desensitization treatment if they have been previously stabilized on the therapy prior to screening. Also, the amended protocol contains additional guidance regarding which details about concomitant treatment or procedures must be recorded in the electronic CRF.

Section 14, Safety Assessments: Text was added to clarify that oral body temperature should be measured for vital signs. Creatine phosphokinase was added as a blood chemistry laboratory safety assessment.

Section 15.5, Contraception Requirements: The contraception requirements were changed from "effective" in the original protocol to "highly effective" in the amended protocol.

Section 19.1.3, Electronic Data Capture: It was specified that all subject-reported outcomes will be captured in an electronic diary, with the exception of the corticosteroid diary, which will be a paper diary.

Appendix A. 1) Descriptions of Efficacy Instruments –Systemic Lupus Erythematosus Disease Activity Index -2000 (SLEDAI-2K): The first sentence under this heading was deleted as it was not necessary as a description of the measure in this Appendix. 2) [redacted]: A typographical error in the order of items in the self-rating scale was corrected.

Appendix B, Topical Corticosteroids Not Permitted During the Study: This new appendix contains a table which provides a list of corticosteroids that are not permitted.

Appendix C, American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus: This new appendix contains a table which provides the 1982 ACR revised criteria for classification of SLE.