BOS161721-02: A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 In Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care

ClinicalTrials.gov Identifier: NCT03371251

Final Protocol, Version 7.0 (Amendment 6), dated 30-April-2020
Final Protocol, Version 6.0 (Amendment 5), dated 23-July-2019
Final Protocol, Version 5.0 (Amendment 4), dated 23-January-2019
Final Protocol, Version 4.0 (Amendment 3), dated 27-July-2018
Final Protocol, Version 3.0 (Amendment 2), dated 21-March-2018
Final Protocol, Version 2.0 (Amendment 1), dated 08-November-2017
Final Protocol, Version 1.0, dated 06-October-2017

A RANDOMIZED DOUBLE-BLIND PHASE 1B/2 COMBINED STAGGERED MULTIPLE DOSE ESCALATION STUDY OF BOS161721 IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS ON A BACKGROUND OF LIMITED STANDARD OF CARE

SPONSOR	Boston Pharmaceuticals, Inc. 55 Cambridge Parkway, Suite 400 Cambridge, MA 02142 United States of America (USA)
INVESTIGATIONAL COMPOUND:	BOS161721
PROTOCOL NUMBER:	BOS161721-02
PHASE	Phase 1b/2
INVESTIGATIONAL NEW DRUG (IND) NUMBER:	131796
ORIGINAL PROTOCOL DATE:	06 October 2017
VERSION NUMBER:	V7.0 (Amendment 6)
VERSION DATE:	30 April 2020

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care. Study Number: BOS161721-02	
Version	Date
Original Protocol	06 October 2017
Protocol Version 2.0 (Amendment 1)	14 November 2017
Protocol Version 3.0 (Amendment 2)	21 March 2018
Protocol Version 4.0 (Amendment 3)	27 July 2018
Protocol Version 5.0 (Amendment 4)	23 January 2019
Protocol Version 6.0 (Amendment 5)	23 July 2019
Protocol Version 7.0 (Amendment 6)	30 April 2020

This study protocol was subject to critical review and has been approved by the sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (Appendix 2), and principles of Good Clinical Practices (GCP) as described in 21 Code of Federal Regulations (CFR) parts 50, 54, 56 and 312 and according to applicable local requirements

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

I agree with these statements and indicate my approval by signature for this protocol:

Name and Title	Signature and Date
PPD , MD, PhD Chief Medical Officer Boston Pharmaceuticals	DocuSigned by: PPD
PPD , MD Vice President Clinical Development Boston Pharmaceuticals	DocuSigned by: PPD

Name and Title	Signature and Date
PPD Clinical Operations Lead Boston Pharmaceuticals	DocuSigned by: PPD

BOS161721-02

A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care.

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to BOS161721 are the confidential and proprietary information of Boston Pharmaceuticals, Inc., and except as may be required by federal, state, or local laws or regulation, may not be disclosed to others without prior written permission of Boston Pharmaceuticals, Inc.

I have read the protocol (Version 7.0, dated 30 April 2020), including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Council for Harmonisation (ICH) guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Boston Pharmaceuticals, Inc., or specified designees. I will discuss the material with them to ensure that they are fully informed about BOS161721 and the study.

_____ _____

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

PROTOCOL SUMMARY

Title:	A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care.
Indication	Adults with moderately to severely active SLE
Background and Rationale	SLE is a chronic systemic autoimmune disease with considerable heterogeneity in clinical manifestations and disease course. There is evidence that B- and T-cells are critical to the development of the disease, and that T-cell-derived cytokines such as interleukin-21 (IL-21) are involved in the SLE-associated inflammatory pathological response. BOS161721 is a humanized immunoglobulin G1 (IgG1) triple mutation monoclonal antibody (mAb) intended to have an extended terminal elimination half-life (t½) that selectively binds to and neutralizes IL-21, which acts on multiple cell types that drive inflammation and autoimmunity. In vivo, BOS161721 inhibits T-cell dependent antigen responses of B-cells and is being developed as a potential treatment for adults with moderately to severely active SLE. Nonclinical studies have evaluated the toxicity, pharmacodynamics (PD), toxicokinetics (TK), pharmacokinetics (PK), and immunogenicity of BOS161721 administered intravenously (IV) and subcutaneously (SC). The no observed adverse effect level (NOAEL) in Cynomolgus monkeys was determined to be 100 mg/kg (SC and IV), the highest dose tested. There were no injection site reactions in animals dosed subcutaneously. In a phase 1 single ascending dose (SAD) study, BOS161721 was administered IV and SC to healthy male and female adult subjects. This double-blind, placebo-controlled study evaluated 8 ascending dose levels (1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg) for safety, tolerability, PK, PD and immunogenicity. Overall, there were no clinically significant safety or tolerability findings from this study. Results from the phase 1 SAD study informed the dose regimens used for the multiple ascending doses (MAD) phase 1b portion of this trial. The MAD portion will involve 3 cohorts. The phase 2 portion will be a proof of concept (POC) part, where dose selection will be based on the data monitoring committee (DMC) and sponsor's assessment of safety, tolerability, immunogenicity, and PK and PD data from the MAD portion of 30 patients treated with BOS161721/placebo. The purpose of the study is to establish a safe and effective dosage for adult patients with moderately to severely active SLE.

Objectives and Endpoints:

MAD Phase 1b

OBJECTIVES	ENDPOINTS
Primary	
• To assess safety, tolerability, and immunogenicity of repeat doses of BOS161721 (20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment, in order to estimate the optimal dose	Safety Endpoints • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • Columbia Suicide Severity Rating Scale (C-SSRS) • 12-lead electrocardiograms (ECGs) parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from baseline • Physical examinations changes from baseline • Anti-drug antibodies (ADAs) • Study drug exposure/compliance

	Secondary	
	• To characterize the PK of BOS161721 and select the optimal dose of BOS161721 based on safety, PK, and PD effects in patients with moderately to severely active SLE	Pharmacokinetic Endpoints • BOS161721 concentration by visit and time point • Maximum observed concentration (C_{max}), first time to maximum concentration (T_{max}), area under the concentration-time curve (AUC), $t_{½}$, systematic clearance (CL), volume of distribution (V_d) Pharmacodynamic Endpoints • Results and changes (or shifts) from baseline to each visit in phosphorylated signal transducer and activator of transcription 3 (pSTAT3), C3 and C4 levels, and leukocyte immunophenotype • Results and changes (or shifts) from baseline in anti-double-stranded DNA (dsDNA), antinuclear antibodies (ANA), anti-Sjögren syndrome A and B (SSA, SSB), Smith (Sm), and antiphospholipid (APL) autoantibodies at each visit • Results and changes (or shifts) from baseline in abrogation of IL-21 gene signature at each indicated visit
	Exploratory	
	• CCI [redacted]	CCI [redacted]

- CCI
- CCI
- CCI
- CCI
- CCI

• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

POC Phase 2

OBJECTIVES	ENDPOINTS
Primary	
• To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on the SLE Responder Index 4 (SRI-4)	Primary Efficacy Endpoint • The proportion of patients with a SRI-4 response at Day 210 (see Section 6.3.4.1)

	Secondary	
	• To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on clinical indicators of SLE activity, in adult patients with moderately to severely active SLE on limited background standard of care treatment	Secondary Efficacy Endpoints • The proportion of patients with: - SRI-4 response at each visit - SRI-5 and SRI-6 response at each visit (Section 6.3.4.2) - a sustained reduction from baseline of oral corticosteroid (CS) (≤ 7.5 mg/day and < Day 0 dose) between Day 150 and Day 210 - new or recurrent BILAG flares (≥ 1 qualifying BILAG A or > 1 qualifying BILAG B) through Day 210 - PGA worsening - a BICLA response - a CLASI response - medication failures • Changes and percent changes from baseline in: - CLASI - PGA - Total number of swollen joints, tender joints, and active joints (swelling and tenderness in the same joint) in the ACR-28 joint count - SLEDAI-2K - SLICC/ACR damage index • Time to medication failure • Group mean percent reduction in corticosteroid administration from baseline Day 0 dose through Day 210 in patients receiving ≥ 7.5 mg/day prednisone equivalent at Day 0 • Duration of longest SRI-4 response

		• Time to first BILAG flare (≥ 1 new or recurrent BILAG A or > 1 new or recurrent BILAG B) relative to baseline through Day 210
	Safety	
	• To assess safety and tolerability of repeat doses of BOS161721 at the chosen dose administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment	Safety Endpoints • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • C-SSRS • 12-lead ECGs parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from baseline • Physical examinations changes from baseline • ADAs • Study drug exposure/compliance
	Exploratory	
	• CCI [redacted]	• CCI [redacted] • CCI [redacted] • CCI [redacted]

	• CCI [redacted] CCI [redacted] CCI [redacted] • CCI [redacted] • CCI [redacted] • CCI [redacted] • CCI [redacted]
Study Design:	This is a phase 1b/2 combined, randomized, multicenter, double-blind, placebo-controlled trial to study the clinical efficacy, safety, and PK of multiple SC doses of BOS161721 in adult patients with moderately to severely active SLE. After successfully completing a screening phase, eligible patients will be randomized to a specified dose of BOS161721 or placebo. The dosing schedule will be monthly. The trial will consist of 2 double-blinded portions: MAD phase 1b and POC phase 2. Patients may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180, followed by safety follow-up visits at Days 210, 240, and 270.

	The MAD phase 1b portion of the study design will consist of 3 cohorts, with Cohort 1 containing 6 patients, where 5 of these patients will receive BOS161721 (active), and 1 will receive placebo. Cohorts 2 and 3 will each contain 12 patients, including 9 active and 3 placebo patients. Dose selection for each cohort is based on 90 day safety, tolerability, PK, and PD data review from the phase 1 SAD study (BOS161721-01) in healthy subjects. Each of the 3 doses (20, 60, and 120 mg) selected for the MAD portion are projected not to exceed the mean exposure of that achieved in the SAD study following the single 240 mg SC dose. Each patient may receive a total of 7 SC monthly doses on Days 0, 30, 60, 90, 120, 150, and 180. The MAD portion design is staggered, where after the 6 patients in Cohort 1 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 2 begins dosing (after the DMC evaluates the safety and tolerability data from Cohort 1). Similarly, after 8 of the 12 patients in Cohort 2 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 3 begins dosing after the DMC evaluation of the safety and tolerability data from Cohort 2 and Cohort 1. Thirty days after the last patient in Cohort 3 receives the third dose, the DMC and Boston Pharmaceuticals will conduct a data review to determine which dose will be carried forward into the POC part of the study. This dose will not exceed doses tested during the MAD portion. For the POC portion, approximately 110 additional patients will be randomized to active or placebo groups in a 2:1 ratio. As in the MAD portion, each patient in the POC portion may receive a total of 7 SC monthly doses on Days 0, 30, 60, 90, 120, 150, and 180. A maximum stable (for at least 6 weeks prior to Day 0) daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study. One oral CS “burst” for increased SLE disease activity may occur during the study between Day 0 and Day 120. Tapering of steroids during the course of the study will be highly encouraged and should be evaluated during the protocol-allowed tapering windows (Day 0 through Day 150) with the target of achieving a CS daily dose of ≤ 7.5 mg and < Day 0 dose between Day 150 and Day 210. Between Day 150 and Day 210, oral CS doses must be held constant due to the Day 210 endpoint evaluations. DMC safety reviews will be conducted periodically throughout the study as described in the DMC charter.
Main Criteria for Inclusion and Exclusion	Inclusion Criteria: 1. Men and women, ages 18 to 70 years, inclusive

	2. Patients must be mentally capable of giving consent and there must be evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study 3. Patients must have SLE as defined by meeting 4 of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE (with at least 1 clinical and 1 immunologic criterion OR Lupus nephritis as the sole clinical criterion in the presence of antinuclear antibodies [ANA] or anti-double-stranded deoxyribonucleic acid [dsDNA] antibodies), either sequentially or simultaneously 4. At screening, patients must have at least 1 of the following: a. Elevated ANA ≥ 1:80 via immunofluorescent assay at the central laboratory b. Positive anti-dsDNA or anti-Smith (Sm) above the normal level as determined by the central laboratory 5. At screening, the total SLEDAI-2K score must be ≥ 8, including points from at least 1 of the following clinical components: a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis Note: Points from lupus headache and organic brain syndrome will also be excluded from qualifying total and clinical SLEDAI-2K scores at screening and Day 0. 6. A clinical SLEDAI-2K score of ≥ 6 at screening at Day 0. Clinical SLEDAI-2K score is defined as follows: a. Contains points from arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, or vasculitis b. Excludes parameters which require central laboratory results: hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia Note: Points from lupus headache and organic brain syndrome will also be excluded from qualifying total and clinical SLEDAI-2K scores at screening and Day 0. 7. Patients must have at least 1 qualifying A or 2Bs from the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer: a. BILAG A or B score in the mucocutaneous body system. If a BILAG B score is due to BILAG number 6, mild skin eruption, the CLASI activity score including erythema and scale/hypertrophy must be ≥ 3 excluding points from mucosal ulcers and alopecia b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis as defined in the protocol Section 4.4

Note: Hips, shoulders, back, neck, and temporomandibular joints do not count towards the total number of joints with active synovitis.

If only one “B” and no “A” score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 “B” must be present in at least 1 other body system for a total of 2 “B” BILAG body system scores.

8. Patients must be currently receiving at least 1 of the following:
    a. Administration for a minimum of 12 weeks, and a stable dose for at least 56 days (8 weeks prior to Day 0) of the following permitted steroid-sparing agents:
        i. Azathioprine (AZA), mycophenolate mofetil or mycophenolic acid, chloroquine, hydroxychloroquine, or methotrexate (MTX)
    b. If AZA, myocophenolate mofetil, mycophenolic acid, hydroxychloroquine, or MTX were discontinued prior to screening, the washout period must be ≥ 12 weeks
    c. Corticosteroids (prednisone or prednisone-equivalent) at a stable dose of up to 30 mg/day for at least 6 weeks prior to Day 0 (see Appendix 3)
        i. For patients whose only SLE treatment is CSs, the stable CS dose must be ≥ 10 mg/day for at least 6 weeks prior to Day 0 and no more than 30 mg/day at the time of randomization
        ii. Topical steroids may be used, but the dose must be stable for at least 6 weeks prior to Day 0. PRN topical steroids are not permitted
9. Women of childbearing potential (WOCBP; see Section 4.7 for full information regarding WOCBP, definition of menopause, and contraception):
    a. Must have a negative serum pregnancy test at screening. Urine pregnancy test must be negative prior to first dose
    b. Must not be breastfeeding
    c. Must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 52 weeks
10. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 52 weeks
11. Patients must demonstrate willingness and ability to comply with the scheduled study visits, treatment plans, laboratory tests, and other procedures

Exclusion Criteria:

Patients presenting with any of the following will not be included in this study:

1. Drug-induced SLE, rather than “idiopathic” SLE

	2. Other systemic autoimmune disease (e.g., erosive arthritis, rheumatoid arthritis [RA], multiple sclerosis [MS], systemic sclerosis, or vasculitis not related to SLE) a. RA-Lupus overlap (Rupus), and secondary Sjögren syndrome are allowed 3. Any major surgery within 6 weeks of study drug administration, (Day 0), or any elective surgery planned during the course of the study 4. Any history or risk for tuberculosis (TB), specifically those with: a. Current clinical, radiographic, or laboratory evidence of active TB b. History of active TB c. Latent TB defined as positive QuantiFERON®-TB Gold In-Tube (QFT-G) or other diagnostic test in the absence of clinical manifestations. Latent TB is not excluded if the patient has documented completion of adequate course of prophylactic treatment with regimen recommended by local health authority guideline, or the patient has started treatment with isoniazid, or other regimen recommended by local health authority guidelines for at least 1 month before Day 0 and continues to receive the prophylactic treatment during study until the treatment course is completed 5. Active or unstable lupus neuropsychiatric manifestations, including but not limited to any condition defined by BILAG A criteria, with the exception of mononeuritis multiplex and polyneuropathy, which are allowed. 6. Severe proliferative lupus nephritis, (WHO Class III, IV), which requires or may require induction treatment with cytotoxic agents or high dose CS. 7. Concomitant illness that, in the opinion of the Investigator or the sponsor or their designee, is likely to require additional systemic glucocorticosteroid therapy during the study, (e.g., asthma), is exclusionary. a. However, treatment for asthma with inhalational CS therapy is allowed 8. Use or planned use of concomitant medication outside of standard of baseline treatment for SLE from Day -1 or for any time during the study. 9. Active and clinically significant infection (bacterial, fungal, viral, or other) within 60 days prior to first dose of study drug. Clinically significant is defined as requiring systemic parenteral antibiotics or hospitalization. 10. A history of opportunistic infection, or a history of recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years.

	11. Chronic viral hepatitis including hepatitis B (HBV) and hepatitis C (HCV) unless patient received curative treatment for HCV and has a documented negative viral load, known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness. 12. Cryptosporidium in the stool sample at screening. 13. White blood cells (WBC) < 1,200/mm^3 (1.2 × 10^9/L) at screening. 14. Absolute neutrophil count (ANC) < 500/mm^3 at screening. 15. CD4+ count < 150/µL at screening. 16. Platelets < 50,000/mm^3 (50 × 10^9/L) or < 35,000/mm^3 (35 × 10^9/L) if related to SLE, at screening. 17. Hemoglobin < 8 g/dL or < 7 g/dL at screening if related to SLE. 18. Proteinuria > 3.0 g/day (3000 mg/day) at screening or equivalent level of proteinuria as assessed by protein/creatinine ratio (3 mg/mg or 339 mg/mmol). 19. Serum creatinine > 2.0 mg/dL at screening or creatinine clearance (CrCL) < 40 mL/minute based on Cockcroft-Gault calculation. 20. Serum alanine aminotransferase (ALT) and/or serum aspartate aminotransferase (AST) > 2 × the upper limit of normal (ULN) at screening, unless explicitly related to lupus based on the Investigator's judgment. 21. Creatinine kinase (CK) > 3.0 × ULN at screening unless related to lupus myositis. 22. Total bilirubin > 1.5 × ULN at screening (unless related to Gilbert's syndrome). 23. Any other laboratory test results that, in the opinion of the Investigator or the sponsor or sponsor's designee, might place a patient at unacceptable risk for participating in this study. 24. History of allergic or anaphylactic reaction to any therapeutic or diagnostic mAb (e.g., IgG protein) or molecules made of components of mAbs. 25. History substance and/or alcohol abuse, or dependence within the past 1 year, at the Investigator's judgment. 26. History of cancer within the last 5 years (except for cutaneous basal cell or squamous cell cancer, or cervical cancer in situ resolved by excision). 27. Any other severe acute or chronic medical or psychiatric condition, including recent (within the past year) medical conditions (e.g., cardiovascular conditions, respiratory illnesses) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, sponsor or sponsor's designee, would make the patient inappropriate for entry into this study.

	28. Investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or patients who are employees of the sponsor or directly involved in the conduct of the trial. 29. Currently participating in, or who have participated in other interventional (drug or device) clinical study within 30 days or 5 half-lives of baseline, whichever is longer. 30. Recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding “yes” to question 3, 4, or 5 on the C-SSRS. 31. Current or pending incarceration. 32. Current or pending compulsory detainment for treatment of either a psychiatric or physical (e.g., infectious disease) illness. 33. Currently taking a total daily dose of > 30 mg morphine or morphine equivalent (see Appendix 7). 34. Body mass index (BMI) ≥ 40.0.
Statistical Considerations	Below is a summary of the statistical methods. Further details can be found in Section 8. Two analyses are planned: 1) an interim analysis to select the POC dose based on the MAD data; and 2) a final analysis at study completion. Additionally, DMC safety analyses will be performed for each MAD cohort and throughout the POC to monitor patient safety as described in the DMC charter. An additional analysis may be performed for the MAD portion of the study when all MAD patients have completed the safety follow-up, or withdrawn from the study, and prior to the final analysis. Data from the POC part of the study will be excluded from this additional analysis. Unless stated otherwise, statistical testing will only be performed on the POC data and will be done using 2-sided overall alpha of 0.10. Data will be summarized descriptively by treatment and overall for each study phase. For the MAD portion, BOS161721 will be summarized overall and by each dose level and placebo patients from each cohort will be combined. The descriptive summaries for the categorical data will include number and percentage. The descriptive summaries for the continuous data will include number, mean, median, standard deviations (SD), 25^{th} and 75^{th} percentiles, minimum, median, and maximum. Counts, medians, 25^{th} and 75^{th} percentiles, and standard error will be presented for time-to-event data.

	All safety analyses will be performed using the safety analysis set (SS), defined as all patients who receive at least 1 dose of study treatment. All efficacy analyses will be performed using the full analysis set (FAS), defined as all patients who receive at least 1 dose of study treatment and have at least 1 evaluable post-baseline efficacy evaluation. Select efficacy analyses may also be performed on the per protocol (PP) set. Binary efficacy endpoints, including the primary efficacy endpoint, will be assessed via Pearson's chi-squared analysis. Continuous efficacy endpoints will be assessed via analysis of variance (ANOVA) or analysis of covariance (ANCOVA) when applicable, adjusting for the baseline value. Repeated measures mixed models may be performed to evaluate data collected at each visit and overall. Time-to-event endpoints will be assessed via Kaplan-Meier methodology and treatment will be compared using the log-rank test. Adverse event data will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients experiencing any treatment-emergent AE, overall, and by system organ class and preferred term will be tabulated. Treatment-emergent AEs will also be summarized by severity and relationship. Concomitant medications will be summarized, based on coded terms, using frequency and percentage of patients. Observed values and changes from baseline in vital signs, ECG readings, and hematology and clinical chemistry parameters, will be summarized at each individual visit.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANC	absolute neutrophil count
ANOVA	analysis of variance
ANCOVA	analysis of covariance
APL	antiphospholipid
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AZA	azathioprine
BICLA	BILAG-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
BW	body weight
C	complement
C-SSRS	Columbia Suicide Severity Rating Scale
CD	cluster of differentiation
CK	creatine kinase
CL	systematic clearance
CLASI	Cutaneous Lupus Erythematosus Area and Severity Index
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CS	corticosteroids
CSR	clinical study report
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
dsDNA	double-stranded deoxyribonucleic acid

ECG	electrocardiogram
EOT	end of treatment
eCRF	electronic case report form
F	female
CCI	[redacted]
FAS	full analysis set
Fc	fragment crystallizable
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
eGFR	estimated glomerular filtration rate
GLP	Good Laboratory Practice
GWAS	genome-wide association studies
γc	gamma chain
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCl	hydrochloride
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IL	interleukin
IL-21R	interleukin 21 receptor
IM	intramuscular
IFNγ	interferon gamma
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
IWRS	interactive web response system

JAK	Janus kinase
kg	kilogram
KLH	keyhole limpet hemocyanin
LOCF	last observation carried forward
M	male
mAb	monoclonal antibody
MAD	multiple ascending dose
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary of Regulatory Activities
MS	multiple sclerosis
MTX	methotrexate
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIAID/FAAN	National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network
NK	natural killer
NOAEL	no observed adverse event level
NO	nitric oxide
NSAID	nonsteroidal anti-inflammatory drug
OTC	over-the-counter
PD	pharmacodynamics
PEF	peak expiratory flow
PGA	Physician’s Global Assessment
PK	pharmacokinetics
POC	proof of concept
PP	per protocol
PR	(interval) from onset of the p-wave to the end of the r-wave
pSS	primary Sjögren’s syndrome
pSTAT3	phosphorylated signal transducer and activator of transcription 3
PT	preferred term
QRS	(interval) from the onset of the q-wave to the end of the s-wave
QT	(interval) from onset of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia’s formula
QFT-G	QuantiFERON®-TB Gold In-Tube
RA	rheumatoid arthritis

RR	(interval) from the onset of the r-wave to the onset of the next consecutive r-wave
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SDMT	safety data monitoring board
CCI	[redacted]
SLE	systemic lupus erythematosus
SLEDAI-2K	SLE Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
Sm	Smith
SOC	system organ class
SRI-4	SLE Responder Index 4
SRI-5	SLE Responder Index 5
SRI-6	SLE Responder Index 6
SS	safety analysis set
SSA	Sjögren syndrome-A (Ro)
SSB	Sjögren syndrome-B (La)
STAT3	signal transducer and activator of transcription 3
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
TB	tuberculosis
TDAR	T-cell dependent antibody response
Tfh	T-follicular helper
Th	T-helper
TK	toxicokinetics
T_{max}	first time to maximum concentration
Treg	regulatory T-cell
ULN	upper limit of normal
US	United States
V_d	volume of distribution
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
YTE	triple mutation

1 INTRODUCTION AND RATIONALE

1.1 Indication

BOS161721 is a humanized monoclonal antibody (mAb), which binds to and inhibits interleukin-21 (IL-21) bioactivity, and is being developed for the treatment of moderately to severely active systemic lupus erythematosus (SLE) in adults.

1.2 Background and Rationale

1.2.1 Overview of the Disease State

SLE is a chronic inflammatory autoimmune disease that has variable manifestations in multiple organ systems and follows a relapsing and remitting course. The disease process includes abnormal immune responses mediated by tissue-binding autoantibodies and immune complex deposition, giving rise to tissue damage often resulting in end organ disease and even mortality. Survival of SLE has improved due to earlier detection, improved overall medical care, and standardized SLE treatment with corticosteroids (CS), immunosuppressants, and cytotoxic agents.[1] However, some of the morbidity in patients with SLE is related to its treatment. Comparison of early and late outcomes in patients with SLE demonstrate that death in early disease is most commonly due to infections and active SLE causing multi-system organ damage, while thromboses were the most common cause of death during later disease.[2]

The reported prevalence of SLE in the United States (US) is 20 to 70 cases per 100,000 people.[3] More than 90% of cases of SLE occur in women, frequently starting at childbearing age. Women of color are disproportionately affected by SLE. This suggests multiple genetic and environmental factors are at play. Accordingly, a multifactorial view of the immunopathogenesis of SLE suggests more than 1 area of interest, including breach in central tolerance in the adaptive arm of the immune system, peripheral amplification of the autoimmune response by the innate immune system, and local processes in the target organ that facilitate end-organ disease.[4]

1.2.2 BOS161721 Development

Boston Pharmaceuticals is developing BOS161721 for the treatment of SLE. BOS161721 is a humanized immunoglobulin G1 (IgG1) mAb with extended half-life directed against human IL-21.

Murine mAb 19E3, the progenitor of BOS161721, was generated using mouse hybridoma technology.19E3 has subpicomolar (pM) affinity to human IL-21 and was selected for its potent neutralization of IL-21 bioactivity. BOS161721 was generated by the humanization of mAb 19E3 where its complementarity-determining regions were grafted onto a human IgG1 kappa backbone. The fragment crystallizable (Fc) portion of BOS161721 contains a YTE (M252Y/S254T/T256E triple mutation) in the constant domain of the IgG1 heavy chain that was introduced into the parental molecule, 19E3, intended to prolong the in vivo terminal elimination half-life (t½) of the mAb.[5] Thus,

BOS161721 retains sub-pM binding to IL-21 and prevents IL-21 from binding to the IL-21 receptor (IL-21R), inhibiting IL-21 bioactivity.

BOS161721 binds to human IL-21 and Cynomolgus monkey IL-21, which are highly homologous, and neutralizes the bioactivity of both. BOS161721 is specific for IL-21 as it does not bind to or inhibit the other gamma-chain (γc) family of cytokines, and acts to specifically neutralize the IL-21 pathway. In in vitro studies, BOS161721 inhibited downstream IL-21-induced signaling, IL-21-induced plasma cell differentiation, and IL-21-induced natural killer (NK) cell activation. In in vivo studies, BOS161721 significantly inhibited the T-cell dependent antibody response (TDAR) to immunization with a protein antigen as well as B-cell expansion following a second protein antigen immunization in Cynomolgus monkeys.

1.2.2.1 Interleukin-21

IL-21 is an inflammatory cytokine, which belongs to a family of cytokines that also includes IL-2, IL-4, IL-7, IL-9, and IL-15, all of which bind to private receptors in complex with the common cytokine receptor γc.[6] Most cytokines in this family are critically important for both the maintenance and function of T-cell and B-cell responses. IL-21 signals through a receptor complex consisting of its own private receptor, the IL-21R and γc.[6,7] Engagement of the IL-21R/γc complex leads to the activation of several signaling pathways, including the Janus kinase/signal transducer and activator of transcription, mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase pathways.[8] IL-21 is produced mainly by T-cells and NK T-cells, but neutrophils have also been reported to produce IL-21.[9,10] The IL-21R is expressed on a broad array of cell types, including B-cells, T-cells, NK-cells, macrophages and dendritic cells, as well as other hematopoietic and nonhematopoietic cells such as fibroblasts, keratinocytes, and intestinal epithelial cells.[9,11] Activation of signal transducer and activator of transcription 3 (STAT3) via phosphorylation is critical in regulating human B-cell responses to IL-21[12]; phosphorylated STAT3 (pSTAT3) forms a homodimer, which translocates to the nucleus where it initiates transcription of the IL-21 gene, forming an autocrine loop for IL-21 production via STAT3 phosphorylation.[13] In addition, IL-21 has been shown to upregulate expression of its own receptor[14] and induces an autocrine feedback loop.[15]

IL-21 modulates various aspects of immune function. It promotes cluster of differentiation 4 (CD4+) T-cell differentiation and promotes the generation of T-helper (Th)17[16] and T-follicular helper (Tfh) cells.[15,17] In mice, IL-21 has been shown to regulate the balance between Th17 and regulatory T-cell (Treg), in that it increases Th17, while inhibiting Treg differentiation.[18] Less is understood with regards to human Tregs, although IL-21 has been reported to counteract Treg suppression of human effector T-cells[19] and blockade of IL-21 promotes Treg generation in a murine model of graft versus host disease induced by human T-cells.[20] IL-21 upregulates CD8+ T-cell and NK-cell expansion and cytolytic activity by increasing granzyme B and perforin.[21,22] IL-21 also has been reported to increase granzyme B in plasmacytoid dendritic cells and B-cells resulting in inhibition of T-cell responses.[23,24] IL-21 also has a variety of

effects on nonhematopoietic cells, such as stromal cells and induces inflammation through matrix metalloproteinase release by gut intestinal fibroblasts.[25]

One principal non-redundant role of IL-21 is the promotion of B-cell activation, differentiation, or death during humoral immune responses.[14] Furthermore, increased IL-21 production is characteristic of several autoimmune diseases and is likely to contribute to autoantibody production as well as pathologic features of autoimmune disease.[26] The critical role of IL-21 in promoting humoral and other immune responses makes it an important focus of potential therapeutic interventions in conditions characterized by overproduction of pathogenic autoantibodies. IL-21 production by Tfh cells in humans is believed to play a major role in driving the autoantibody production through its role in plasma cell differentiation. Importantly, Tfh cell populations are expanded in patients with autoimmune diseases such as lupus, bullous pemphigoid, rheumatoid arthritis (RA) and primary Sjögren's syndrome (pSS) and have been reported to correlate with IL-21 levels, autoantibodies, and disease severity.[26,27,28,29] Furthermore, loss of number and functionality of Tregs has been associated with autoimmune diseases such as SLE and giant cell arteritis, which IL-21 is expected to modulate.[30,31] Thus, neutralization of IL-21 in settings of autoimmunity is expected to impact several cell populations believed to be involved in the pathogenesis of autoimmune disorders including SLE.

BOS161721 selectively binds IL-21 with high affinity to neutralize IL-21, and due to its pleiotropic nature, neutralization of IL-21 is expected to impact several cell populations believed to be involved in the pathogenesis of SLE. Importantly, patients with SLE have elevated IL-21 plasma levels that correlate with the severity of the disease. Recently, genome-wide association studies (GWAS) have provided convincing evidence that the chromosomal 4q 27 region harbors the IL-21 genes and is associated with chronic inflammatory disorders, including SLE.[29]

1.2.2.2 Preclinical Studies

The pharmacokinetics (PK) of BOS161721 were characterized following single-dose intravenous (IV) administration of BOS161721 (0.01 to 30 mg/kg) in male Cynomolgus monkeys or repeat, every 2 weeks IV administration (15 to 100 mg/kg) and subcutaneous (SC) administration (50 mg/kg) in male and female Cynomolgus monkeys. Systemic exposure was approximately dose-proportional within the tested dose range. SC bioavailability was determined to be 64.3%. CCI [redacted].

Two single-dose (IV) non-good laboratory practice (GLP) studies conducted in Cynomolgus monkeys evaluated the toxicity, pharmacodynamics (PD), toxicokinetics (TK), and immunogenicity of BOS161721. Following a single IV administration (slow bolus), there were no BOS161721-related adverse changes, resulting in a no-observed-adverse-effect-level (NOAEL) value of 30 mg/kg, the highest dose tested among 2 studies. CCI [redacted]

CCI [redacted].

In a repeat-dose GLP toxicology study in Cynomolgus monkeys, BOS161721 was administered every 2 weeks by IV or SC (50 mg/kg) administration for 3 months (a total of 7 doses). CCI [redacted]. The NOAEL was determined to be 100 mg/kg (SC and IV), the highest dose tested.

An additional GLP, repeat-dose toxicity study was conducted in Cynomolgus monkeys (4 males and 4 females per dose group) following every 2 weeks (Q2W) administration by SC (10, 30, and 100 mg/kg) injection for a total of 14 doses. CCI [redacted] There were no BOS161721-related effects on survival, clinical signs, male body weights, ophthalmologic parameters, electrocardiogram (ECG) findings, clinical pathology, macroscopic observations, organ weights, or microscopic observations. CCI [redacted] The 100 mg/kg/dose was the NOAEL CCI [redacted].

1.2.2.3 Clinical Studies

BOS161721-01 was a double-blind, phase 1, single ascending dose (SAD) study to assess the safety, PK, and PD of BOS161721 in healthy subjects. The primary objective of the study was to characterize the safety and tolerability of IV and SC SADs of BOS161721 in an otherwise healthy subject population without concomitant illnesses, immune abnormalities, or concomitant medications. Secondary objectives included characterization of the PK and immunogenicity of BOS161721, and exploratory objectives included the evaluation of the effect of BOS161721 on TDAR to keyhole limpet hemocyanin (KLH) (primary and secondary immunizations) in healthy subjects, the effects of BOS161721 on plasma levels of IL-21 (free and bound), and the evaluation of the effect of BOS161721 on IL-21 gene expression (via gene signature) in blood. This study consisted of 8 cohorts. Subjects were randomized in a 3:1 ratio (BOS161721: placebo) and received either a single dose of BOS161721 (1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg) or placebo, with safety follow-up. For the first cohort, after the first 2 subjects were dosed (1 active and 1 placebo), there was a minimum gap of 48 hours before the remaining subjects from that cohort were dosed, to allow for an initial review of any emerging safety and tolerability data. For all cohorts, escalation to the next dose was not sooner than 8 days after all the subjects in the prior cohort had been dosed and were based on a review of at least 7 days of safety and tolerability data by the Safety Data Monitoring Team (SDMT).

Blood samples were collected at every in-house study visit for BOS161721 concentration determinations. Blood samples were also collected for determination of IL-21 plasma levels (free and total). Safety was assessed based on the occurrence of treatment-emergent AEs, hepatic function abnormality, and acute and delayed hypersensitivity reactions. Other safety variables included ECGs, vital signs (blood pressure [BP], heart rate, and temperature), safety laboratory assessments, blood sampling for ADAs, total IgG and immunoglobulin M (IgM) levels, CD4+ count, and full and targeted physical examinations. Overall, there were no clinically significant findings from this study. Adverse events reported as related to the study drug, particularly infections, were expected for the compound, and there were no clinically relevant changes in laboratory and ECG results or vital signs. There was 1 serious adverse event (SAE; death due to pulmonary embolism) that occurred 127 days after a single administration of 240 mg SC dose of BOS161721. The causality of this single SAE was not attributed to study drug and further information can be found in the Investigator's Brochure. Final PK data from the SAD study demonstrates BOS161721 has a mean t½ ranging from 80 to 87 days for doses of ≥ 30 mg in healthy subjects.

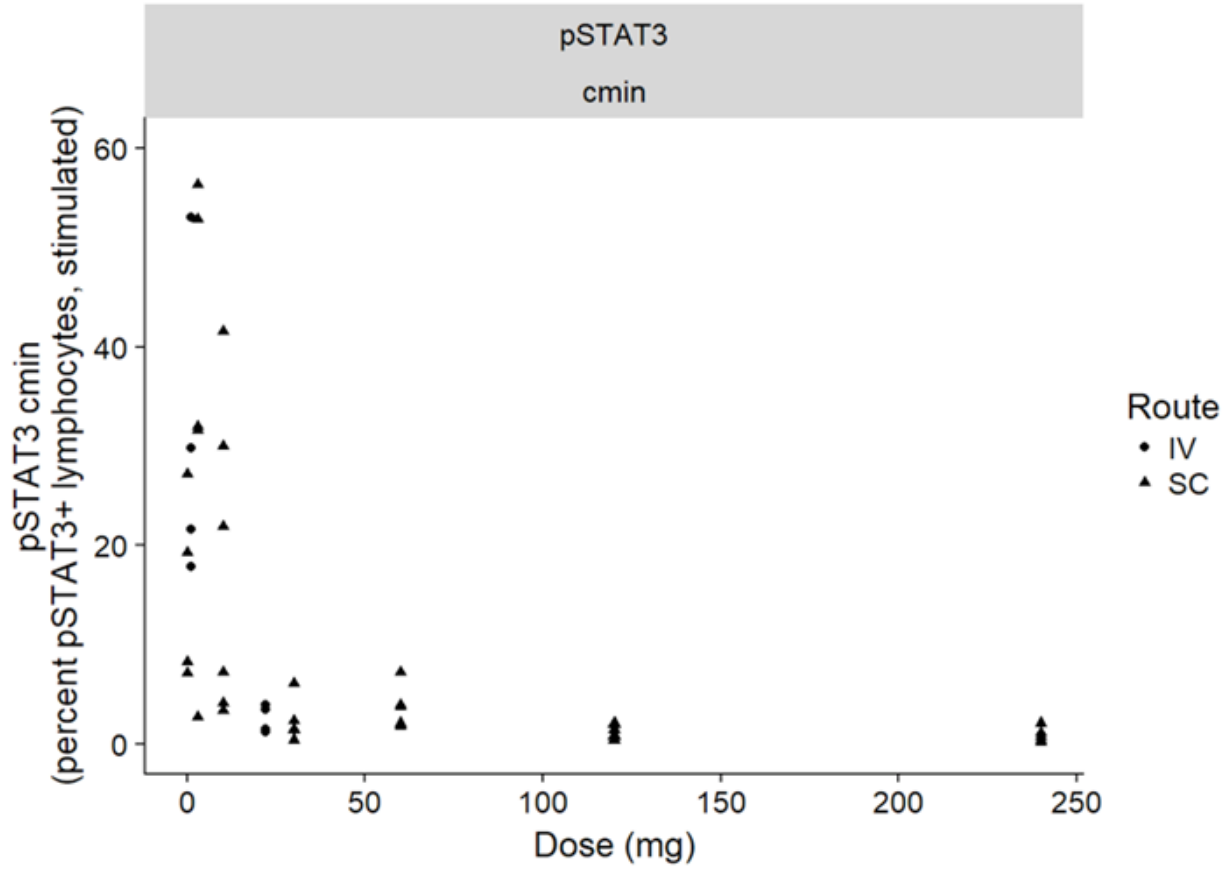
1.2.3 Study Dose Selection

Doses have been selected for the multiple ascending dose (MAD) phase 1b portion based on a 90 day safety, tolerability, PK, and PD data review from the phase 1 SAD study (BOS161721-01); the SDMT reviewed the blinded safety data from subjects for each dose cohort (8 cohorts, evaluating 1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg), along with the accumulated safety and available PK/PD data

from all subjects in the previous dose cohorts, to make a decision on whether to proceed to the next higher dose level, repeat a dose level, or stop dose escalation. Overall, there were no clinically significant safety or tolerability findings from this study.

Based on the Day-90 interim cut of the PK and biomarker data in the BOS161721-01 study, the recommended doses for evaluation in the MAD portion of this study are 20, 60, and 120 mg SC monthly. This dose recommendation is supported by evidence of linear PK with BOS161721 resulting in a median first time to maximum concentration (T_{max}) of 6 days and an apparent terminal half-life of 44 days. Furthermore, pSTAT3 suppression, a marker of IL-21 target engagement, follows a similar time course of the mAb levels, with maximal and sustained suppression apparent with doses greater than 30 mg SC (Figure 1).

Figure 1. Individual pSTAT3 C_{min} Levels Versus Dose



IV = intravenous, pSTAT3 = phosphorylated signal transducer and activator of transcription 3; SC = subcutaneous

All doses selected for the MAD portion are projected not to exceed the mean exposure of that achieved following the highest single dose of 240 mg SC administered in the phase 1 SAD study. Cohort 1 will include randomized treatment to the 20 mg dose. Based on the staggered study design, the data monitoring committee (DMC) will perform a scheduled review of safety data and sequentially consider dose escalation for Cohorts 2 and 3. In addition, the DMC and Boston Pharmaceuticals will conduct a data

review to determine which dose will be carried forward into the proof of concept (POC) phase 2 portion. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2 and 3 from the MAD portion (see Section 3.1.2.1 for the chosen POC dose and justification).

1.2.4 Risk-Benefit Assessment

The available preclinical data on BOS161721, the findings in clinical study BOS161721-01, and existing clinical information on IL-21 inhibitors suggest that the present clinical study has an acceptable risk-benefit ratio. In this study, the risk-benefit assessment of BOS161721 in adult patients with moderately to severely active SLE will be ongoing, with step-wise evaluations during the staggered MAD portion. The DMC used in this study is charged with assessing such actions in light of an acceptable benefit-risk profile for BOS161721 as an anti-IL-21 mAb. Formal DMC monitoring meetings will occur as described in the DMC Charter. Two weeks after Cohort 1 has received a second dose of study drug, the DMC will evaluate the safety and tolerability data from Cohort 1 to determine the recommended dose for Cohort 2. Two weeks after 8 patients in Cohort 2 receive a second dose, the DMC will determine if dose escalation to Cohort 3 can proceed. Thirty days after the last patient in Cohort 3 receives the third dose, the DMC and Boston Pharmaceuticals will conduct a data review to determine which dose will be carried forward into the POC part of the study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2, and 3 during the MAD part of study. Thereafter, DMC safety reviews will be conducted periodically throughout the study as described in the DMC charter. With the agreement of the DMC and sponsor, this schedule may be modified depending on the rate of patient accrual. Additional details can be found in the DMC Charter.

The benefit of participation for all patients in this study is close monitoring of their medical condition and safety of their treatment. Those randomized to the active treatment arm may potentially experience improvement in their SLE disease. Those randomized to the placebo (in combination with standard of care) arm are not expected to obtain any additional benefit, beyond those of their background treatment, though close monitoring of their medical condition and safety may itself be associated with improving their SLE.

1.2.5 Potential Risks

Potential risks based on the mechanism of action of BOS161721 include infections, risks associated with the administration of any foreign protein or biologic agent, including injection site reaction, anaphylaxis, serious allergic reaction, and development of ADAs. ADAs could result in immune complex disease (with manifestations such as arthralgias, serum-sickness, and vasculitis), or altered BOS161721 levels or activity. Further details can be found in the current Investigator's Brochure (IB) for BOS161721, which contains comprehensive toxicology, preclinical and clinical information on BOS161721.

Two investigational drug products are considered to be in the same pharmacological class as BOS161721 based on interruption of signaling through the IL-21 signaling pathway. No potential risk generalizable across the class has been observed with these investigational products. Based on the clinical phase 1 SAD study (BOS161721-01), AEs reported as related to the study drug, particularly infections (flu-like symptoms, etc.), were expected for the compound, and there were no clinically relevant changes in laboratory and ECG results or vital signs.

The majority of IgG elimination occurs via intracellular catabolism, following fluid-phase or receptor-mediated endocytosis. This type of endocytosis and elimination is a form of target-mediated disposition where the interaction of the drug and its pharmacological target (e.g., a target receptor) serves as a significant contributor to the kinetics of antibody distribution and elimination. Renal elimination, which is a primary pathway of clearance of small-molecule drugs, is relatively unimportant for IgG, as its large size prevents efficient filtration through the glomerulus. Secretion into the bile is an important pathway of elimination of IgA antibodies, but this route is not a significant contributor to the elimination of IgG antibodies. Thus, risk to renal and hepatic systems due to metabolism of BOS161721 is low.[33]

1.2.5.1 Anaphylaxis and Serious Allergic Reactions

As with the administration of any foreign protein and/or other biological agents, acute hypersensitivity reactions, including acute anaphylactic/hypersensitivity, severe allergic, and anaphylactoid reactions may follow infusion of mAbs and can be caused by various mechanisms. These acute hypersensitivity reactions may be severe and result in death.

Anaphylaxis will be defined according to the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria,[34] and are discussed in Section 6.2.2.6.1.

Based on the phase 1 SAD study (BOS161721-01), anaphylaxis and serious allergic reactions in subjects who received BOS161721 was not observed.

Patients with a known history of allergy or severe hypersensitivity reaction to any component of BOS161721 formulation or patients with a history of anaphylaxis to any other biological therapy such as mAbs will be excluded from studies with BOS161721. In addition, appropriate drugs and medical equipment to treat acute hypotensive, bronchoconstrictive, or anaphylactic reactions will be immediately available at the unit and study personnel will be trained to recognize and treat these reactions.

1.2.5.2 Injection Site Reactions

In a repeat-dose GLP toxicology study in Cynomolgus monkeys, BOS161721 was administered every 2 weeks by IV or SC for 3 months (a total of 7 doses). There were no injection site reactions in animals dosed subcutaneously. Further, there were no reports of injection site reactions in the 26-week GLP toxicology study in Cynomolgus monkeys.

Based on the phase 1 SAD study (BOS161721-01), incidence of injection site reactions in subjects who received BOS161721 was similar to placebo.

Patients will be monitored for local injection site reactions in this study (see Section 6.2.7).

1.2.5.3 Immune Complex Disease

The potential risk of immune complex disease for BOS161721 is theoretical, based on the known risks associated with mAbs. The administration of a mAb can result in the formation of ADAs. Administration of the mAb in the presence of ADA may result in the formation of circulating antibody-antigen complexes potentially resulting in altered BOS161721 levels or activity or deposition of the complexes in microvasculature. Complement is frequently involved in the latter setting, and the breakdown products of complement attract polymorphonuclear leukocytes to the site of deposition where they can provoke local tissue damage through specific or nonspecific release of enzymes. Two of the more common end-organ targets are the blood vessels (vasculitis) and kidney (nephritis). These clinical manifestations represent immune complex disease or Type III hypersensitivity. Although BOS161721 is a humanized mAb, ADAs may develop; however, the likelihood of occurrence of immune complex disease with BOS161721 is low. The findings of immune complex disease are typically reversible when mAb administration stops and the antibody-antigen complexes are cleared from the body.

Based on the phase 1 SAD study (BOS161721-01), immune complex disease in subjects who received BOS161721 was not observed.

1.2.5.4 Infections

BOS161721 is expected to diminish the activity of T-cell, B-cell and NK-cell lines. Like other medications modulating immune response, BOS161721 may increase the potential risk for infection, including serious infections. IL-21 produced by CD4+ T-cells is required to sustain the anti-viral function of CD8+ T-cells against chronic viral infections. Nonclinical evidence suggests that the risk of chronic viral infection recurrence or increased severity may occur with IL-21 inhibition.[35]

These conditions will be fully characterized with clinical descriptions and routine laboratory and/or specialty testing and treated where indicated with appropriate local standard of care.

Patients with a history of opportunistic infection, including recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years, or any other underlying pathology predisposing to serious infection, are excluded from studies with BOS161721 (for further details please refer to the current IB for BOS161721).

Patients will be assessed for hepatitis B, and C, and HIV-1/2 combination, at screening.

Cryptosporidium Infection

Cryptosporidium infection was noted in patients with an IL-21 receptor loss-of-function gene mutation and similar findings of cryptosporidium infection have been observed in immunosuppressed liver transplant and human immunodeficiency virus patients.[36,37] Since BOS161721 is expected to diminish the immunosurveillance activity of T-cell, B-cell, and NK-cell lines, a similar risk is biologically plausible with prolonged exposure to BOS161721.

Since the risk of opportunistic cryptosporidium infection increases with low levels of CD4+ T-cells,[37] patients with a CD4+ count < 500 cell/mm^3 were excluded from the phase 1 SAD study (BOS161721-01). Patients with CD4+ count < 350 cells/mm^3 and CD4+ count < 150 cells/mm^3 will be excluded from the MAD and POC parts of the study, respectively. Patients exposed to investigational product who develop diarrhea during the course of the study should immediately undergo an assessment for opportunistic infection including stool for ova and parasites and stool examination for cryptosporidium. Positive cryptosporidium in stool sample at screening is an exclusion. Treatment by the Investigator where indicated should be guided by findings and be consistent with local standard of care.

Based on the phase 1 SAD study (BOS161721-01), infections in subjects who received BOS161721 was not observed.

1.2.5.5 Malignancy

The stimulatory effect of IL-21 on NK cells and CD8+ T-cells suggests the cytokine may have anti-tumor activity. Nonclinical studies have demonstrated significant anti-tumor effects of IL-21 in a number of tumor models. IL-21 therapy of human metastatic melanoma and renal cell carcinoma has demonstrated POC with significant increases in levels of perforin, granzyme B, and interferon gamma (IFNγ) expression in CD8+ T-cells and NK T-cells. Clinical response has been limited in these generally unmanageable diseases.

The impact of treatment with anti-IL-21 therapy on the development or growth of malignancies is not known; however, as with other immunomodulatory biologic agents, treatment with BOS161721 may result in an increase in the risk of malignancies. NK cell suppression by IL-21 neutralization may represent a biological mechanism for a potential risk for malignancy. Patients with a history or current diagnosis of cancer within the past 5 years, with the exception of non-melanoma skin cancer or cervical cancer in situ treated with apparent success with curative therapy, are excluded from the study.

Based on the phase 1 SAD study (BOS161721-01), malignancy in subjects who received BOS161721 was not observed.

1.2.5.6 Hepatic Function Abnormality

There is no substantial evidence suggesting BOS161721 is associated with liver function abnormality. However, as a precaution, patients with a history of abnormal

alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), or bilirubin at screening (ALT/AST > 2 × upper limit of normal [ULN]; total bilirubin > 1.5 × [ULN] and judged by the Investigator to be clinically significant) were excluded from the phase 1 SAD study (BOS161721-01), and will be excluded from this trial. Patients with a positive hepatitis B or C test or a history of alcohol dependence will also be excluded.

Based on the phase 1 SAD study (BOS161721-01), hepatic function abnormality in subjects who received BOS161721 was not observed.

1.2.5.7 Failure of Vaccination

IL-21 is a key cytokine in development of B-cells into immunoglobulin-secreting plasma cells. Abnormal signaling through the IL-21R/Janus Kinase (JAK)3/signal transducer and activator of transcription (STAT3) pathway leads to defective humoral immune responses to both T-dependent and T-independent antigens and impairs the establishment of long-lasting B-cell memory. Abnormal signaling through the pathway has been related to decreased specific antibody responses following vaccination, and to increased susceptibility to encapsulated bacterial infections.[38]

The effect of BOS161721 was evaluated in in vivo single dose studies in Cynomolgus monkey in which the animals received vaccination to T-cell dependent KLH antigen to stimulate a TDAR. These in vivo studies demonstrated that BOS161721 significantly inhibited B-cell proliferation and IgG antibody responses to the KLH protein antigen in a dose-dependent fashion; however, BOS161721 administration did not affect anti-tetanus toxoid antibody data for IgM, IgG, IgG1, or immunoglobulin E (IgE) during the dosing phase in the same study.

1.2.5.8 Potential for Drug-Drug Interactions

Drug-drug interactions were not evaluated in the phase 1 SAD study (BOS161721-01), which included only healthy adult subjects. Use of prescription medications (with the exceptions of oral contraceptives), and over-the-counter (OTC) treatments including herbal supplements such as St John's Wort (except multivitamins), in the 2 weeks prior to screening was prohibited in the SAD study.

See Section 4.5 for other specific exclusion criteria which support lowered risk of interactions, and Section 4.6.1 for corticosteroid (CS) dosing. In addition, Section 1.2.5.6 describes considerations for hepatic function for this study.

1.2.5.9 Potential Risk to Fetal Development

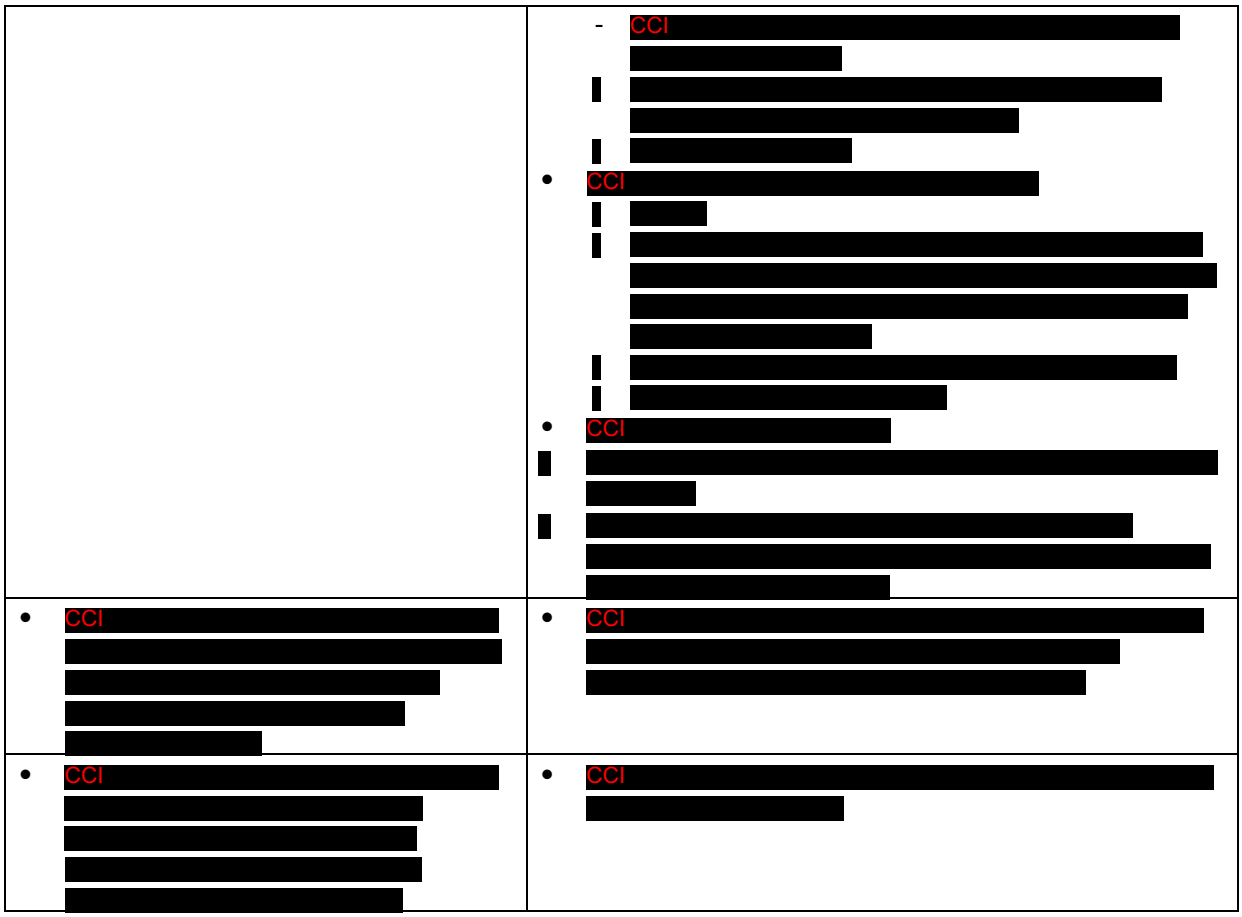
No data on preclinical reproductive toxicity are available at the time of this study.

2 STUDY OBJECTIVES AND ENDPOINTS

This trial has separate objectives and endpoints for the MAD phase 1b and POC phase 2 portions of the study. The primary, secondary, and exploratory objectives for each phase, as applicable, are described below with their corresponding endpoints.

2.1 Phase 1b Multiple Ascending Dose

OBJECTIVES	ENDPOINTS
Primary	
• To assess safety, tolerability, and immunogenicity of repeat doses of BOS161721 (20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment, in order to estimate the optimal dose	Safety Endpoints • Incidence and severity of AEs and SAEs, related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • Columbia Suicide Severity Rating Scale (C-SSRS) • 12-lead ECGs parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from baseline • Physical examinations changes from baseline • ADAs • Study drug exposure/compliance
Secondary	
• To characterize the PK of BOS161721 and select the optimal dose of BOS161721 based on safety, PK, and PD effects in patients with moderately to severely active SLE	Pharmacokinetic Endpoints • BOS161721 concentration by visit and time point • Maximum observed concentration (C_{max}), T_{max}, area under the concentration-time curve (AUC), terminal elimination half-life ($t_{½}$), systematic clearance (CL), volume of distribution (V_d) Pharmacodynamic Endpoints • Results and changes (or shifts) from baseline to each visit in phosphorylated signal transducer and activator of transcription 3 (pSTAT3), C3 and C4 levels, and leukocyte immunophenotype • Results and changes (or shifts) from baseline in anti-double-stranded DNA (dsDNA), antinuclear antibodies (ANA), anti-Sjögren syndrome A and B (SSA, SSB), Smith (Sm), and antiphospholipid (APL) autoantibodies at each visit • Results and changes (or shifts) from baseline in abrogation of IL-21 gene signature at each indicated visit
Exploratory	
• CCI [redacted]	CCI [redacted]



2.2 Phase 2 Proof of Concept

OBJECTIVES	ENDPOINTS
Primary	
• To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on the SRI-4	Primary Efficacy Endpoint • The proportion of patients with a SRI-4 response at Day 210 (see Section 6.3.4.1)
Secondary	
• To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on clinical indicators of SLE activity, in adult patients with moderately to severely active SLE on limited background standard of care treatment	Secondary Efficacy Endpoints • The proportion of patients with: - SRI-4 response at each visit - SRI-5 and SRI-6 response at each visit (Section 6.3.4.2) - a sustained reduction from baseline of oral corticosteroid (CS) (≤ 7.5 mg/day and < Day 0 dose) between Day 150 and Day 210 - new or recurrent BILAG flares (≥ 1 qualifying BILAG A or > 1 qualifying BILAG B) through Day 210 - PGA worsening - a BICLA response - a CLASI response

	- medication failures • The changes and percent changes from baseline in: - CLASI - PGA - Total number of swollen joints, tender joints, and active joints (swelling and tenderness in the same joint) in the ACR-28 joint count - SLEDAI-2K - SLICC/ACR damage index • Time to medication failure • Group mean percent reduction in CS administration from baseline Day 0 dose through Day 210 in patients receiving ≥ 7.5 mg/day prednisone equivalent at Day 0 • Duration of longest SRI-4 response • Time to first BILAG flare (≥ 1 new or recurrent BILAG A or > 1 new or recurrent BILAG B) relative to baseline through Day 210
Safety	
• To assess safety and tolerability of repeat doses of BOS161721 at the chosen dose administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment	Safety Endpoints • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • C-SSRS • 12-lead ECGs parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from baseline • Physical examinations changes from baseline • ADAs • Study drug exposure/compliance

Exploratory	
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	CCI [redacted]

3 STUDY PLAN

3.1 Study Design

This is a phase 1b/2 combined, randomized, multicenter, double-blind, placebo-controlled trial to study the clinical efficacy, safety, and PK of SC doses of BOS161721 in adult patients with moderately to severely active SLE. After successfully completing a screening phase, eligible patients will be randomized to a specified dose of BOS161721 or placebo. The dosing schedule will be monthly.

The trial will consist of 2 double-blinded portions: MAD phase 1b and POC phase 2. Patients may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180, followed by safety follow-up visits at Days 210, 240, and 270.

SLE disease activity assessment data will be centrally reviewed by medical monitor and sponsor to ensure the scores are clinically meaningful and compliant with specific definition. The scope of responsibility includes, but is not limited to, review and confirmation of “A” and “B” BILAG system organ disease, confirmation of clinical components of the SLEDAI-2K score at screening and during the study, and cross-validation of the instruments used in this study to assess the disease activity. Further details on the content and methods of data reports by the medical monitor and sponsor will be outlined in the Medical Data Review Plan along with the processes and procedures that will be followed.

3.1.1 Multiple Ascending Dose Phase 1b

The MAD portion will consist of 3 cohorts:

- Cohort 1 (20 mg SC) will include 6 patients
  - 5 patients will receive BOS161721 (active group) and 1 patient will receive placebo (placebo group)
- Cohorts 2 (60 mg SC) and 3 (120 mg SC) will include 12 patients each
  - 9 patients in the active group and 3 in the placebo group

Doses selected for each of the 3 cohorts is based on a 90 day safety, tolerability, PK and PD data review from the phase 1 SAD study (BOS161721-01) in healthy subjects. All doses selected for the MAD part of the study are projected not to exceed the mean exposure of that achieved at the highest dose in the SAD study.

3.1.1.1 Dose Escalation for the MAD Portion

The MAD portion of the study design is staggered, where after the 6 patients in Cohort 1 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 2 begins dosing (after the DMC evaluation of the safety and tolerability data from Cohort 1). Similarly, after 8 of the 12 patients in Cohort 2 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 3 begins dosing after the DMC evaluation of the safety and tolerability data from Cohorts 1 and 2. Each cohort will continue at their assigned dose level through their respective 6-month treatment periods (see Study Schematic, Section 3.3). If patients discontinue the study in a cohort prior to adequate safety follow-up, he/she may be replaced.

Criteria for dose escalation are further described in the DMC Charter. See Section 3.1.1.2 for additional details about DLTs.

3.1.1.2 Dose Limiting Toxicity (DLT)

Severity of adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. For the purpose of dose escalation, any of the following AEs occurring after study drug administration, which are attributable to the study drug, will be considered DLTs:

Hematologic:

- Grade 4 neutropenia
- Grade 3 neutropenic infection
- Grade 3 thrombocytopenia with bleeding
- Grade 4 thrombocytopenia

Non-Hematologic:

- Grade 3 or above toxicities, persisting after optimal treatment with standard medical therapy (e.g., anti-emetics, anti-diarrheals)
- Drug-induced liver injury ([DILI], Hy's Law), as defined in Section 6.2.2.6.3

Investigators should always manage their patients according to their medical judgment which may include interruption of study drug based on the particular clinical circumstances.

3.1.1.3 DMC Recommendations

During scheduled meetings, the DMC will review relevant study data for safety or benefit-risk concern. During the MAD part of the study, the DMC may provide the following recommendations to the sponsor:

- Expanding a cohort at a specific dosing level, or repeating a lower dose in a subsequent cohort
- Continuing a dose level for a given cohort
- Escalating a dose level for a subsequent cohort
- Termination of current or previous cohort(s)

Further dosing in a given cohort will be halted if 2 or more DLTs are identified intra- and inter-patients dosed. For the POC portion, the DMC and Boston Pharmaceuticals will conduct a data review to determine which dose will be carried forward into the POC phase 2 part of the study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2, and 3; this dose will not exceed doses tested during the MAD portion. The DMC will be reviewing all relevant data from Cohorts 1, 2, and 3 that is available 30 days after the last patient from Cohort 3 receives the third dose. Details are provided in the DMC Charter.

3.1.2 POC Phase 2

3.1.2.1 BOS161721 POC Dose Selection and Justification

The dose for the POC portion of the study is 120 mg administered SC monthly (a total of 7 doses). The rationale for the BOS161721-02 phase 2 POC dose selection was based on cumulative safety, tolerability, immunogenicity, PK, and PD data available from an interim analysis (IA) performed during the MAD phase 1b portion of the trial.

The data cut-off for this IA occurred on CCI [redacted] and included all 6 patients and 7 doses from Cohort 1 (20 mg), 12 patients and 6 doses from Cohort 2 (60 mg), and 12 patients and 4 doses from Cohort 3 (120 mg).

The safety analysis focused on incidence and severity of all AEs, SAEs, and pre-determined adverse events of special interest (see Section 6.2.2.6). The DMC and designated unblinded Boston Pharmaceuticals team met on CCI [redacted] and did not identify any untoward safety signals at any BOS161721 dose levels.

Because there were no safety, tolerability, or immunogenicity trends observed at the time of the IA, the phase 2 POC dose selection was made based on available PK and PD data. pSTAT3 levels were assessed as the primary PD biomarker of IL-21R signaling levels. This is because IL-21R signaling, upon IL-21 binding, initially involves phosphorylation of JAK1/JAK3 which dissociate from the receptor complex, and phosphorylate STAT3 which translocates to the nucleus and drives IL-21-regulated gene expression. CCI [redacted]

CCI [redacted].

The 120 mg dose was communicated to site Investigators participating in the POC phase 2 portion, and to Institutional Review Boards (IRBs) and the Independent Ethics Committee (IEC).

3.1.2.2 POC Study Design

For the POC part of the study, approximately 110 additional patients will be randomized to active or placebo groups in a 2:1 ratio.

As in the MAD part of the study, each patient in the POC portion may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180. Assessments will be completed according to the Schedule of Assessments (Table 1 and Table 4).

DMC safety reviews will be conducted periodically throughout the study as described in the DMC charter.

3.2 Randomization and Blinding

This is a randomized, double-blind study.

Patients meeting all inclusion and exclusion criteria will be centrally randomized to either placebo or BOS161721 using an IWRS according to a randomization list generated by an independent, non-study statistician. Randomization will be performed separately for each study portion and separately for each cohort in the phase 1b and 2 portions as follows:

Phase/Cohort	Number of Patients	Randomization Ratio BOS161721:Placebo
Phase 1b/Cohort 1	6	5:1
Phase 1b/Cohort 2	12	3:1
Phase 1b/Cohort 3	12	3:1
Phase 2	Approximately 110	2:1

*Additional patients may be enrolled to ensure sufficient numbers of patients are in the full analysis set (FAS).

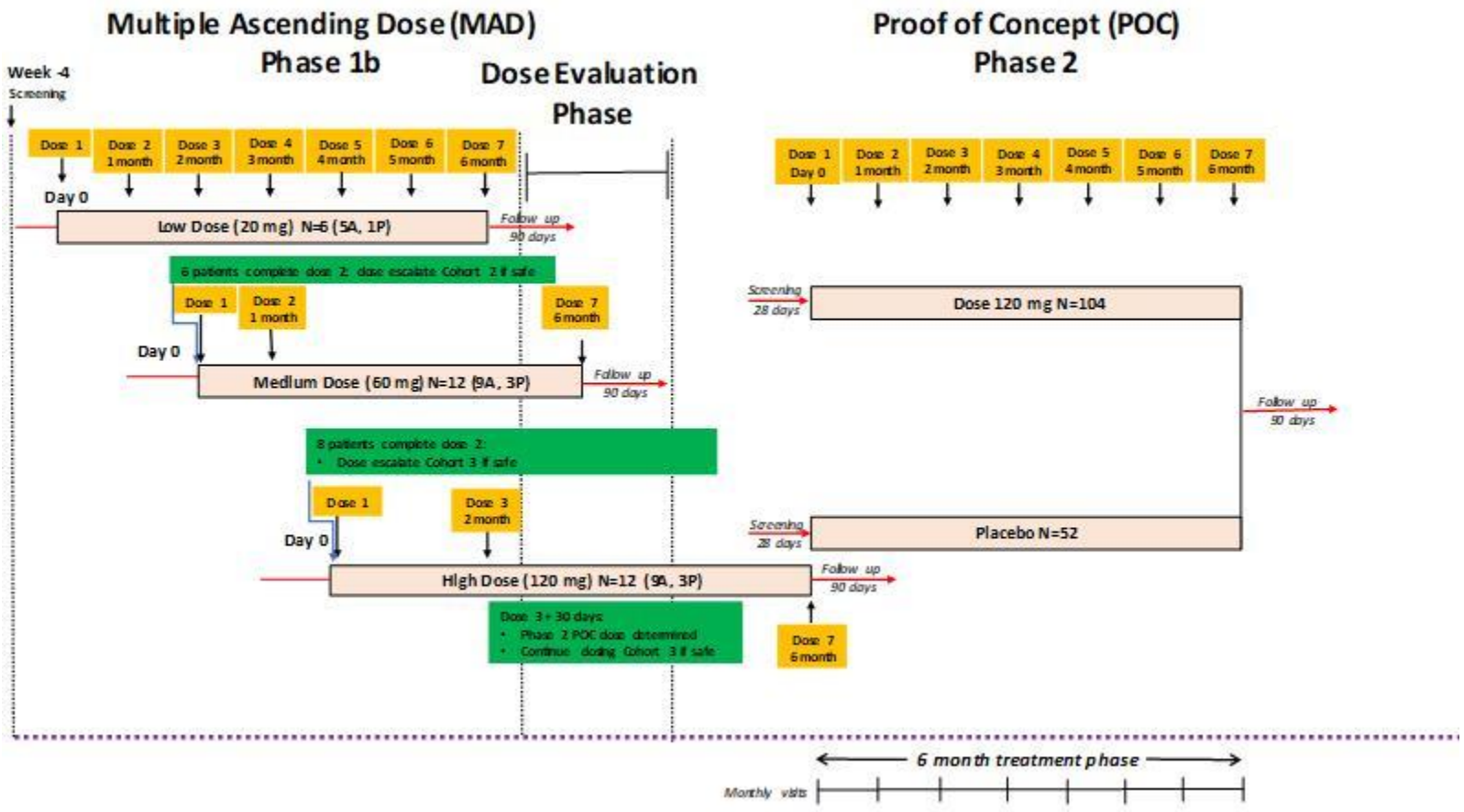
Eligible patients will be assigned to the study portion which is active at time of enrollment. Similarly, patients in the phase 1b MAD will be assigned to the cohort which is active. Each patient will be assigned a unique randomization number which will not be reused.

All patients, Investigators, and study team participants will be blinded to treatment assignment. An independent biostatistician not otherwise involved on the study will be unblinded and prepare materials for the IA, ad hoc analyses as needed, and the DMC

safety reviews. The DMC will review unblinded data during safety reviews and the IA. A limited team at Boston Pharmaceuticals will review unblinded results from the phase 1b MAD portion during the IA to determine the dose that will be used for the phase 2 POC portion of the study. Details regarding maintenance of the blinding and content of data reviews will be described in the DMC charter or related study documentation.

3.3 Study Schematic

Figure 2. Study Diagram for MAD Phase 1b and POC Phase 2



A = active drug (BOS161721); P = placebo

3.4 Schedule of Assessments

Table 1. Schedule of Assessments - Phase 2 Proof of Concept (POC)

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187[b] (± 3)**	**195[b] (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
GENERAL ASSESSMENTS														
Informed consent	X													
Inclusion/Exclusion criteria	X													
Medical history	X													
Demographics	X													
SLICC Criteria for SLE	X													
Concomitant medication[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[d]		X												
BOS161721 or placebo dosing		X		X	X	X	X	X	X					
SAFETY ASSESSMENTS														
Full physical exam	X	X												

[a] Screening assessments will be performed over more than 1 visit.

[b] PK samples will only be collected at the investigational sites that participate in the PK portion of the study. On PK only days (i.e., Day 187 and Day 195 when no laboratory assessments are scheduled) samples will be collected at the investigational sites of the selected countries that participate in the PK portion of the study. Patients not participating in PK are not required to return for investigation site visits on Days 187 and 195.

[c] Concomitant use of oral corticosteroids: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the dose must be stable for at least 6 weeks prior to Day 0 (randomization day). See Section 4.6.1 for further details.

[d] Randomization should occur after patient eligibility has been confirmed. The actual randomization procedure can be completed on Day -1 after eligibility confirmation or the morning of Day 0 prior to dosing for logistical purposes.

Table 1. Schedule of Assessments - Phase 2 Proof of Concept (POC)

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187[b] (± 3)**	**195[b] (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
Chest x-ray[e]	X													
C-SSRS	X	X				X			X					
AEs and SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[f]	X	X		X		X								X
Injection site reaction assessment		X[g]		X	X	X	X	X	X	X	X	X	X	X
Targeted physical examination			X	X	X	X	X	X	X			X	X	X
Vital signs (BP, HR, and temperature)[h]	X	X	X	X	X	X	X	X	X			X	X	X
EFFICACY ASSESSMENTS														
BILAG-2004 Index	X	X		X	X	X	X	X	X			X	X	X

[e] If patients have had a TB test and chest x ray within 3 months prior to screening, then these assessments do not need to be repeated during screening. The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0)

[f] ECGs will be performed after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws

[g] Injection site reaction assessments to be performed at 2 hours postdose

[h] Vital signs will be assessed after the patient has been supine and at rest ≥ 5 minutes. Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours (± 15 minutes) postdose, as well as on each of the scheduled outpatient days in the table above (excluding PK-only site visits at Days 187 and 195). When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection

Table 1. Schedule of Assessments - Phase 2 Proof of Concept (POC)

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187[b] (± 3)**	**195[b] (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
SLEDAI-2K	X	X[i]		X	X	X	X	X	X			X	X	X
PGA	X	X		X	X	X	X	X	X			X	X	X
ACR-28 joint count	X	X		X	X	X	X	X	X			X	X	X
CLASI	X	X		X	X	X	X	X	X			X	X	X
CCI		X		X	X	X	X	X	X			X	X	X
SLICC/ACR Damage Index		X							X					
CCI		X		X	X	X	X	X	X			X	X	X
LABORATORY ASSESSMENTS														
CD4+ count	X	X	X	X		X			X					
Clinical laboratory assessments (hematology and clinical chemistry)[j]	X	X		X	X	X	X	X	X			X	X	X
Coomb's test direct[k]	X	X		X	X	X	X	X	X			X	X	X
Total IgG and IgM	X	X	X	X		X			X					
Plasma CCI	X	X		X	X	X	X	X	X			X	X	X
Plasma CCI & CCI		X	X	X		X			X					

[i] SLEDAI-2K should be done before randomization and dosing on Day 0 as SLEDAI-2K < 6 is exclusionary

[j] Clinical laboratory assessments will include a fasting glucose and lipid panel, with exception of screening (Visit 1) which will be nonfasting

[k] When clinically indicated for hemolytic anemia

Table 1. Schedule of Assessments - Phase 2 Proof of Concept (POC)

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187[b] (± 3)**	**195[b] (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
ADA[l]		X	X	X	X	X			X					X
nAb[m]						X			X					
CCI [redacted]		X	X			X			X					X
CCI [redacted]		X												
CCI [redacted]	X	X		X	X	X	X	X	X			X[n]	X[n]	X[n]
CRP	X					X								X
Serum pregnancy test (women)	X													
FSH (postmenopausal women)	X													
Urine pregnancy test (women)[o]		X		X	X	X	X	X	X					X
TB test (QuantiFERON®-TB Gold In-Tube)[e]	X													
Serology (hepatitis B and C, HIV-1/2 combination)	X													

[l] Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only assayed (analyzed) if the patient had a positive ADA on Day 90

[m] nAb is collected for all patients, though will only be analyzed by central lab if patient is positive for ADA at Day 90

[n] CCI [redacted] will not be analyzed during safety follow-up visits

[o] Urine pregnancy test will be collected on WOCBP prior to study drug administration on dosing visits

Table 1. Schedule of Assessments - Phase 2 Proof of Concept (POC)

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187[b] (± 3)**	**195[b] (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
Stool sample[p]	X													
Spot urine for protein/creatinine ratio	X	X		X	X	X	X	X	X			X	X	X
Urinalysis	X	X		X	X	X	X	X	X			X	X	X
PK Labs[b]														
Predose		X		X	X	X	X	X	X					
Postdose			X							X	X	X	X	X

Abbreviations: ACR = American College of Rheumatology; ADA = anti-drug antibody; AE = adverse event; CCI ; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; CD4+ = cluster of differentiation 4; CLASI = Cutaneous Lupus Area and Severity Index; CRP = C-reactive protein; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; CCI ; FSH = follicle stimulating hormone; HR = heart rate; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IL-21 = interleukin 21; nAb = neutralizing antibody; PGA = Physician's Global Assessment; PK = pharmacokinetic; SAE = serious adverse event; CCI ; SLEDAI-2K = SLE Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; CCI CCI TB = tuberculosis.

[p] Cryptosporidium test is required at screening. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium

3.5 End of Study

End of Study (Individual Patient): A patient is considered at the end of study if he/she has withdrawn, prematurely discontinued, or completed all of the study procedures including the last visit.

End of Study (End of trial): The end of the study is defined as the date of the last visit of the last patient in the study globally, or the date of which the last patient withdraws or discontinues if all prior enrolled patients have already completed/withdrawn.

4 POPULATION

4.1 Participant Recruitment

Advertisements approved by the IRB, and Investigator databases, may be used as recruitment procedures for adult men and women with moderately to severely active SLE.

4.2 Number of Patients

Approximately 140 male and female patients are planned for enrollment, but may be adjusted upward according to the dropout (noncompliance) rate, which will be monitored in a blinded fashion in an ongoing basis. Approximately 30 patients will be randomized for the MAD phase 1b portion, and approximately 110 additional patients will be randomized in the POC phase 2 portion. Note that approximately 14 dropouts are assumed in the POC phase 2 portion.

4.3 Patient Screening

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular individual. Patient eligibility will be reviewed and confirmed by the medical monitor or designee prior to randomization. Screening assessments (see the Schedule of Assessments [Table 1 and Table 4]) for this study must be performed between Day -28 and Day -1.

4.4 Inclusion Criteria

Patients who meet the following criteria will be considered eligible to participate in this clinical study:

1. Men and women, ages 18 to 70 years, inclusive.

2. Patients must be mentally capable of giving consent and there must be evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

3. Patients must have SLE as defined by meeting 4 of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE (with at least 1 clinical and 1 immunologic criterion or Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies), either sequentially or simultaneously.

4. At screening, patients must have at least 1 of the following:

   a. Elevated ANA ≥ 1:80 via immunofluorescent assay at the central laboratory
   b. Positive anti-dsDNA or anti-Smith (Sm) above the normal level as determined by the central laboratory

5. At screening, the total SLEDAI-2K score must be ≥ 8, including points from at least 1 of the following clinical components:

   a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis

   Note: Points from lupus headache and organic brain syndrome will also be excluded from qualifying total and clinical SLEDAI-2K scores at screening and Day 0.

6. A clinical SLEDAI-2K score of ≥ 6 at screening at Day 0. Clinical SLEDAI-2K score is defined as follows:

   a. Contains points from arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, or vasculitis
   b. Excludes parameters which require central laboratory results: hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia

   Note: Points from lupus headache and organic brain syndrome will also be excluded from qualifying total and clinical SLEDAI-2K scores at screening and Day 0.

7. Patients must have at least 1 qualifying A or 2Bs from the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer:

   a. BILAG A or B score in the mucocutaneous body system. If a BILAG B score is due to BILAG number 6, mild skin eruption, the CLASI activity score including erythema and scale/hypertrophy must be ≥ 3 excluding points from mucosal ulcers and alopecia.
   b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis defined as follows:
      i. “BILAG A:” Severe Arthritis, (BILAG item number 41), manifested by observed active synovitis defined by BOTH swelling and tenderness in ≥ 6 joints with marked loss of functional range of movements and significant impairment of basic activities of daily living (ADLs) that has been present on several days

(> 4 days) cumulatively over the past 30 days, including at the time of the screening visit. See Appendix 5 for additional detailed specifications.

- Basic ADLs are defined as the following activities which require assistance or assistive devices, (at least 1 must be present and documented in source):
  - Ambulation, toileting, grooming- including bathing and dressing; feeding oneself

ii. "BILAG B:" Moderate Arthritis, Tendonitis or Tenosynovitis, (BILAG item number 42), defined as tendonitis/tenosynovitis, or active synovitis defined by BOTH swelling and tenderness in ≥ 3 joints, (observed or through patient history), with some loss of functional range of movements manifested by effects on instrumental ADLs such as:

- Cooking, driving, using the telephone or computer, shopping, cleaning, etc., and has been present on several days over the last 30 days, and is present at the time of the screening visit

Note: Hips, shoulders, back, neck, and temporomandibular joints do not count towards the total number of joints with active synovitis.

If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in at least 1 other body system for a total of 2 "B" BILAG body system scores.

8. Patients must be currently receiving at least 1 of the following:

   a. Administration for a minimum of 12 weeks, and a stable dose for at least 56 days (8 weeks prior to Day 0) of the following permitted steroid-sparing agents:
      i. Azathioprine (AZA), mycophenolate mofetil or mycophenolic acid, chloroquine, hydroxychloroquine, or methotrexate (MTX)
   b. If AZA, myocophenolate mofetil, mycophenolic acid, hydroxychloroquine, or MTX were discontinued prior to screening, the washout period must be ≥ 12 weeks
   c. Corticosteroids (prednisone or prednisone-equivalent) at a stable dose of up to 30 mg/day for at least 6 weeks prior to Day 0 (see Appendix 3)
      i. For patients whose only SLE treatment is CS, the stable CS dose must be ≥ 10 mg/day for at least 6 weeks prior to Day 0 and no more than 30 mg/day at the time of randomization
      ii. Topical steroids may be used, but the dose must be stable for at least 6 weeks prior to Day 0. PRN topical steroids are not permitted
9. Women of childbearing potential (WOCBP; see Section 4.7 for full information regarding WOCBP, definition of menopause, and contraception):

   a. Must have a negative serum pregnancy test at screening. Urine pregnancy test must be negative prior to first dose
   b. Must not be breastfeeding

   c. Must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 52 weeks.

10. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 52 weeks.

11. Patients must demonstrate willingness and ability to comply with the scheduled study visits, treatment plans, laboratory tests, and other procedures.

4.5 Exclusion Criteria

Patients presenting with any of the following will not be included in this study:

1. Drug-induced SLE, rather than “idiopathic” SLE.

2. Other systemic autoimmune disease (e.g., erosive arthritis, rheumatoid arthritis [RA], multiple sclerosis [MS], systemic sclerosis, or vasculitis not related to SLE).

   a. RA-Lupus overlap (Rupus), and secondary Sjögren syndrome are allowed

3. Any major surgery within 6 weeks of study drug administration, (Day 0), or any elective surgery planned during the course of the study.

4. Any history or risk for tuberculosis (TB), specifically those with:

   a. Current clinical, radiographic, or laboratory evidence of active TB
   b. History of active TB
   c. Latent TB defined as positive QuantiFERON-TB Gold In-Tube (QFT-G) or other diagnostic test in the absence of clinical manifestations. Latent TB is not excluded if the patient has documented completion of adequate course of prophylactic treatment with regimen recommended by local health authority guideline, or the patient has started treatment with isoniazid, or other regimen recommended by local health authority guidelines for at least 1 month before Day 0 and continues to receive the prophylactic treatment during study until the treatment course is completed.

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

6. Severe proliferative lupus nephritis, (WHO Class III, IV), which requires or may require induction treatment with cytotoxic agents or high dose CS.

7. Concomitant illness that, in the opinion of the Investigator or the sponsor or their designee, is likely to require additional systemic glucocorticosteroid therapy during the study, (e.g., asthma), is exclusionary.

   a. However, treatment for asthma with inhalational CS therapy is allowed.

8. Use or planned use of concomitant medication outside of standard of baseline treatment for SLE from Day -1 or for any time during the study. (See Section 4.6.2 for prohibited concomitant medication).

9. Active and clinically significant infection (bacterial, fungal, viral, or other) within 60 days prior to first dose of study drug. Clinically significant is defined as requiring systemic parenteral antibiotics or hospitalization.

10. A history of opportunistic infection, or a history of recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years.

11. Chronic viral hepatitis including hepatitis B (HBV) and hepatitis C (HCV) unless patient received curative treatment for HCV and has a documented negative viral load, known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness.

12. Cryptosporidium in the stool sample at screening.

13. White blood cells (WBC) < 1,200/mm^3 (1.2 × 10^9/L) at screening.

14. Absolute neutrophil count (ANC) < 500/mm^3 at screening.

15. CD4+ count < 150/µL at screening.

16. Platelets < 50,000/mm^3 (50 × 10^9/L) or < 35,000/mm^3 (35 × 10^9/L) if related to SLE, at screening.

17. Hemoglobin < 8 g/dL or < 7 g/dL at screening if related to SLE.

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

19. Serum creatinine > 2.0 mg/dL at screening or creatinine clearance (CrCL) < 40 mL/minute based on Cockcroft-Gault calculation[39]:

    GFR = ([1 for male] or [0.85 for female]) × (140 – Age) × BW/(72 × Creatinine).

20. Serum ALT and/or serum AST > 2 × ULN at screening, unless explicitly related to lupus based on the Investigator's judgment.

21. Creatinine kinase (CK) > 3.0 × ULN at screening, unless it is related to lupus myositis.

22. Total bilirubin > 1.5 × ULN at screening (unless related to Gilbert's syndrome).

23. Any other laboratory test results that, in the opinion of the Investigator or the sponsor or sponsor's designee, might place a patient at unacceptable risk for participating in this study.

24. History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody (e.g., IgG protein) or molecules made of components of monoclonal antibodies.

25. History substance and/or alcohol abuse or dependence within the past 1 year, at the Investigator's judgment.

26. History of cancer within the last 5 years (except for cutaneous basal cell or squamous cell cancer, or cervical cancer *in situ* resolved by excision).

27. Any other severe acute or chronic medical or psychiatric condition, including recent (within the past year) medical conditions (e.g., cardiovascular conditions, respiratory illnesses) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, sponsor or sponsor's designee, would make the patient inappropriate for entry into this study.

28. Investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or patients who are employees of the sponsor or directly involved in the conduct of the trial.

29. Currently participating in, or who have participated in other interventional (drug or device) clinical study within 30 days or 5 half-lives of baseline, whichever is longer.

30. Recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4 or 5 on the C-SSRS.

31. Current or pending incarceration.

32. Current or pending compulsory detainment for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

33. Currently taking a total daily dose of > 30 mg morphine or morphine equivalent (see Appendix 7).

34. Body mass index (BMI) ≥ 40.0.

4.6 Concomitant Medications

Any medicinal product, prescribed or OTC, including herbal and other nontraditional remedies, is considered a concomitant medication. Patients should stay on stable regimen (not PRN) of other concomitant medications for the treatment of SLE (e.g., analgesics, nonsteroidal anti-inflammatory drugs [NSAIDs], statins, ACE inhibitors/ARBs and other antihypertensive drugs), unless changes in these treatments are clinically indicated. Patients should refrain from Tylenol, NSAIDs, and any pain medications including tramadol and other opiates for at least 12 hours before each visit, with the exception of the Screening Visit.

Use of any other drugs for non-SLE conditions, including over-the-counter medications and herbal preparations, should remain stable unless change or addition is clinically necessary. Discussion with the medical monitor prior to initiation of new medication is strongly recommended. Any concomitant therapies must be recorded on the eCRF. Prior and concomitant medication use will be recorded for the 30 days prior to screening until the last follow-up visit. In addition, historical treatment for SLE (including immunosuppressant, anti-malarial, corticosteroid, and/or biologic agent including investigational agents) will be recorded for the 48 weeks prior to screening in the eCRF.

4.6.1 Corticosteroid

Prior to randomization, oral CSs (prednisone or prednisone equivalent), may be used in accordance with the Investigator's clinical judgment and best standard of care. See Appendix 3 for examples of equivalents.

- A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study. For patients whose only SLE treatment is steroids, their stable steroid dose must be at least 10 mg/day and no more than 30 mg/day for a minimum of 6 weeks at time of randomization on Day 0
- Topical steroids may be used, but the dose must be stable for at least 6 weeks prior to Day 0, and be maintained at a constant dose throughout the study duration until the rashes resolve. PRN topical steroids are not permitted
- Once the patient has received the first dose of study drug (Day 0), tapering of oral steroids will be highly encouraged and should be continually evaluated during the protocol-allowed tapering windows (Day 0 through Day 150) with the target of achieving a CS daily dose of < 7.5 mg and < Day 0 dose between Day 150 and Day 210
- Between Day 150 and Day 210 (i.e., within 60 days of primary endpoint assessments), oral CS doses must be held constant
- CS Burst for SLE-related Indications

  After Day 0 (first dose of study drug), a maximum of 1 oral CS "burst" equivalent to ≤ 40 mg/day prednisone for increased SLE disease activity will be allowed between Day 0 and Day 120, which must be tapered down to the baseline (Day 0) CS dose or lower within 14 days of initiation of the "burst". Any "burst" continuing after Day 120 or occurring after Day 120 is considered a protocol deviation.

  - Alternatively, a single intramuscular (IM) dose of methylprednisolone (< 40 mg) is permitted during this period

  CS Burst for Non-SLE-related Indications.

  A single treatment of oral prednisone equivalent of ≤ 40 mg/day for 14 days is permitted for a non-SLE indication, though it must be completed prior to Day 120. No long acting steroid injections are permitted.

  Note: Treatment with inhaled CS are allowed for the treatment of non-SLE-related indications only (e.g., for asthma).

Any other increase from baseline of CS dose or systemic use of CS of any kind (including intra-articular and intravenous administration) are not permitted from Day 0 through Day 210 and will result in the patient being considered a treatment failure. There is no restriction of CS usage after Day 210.

4.6.2 Other Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study drug administration and during the study are described below, and washout requirements are provided in Appendix 4. All medications taken within 30 days prior to screening must be recorded on the eCRF.

1. Prior exposure to BOS161721

2. Patients who have received treatment with anti-CD20 monoclonal antibodies within 24 weeks of screening

3. Patients who have received treatment with cyclophosphamide within the 24 weeks prior to screening

4. Patients who have received treatment with cyclosporine (with exception of ophthalmic use), any other calcineurin inhibitor or other immunosuppressive medication not specified in the inclusion criteria within 4 weeks for oral use or 8 weeks for topical use of screening

5. Patients who are currently receiving or are scheduled to receive plasmapheresis or lymphapheresis therapy, or have received such therapy within 24 weeks prior to screening

6. Patients who have received any live vaccines within 30 days of screening. Note: Furthermore, live vaccines should not be used during the course of the study and within the 2 months following last dose. Other inactivated vaccines such as tetanus, etc., may be used according to local guidelines during treatment period

7. Patients who are scheduled or anticipated to have elective surgery during the course of the study

8. Initiation of new immunosuppressant or anti-malarial agent is not permitted. Note: Dose reduction or replacement may be allowed due to intolerability or shortage for patients on a stable dose prior to study initiation

4.7 Women of Childbearing Potential

WOCBP is defined as any woman who has experienced menarche and who has not undergone surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) and is not postmenopausal.

See Section 4.7.2 for detailed information regarding contraceptive requirements for WOCBP.

4.7.1 Determination of Menopause

Menopause is defined as at least 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. Women under the age of 55 years must have a documented serum FSH level > 40 mIU/mL at screening to confirm menopause.

4.7.2 Contraception

WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 52 weeks, due to the mean terminal ½ life of the study drug.

Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 52 weeks, due to the mean terminal ½ life of the study drug.

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

- Patients must agree to either complete abstinence, defined as a complete avoidance of heterosexual activity, or the use of 2 methods of effective contraception from the following:
- Male condoms with spermicide
- Diaphragm with spermicide
- Cervical cap with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, patches and intrauterine devices (IUDs) such as Mirena® by patients who are WOCBP or a male patient's WOCBP partner. Women who are partner of men who are patients participating in the study may use hormone-based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- IUDs, such as ParaGard®
- Vasectomy
- Note: Women who are abstinent while participating in the study must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the patient chooses to forego complete abstinence

- Azoospermic men and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP must still undergo pregnancy testing

4.8 Deviation from Inclusion/Exclusion Criteria

Deviation from the inclusion or exclusion criteria will not be allowed. If deviation of inclusion/exclusion criteria is discovered after randomization, the Investigator should contact the medical monitor for discussion. A decision will be made whether to allow a patient to continue or withdrawal from the study medication.

See Section 6.8 for additional details.

4.8.1 Patient Withdrawal and Replacement

See Section 5.5 for reasons for removal from the trial. Withdrawn patients may be replaced during the MAD part of the study after discussion between the Principal Investigator or designee and sponsor.

5 STUDY PROCEDURES

Refer to the eCRF completion guidelines for data collection requirements and documentation of study assessments/procedures.

5.1 Screening

Screening will be the same for both the MAD and POC portions of the study.

Screening will take place from Day -28 to Day -1, and assessments may be performed over more than 1 visit. Confirmation that the most current IRB/IEC approved informed consent form (ICF) has been signed must occur before any study-specific screening procedures are performed. Procedures that are part of standard of care are not considered study-specific procedures and may be performed prior to informed consent and used to determine eligibility.

All screened patients will be assigned a unique screening number. The screening number will include a 3-digit site number and a 4-digit sequential number to identify patients from the time of screening. Only eligible patients who are confirmed by central review as meeting the inclusion/exclusion criteria, listed in Section 4.4 and Section 4.5 respectively, will be enrolled in the study. Screened patients who drop out of the clinical study before randomization will be recorded as screen failures. If rescreening occurs, the site will assign a new screening number.

Specific procedures at the screening visit will include:

- Medical history documentation
- Review of inclusion and exclusion criteria

  - Patient medical records must contain documentation of SLE diagnosis
  - C-SSRS
- Concomitant medication documentation
- Demographics
- Full physical examination
- Vital signs
- Chest x-ray (a prior x-ray can be used if taken within 12 weeks of screening date)
- Laboratory evaluations (non-fasting):
  - Hematology and clinical chemistry
  - Serology (Hepatitis B and C; HIV-1/2 combination)
  - TB test
  - CRP
  - Direct Coomb's test (if indicated for hemolytic anemia)
  - CD4+ count, total IgG and IgM levels, plasma [redacted], [redacted]
  - Serum pregnancy test (WOCBP)
  - FSH (postmenopausal women under age 55 years)
  - Spot urine for protein/creatinine ratio
  - Urinalysis
  - Stool sample
- 12-lead ECG
- SLE-related indices [BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, Physician's Global Assessment (PGA) of disease activity]
- Screening procedures are listed in the Schedule of Assessments (Table 1 and Table 4), and details are provided in Section 6.

5.1.1 Retesting During Screening Period

A single retesting of laboratory parameters and/or other assessments during the screening period is permitted (in addition to any parameters that require a confirmatory value) only if:

- medically indicated
- there is evidence a laboratory sample was mislabeled, indeterminate, inadequately processed, and/or deteriorated in transit to the central laboratory

Any new result will override the previous result (i.e., the most current result prior to randomization) and is the value by which study inclusion/exclusion will be assessed, as it represents the patient's most current clinical state. This will also apply to patients who are being rescreened.

5.2 Enrollment/Randomization and Day 0 Treatment

Randomization should occur after patient eligibility for enrollment has been confirmed by the central eligibility review. The central eligibility review team has the final decision on patient eligibility and can decide the patient is not eligible for the study based on their review of the eligibility packet.

Prior to randomization, the study site should confirm that the patient still meets inclusion/exclusion criteria (especially SLE disease activity and treatment). The site will obtain a randomization number when registering the patient in interactive web response system (IWRS). All patients will receive BOS161721 or placebo according to the kit number assigned by the IWRS randomization scheme.

After randomization, procedures include:

- PROs: CCI
- C-SSRS
- Laboratory evaluations (fasting):
  - Hematology and clinical chemistry
  - Direct Coomb's test (if indicated for hemolytic anemia)
  - CD4+ count, total IgG and IgM levels, plasma CCI, plasma CCI and CCI, whole blood for leukocyte immunophenotype (leukocyte immunophenotype for MAD patients only)
  - ADA
  - pSTAT3 (predose [trough] samples only in phase 1b)
  - CCI
  - CCI
  - CCI
  - See Table 4 and Table 1 for details of PK sampling in the MAD and POC portions
  - Urine pregnancy test will be collected on WOCBP prior to study drug administration
  - Spot urine for protein/creatinine ratio
  - Urinalysis
- Concomitant medication documentation
- Documentation of AEs and SAEs (see Section 6.2.2.5 on SAE reporting requirements)
- Full physical examination
- Vital signs (prior to PK blood draw, predose, and at 1 and 2 hours [± 15 minutes] postdose on Day 0)
- 12-lead ECG (prior to PK blood draw)
- SLE-related indices (BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, PGA)

- SLICC/ACR damage index
- Study drug administration:
  - Administration of BOS161721 or placebo will take place on-site, and is discussed in Section 7.3.
- Injection site reaction assessment performed at 2 hours postdose

Procedures on Day 0 are listed in the Schedule of Assessments (Table 1 and Table 4), and details are provided in Section 6.

All patients who are enrolled, randomized, and receive study drug, or undergo study-specific procedures should reconsent with any updated versions of IRB/IEC approved informed consents during study participation as applicable and per institutional guidelines.

5.3 Treatment Period/Follow-Up Visits

The following procedures will be performed as indicated in the Schedule of Assessments (Table 1 and Table 4). See Schedule of Assessment tables for allowable windows for each visit.

- Targeted physical examination
- Vital signs (prior to PK blood draw)
- Concomitant medication documentation
- Documentation of AEs and SAEs (see Section 6.2.2.5 on SAE reporting requirements)
- PROs: CCI
- Urine pregnancy tests will be collected on WOCBP prior to study drug administration
- Injection site reaction assessments will be performed predose
- Direct Coomb's test (if indicated for hemolytic anemia)
- Spot urine for protein to creatinine ratio
- Urinalysis
- CCI
- Plasma CCI
- PGA, BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, and the CLASI will be completed
- SLICC/ACR Damage Index will be completed at Day 180
- C-SSRS
- ECGs prior to PK blood draw
- See Table 4 and Table 1 for details of PK sampling in the MAD and POC studies, respectively
- Fasting hematology and chemistry assessments
- The CD4+ count and total IgG and IgM levels

- Plasma CCI and CCI, ADA, and whole blood for leukocyte immunophenotype (leukocyte immunophenotype for MAD patients only)
- pSTAT3 (predose [trough] samples only phase 1b)
- nAb will be analyzed by central lab if patient is positive for ADA
- CRP
- CCI

5.4 Safety Follow-Up Visits

Safety follow-up visits will take place at Days 210, 240, and 270. These visits will include the following assessments as indicated in the Schedule of Assessments (Table 1 and Table 4):

- PROs: CCI
- Documentation of AEs and SAEs (see Section 6.2.2.5 on SAE reporting requirements)
- Injection site reactions
- Targeted physical examination
- Vital signs (prior to PK blood draw)
- Spot urine for protein/creatinine ratio and urinalysis
- Concomitant medication documentation
- BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, and PGA
- Fasting clinical laboratory assessments (hematology and clinical chemistry)
- Direct Coomb's test (if indicated for hemolytic anemia)
- Plasma CCI
- CCI
- 12-lead ECG (prior to PK blood draw)
- CRP
- ADA
- CCI
- Urine pregnancy test
- See Table 1 and Table 4 for details of PK sampling in the MAD and POC portions, respectively

5.5 Premature Discontinuation

While patients are encouraged to complete all study evaluations, they may withdraw from the study at any time and for any reason. Every effort will be made to determine why any patient withdraws from the study prematurely. If the patient is unreachable by telephone, a registered letter, at the minimum, should be sent to the patient requesting him/her to contact the clinic.

All patients who withdraw from the study with an ongoing AE or SAE must be followed until the end of study or until the event is resolved or deemed stable, respectively.

If a patient withdraws prematurely after dosing, an end of treatment (EOT) visit should be performed (Day 180) and a last follow-up visit 90 days after dosing should be scheduled (Day 270). Safety follow-up visit procedures based on the Schedule of Assessments (see Section 5.4).

Patient participation may be terminated prior to completing the study and the reason recorded as follows:

- AE/SAE
- Protocol deviation
- Lost to follow-up
- Patient withdraws consent at their own request
- Investigator decision
- Decision by the sponsor (other than AE/SAE, protocol deviation, or lost to follow-up)

Withdrawn patients may be replaced after discussion between the Investigator or designee and sponsor.

5.6 Contingency Plans During the COVID-19 Pandemic

- Safety oversight: In case a patient cannot return to the study site for the scheduled visit, the site staff will contact the patient remotely for safety follow up, for example, via telephone or video conferencing.

- Central Laboratory: In the case there are courier issues that will prevent the protocol-required laboratory specimens to be sent to the study core laboratory, the site should have the safety laboratory speciments (Table 2: Hematology, Chemistry, and Urinalysis) sent to their local laboratory for analysis and review by the study physician.

- Investigational Product Dosing: In cases when dosing cannot be performed during the protocol-designated windows, the Investigator should discuss each case with the Sponsor to determine whether it is a missed visit or whether the dosing can be performed outside protocol windows (as a protocol deviation). A minimum of 2 weeks must be maintained between consecutive doses. Patients who miss more than 2 doses of the study drug (whether consecutive or not) will be discontinued from the study and will undergo assessments as outlined in Section 5.5 (Premature Discontinuation).

6 ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the Investigator, which may make it unfeasible to perform the test. In these cases, the Investigator will take all steps necessary to ensure the safety and wellbeing of the patient. When a protocol required test cannot be performed the Investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. All protocol violations are entered directly into the eCRFs.

6.1 Medical History, Demographic and Other Baseline Information

The medical history comprises:

- General medical history
- Documentation of SLE diagnosis
- Historical medication therapy for SLE

The following demographic information will be recorded:

- Age
- Ethnic origin (Hispanic/Latino or not Hispanic/not Latino)
- Race (White, American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black/African American)
- Height (without shoes, in cm)
- Body weight, without shoes (kg)
- BMI [kg/m^2]

Other baseline characteristics will be recorded as follows:

- Concomitant medication documentation (see Section 4.6)
- Status of child bearing potential and contraception

6.2 Safety Assessments

6.2.1 Laboratory Assessments

Laboratory tests will be performed at times defined in the Schedule of Assessments (Table 1 and Table 4). Patient eligibility will be determined based on these tests at screening. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

A central laboratory will be used (with the exception of urine pregnancy tests) to ensure accuracy and consistency in test results. Laboratory/analyte results that could unblind the study (i.e., biomarker results) will not be reported to investigative sites. Urinalysis

will be performed on midstream, clean catch specimens. Some biomarkers listed above will not be drawn at some sites due to geographical logistical challenges. See the laboratory manual for details.

Endpoint analyses will be based on changes from baseline assessments at Days 120 and 210.

Table 2. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other Safety Tests
Hemoglobin	BUN	pH	Spot urine for protein/creatinine ratio
Hematocrit	Creatinine	Glucose (qual)	FSH[b]
RBC count	Glucose (fasting)	Protein (qual)	Urine pregnancy test[c]
RDW	Calcium	Blood (qual)	QuantiFERON®-TB Gold In-Tube test (QFT-G)[d]
MCV	Sodium	Ketones	Serology[d] (Hepatitis B and C; HIV-1/2 combination)
MCH	Potassium	Nitrites	Stool sample[e]
MCHC	Chloride	Leukocyte esterase	Serum pregnancy test
Platelet count	Total CO_2 (bicarbonate)	Urobilinogen	
WBC count	AST, ALT	Urine bilirubin	
CD4+ count	Total bilirubin	Microscopy[a]	
Total neutrophils (Abs)	Alkaline phosphatase		
Eosinophils (Abs)	Creatine kinase		
Monocytes (Abs)	Uric acid		
Basophils (Abs)	Albumin		
Lymphocytes (Abs)	Total cholesterol (fasting)		
	LDL-C (fasting)		
	HDL-C (fasting)		
	Triglycerides (fasting)		
	Total protein		
	PT/INR		

Additional Tests[f] (potential Hy's Law)	Immunogenicity, PD and other Biomarker Tests
AST, ALT (repeat)	ADA
Total bilirubin (repeat)	nAb[g]
Albumin (repeat)	pSTAT3 (predose [trough] samples only in phase 1b)
Alkaline phosphatase (repeat)	Total IgG & IgM
Direct bilirubin	Plasma [redacted]
Indirect bilirubin	Plasma [redacted] & [redacted]
GGT	Whole blood for leukocyte immunophenotype (for MAD patients only)
Prothrombin time/international normalized ratio (repeat)	[redacted]
Creatine kinase (repeat)	[redacted]
	[redacted]
	CRP
	Direct Coomb's test[h]

Table 2. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other Safety Tests

Abbreviations: Abs = absolute; ADA = anti-drug antibody; ALT = alanine aminotransferase; CCI; CCI; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C = complement; CD4+ = cluster of differentiation 4; CRP = C-reactive protein; dsDNA = double-stranded deoxyribonucleic acid;; FSH = follicle stimulating hormone; GGT = gamma-glutamyltransferase; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ration; IL-21 = interleukin 21; LDL-C = low-density lipoprotein cholesterol; MAD = multiple ascending doses; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = Mean corpuscular volume; nAb = neutralizing antibody; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; PT = prothrombin time; qual = qualitative; RBC = red blood cell; RDW = RBC distribution width; SAE = serious adverse event; SC = subcutaneous; CCI; TB = tuberculosis.

[a] On all urine samples
[b] At screening only, in women who are amenorrheic for at least 12 consecutive months and under 55 years old
[c] For WOCBP
[d] Screening only
[e] At screening, and if a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium
[f] Additional testing for potential Hy's Law cases only (See Section 6.2.2.6.3)
[g] If patient is positive for ADA
[h] If clinically indicated for hemolytic anemia

6.2.1.1 Pregnancy testing

For WOCBP, a serum pregnancy test will be performed at screening. Following a negative serum pregnancy result at screening, appropriate contraception must be commenced or continued and a further negative urine pregnancy test results will then be required at the baseline visit before the patient may receive the investigational product. Urine pregnancy tests will also be routinely repeated at study drug administration visits prior to study drug administration, at the last follow up visit day (Day 270) and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive pregnancy test or confirmed pregnancy, the patient will be discontinued from study drug, an EOT visit should be performed (Day 180), and a last follow-up visit 90 days after last dose should be scheduled (Day 270). Safety follow-up visit procedures (see Section 5.4) are specified in the Schedule of Assessments (see Table 1 and Table 4).

See Section 6.2.2.7.1 for information on reporting of pregnancies as AEs/SAEs during the study.

6.2.1.2 Tuberculosis Screening

During the screening period, it must be determined and documented that a patient does not have evidence of active or latent or inadequately treated TB per the exclusion criteria (Section 4.5). The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the

3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

6.2.1.2.1 Mycobacterium Tuberculosis Testing Using QuantiFERON Test[40]

QuantiFERON-TB Gold In-Tube (QFT-G) is an *in vitro* diagnostic test using a peptide cocktail simulating ESAT-6, CFP-10, and TB 7.7 proteins to stimulate cells in heparinized whole blood. Detection of INFγ performed by enzyme-linked immunosorbent assay (ELISA) is used to identify *in vitro* responses to these peptide antigens that are associated with Mycobacterium tuberculosis infection. QFT-G is an indirect test for M. tuberculosis infection (including disease) and is intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.

Test results will be reported as positive, negative, or indeterminate. A negative QFT-G test result is required to meet the inclusion criterion. In the case of an indeterminate result, repeat tests should be permitted for the purpose of determining eligibility of patients to enroll in this study. If a repeat test is indeterminate again, the patient is a screen failure. The procedure for using this test and interpreting the results will be described fully in the laboratory manual, which will be provided to Investigators.

6.2.2 Adverse Events

6.2.2.1 Definitions

An AE is defined as any untoward medical occurrence experienced by a study patient, whether or not considered drug related by the principal Investigator.

AEs are unfavorable changes in a general condition, subjective or objective signs or symptoms, worsening of pre-existing concomitant disease, and clinically significant abnormality in laboratory parameters observed in a patient in the course of a clinical study.

Non-serious SLE manifestations or abnormal laboratory results related to SLE disease activity would not be recorded as AEs unless they meet the definition for SAEs (Section 6.2.2.5).

6.2.2.2 Recording of Adverse Events

AEs should be collected and recorded for each patient from the date of the first dose of study drug until the end of their participation in the study, including the safety follow up period.

AEs may be volunteered spontaneously by the study patient, or discovered by the study staff during physical examinations or by asking an open, nonleading question such as ‘How have you been feeling since you were last asked?’ All AEs and any required remedial action will be recorded on the Adverse Events eCRF and Safety Adverse Event Form. The details of the AE, date of AE onset, date of AE outcome, and action

taken for the AE will be documented together with the principal investigator's assessment of the seriousness of the AE and causal relationship to the study drug and/or the study procedure.

All AEs should be recorded individually, using diagnostic terms where possible. If the diagnosis is not established, individual symptoms may be reported. The AEs will subsequently be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

6.2.2.3 Severity of Adverse Events

Each AE will be assessed by the principal Investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03 criteria.[41] When changes in the severity (grade) of an AE occur more frequently than once a day, the maximum severity for the event should be noted for that day. Any change in severity of signs and symptoms over a number of days will be captured by recording a new AE, with the amended severity grade and the date (and time, if known) of the change.

6.2.2.4 Causality of Adverse Events

The principal Investigator will assess the causal relationship between BOS161721 or placebo and the AE. One of the following categories (Table 3) should be selected based on medical judgment, considering the definitions below and all contributing factors.

Table 3. Causality Definitions

Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment (dechallenge[a]) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge[b] procedure if necessary
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors, or other drugs or chemicals)

[a] Dechallenge: Upon discontinuation of a drug suspected of causing an AE, the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation (positive dechallenge), or the symptoms continue despite withdrawal of the drug (negative dechallenge). Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists (for example, as in bone marrow suppression, fixed drug eruptions, or tardive dyskinesia)

[b] Rechallenge: Upon re-administration of a drug suspected of causing an AE in a specific patient in the past, the AE recurs upon exposure (positive rechallenge), or the AE does not recur (negative rechallenge)

An unexpected adverse drug event is any adverse drug event for which the specificity or severity is not consistent with the current IP.

6.2.2.5 Seriousness of Adverse Events

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

- Results in death
- Is life threatening; this means that the patient was at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires hospitalization or prolongation in existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly or birth defect
- Is other important medical event (see below)

Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in inpatient hospitalization
- Development of drug dependency or drug abuse

Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'nonserious' according to the usual criteria.

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are associated with the use of the drug and are serious and unexpected.

6.2.2.6 Adverse Events of Special Interest

AEs of special interest in this study include the following:

1. Anaphylaxis and serious allergic reactions
2. Grades 2 to 5 injection site reaction, including erythema, pain, and induration (see Appendix 6)
3. Drug Induced Liver Injury (DILI) assessed following Hy's Law
4. Malignancy (not including basal cell carcinoma or squamous cell carcinoma of skin)
5. Opportunistic infections such as disseminated histoplasmosis, cryptococcosis, disseminated herpes simplex, disseminated tuberculosis, *Aspergillus* sp., *Candida albicans*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Cytomegalovirus*, *Histoplasma capsulatum*, *Isospora belli*, and *Polyomavirus JC polyomavirus*

6. Cryptosporidiasis

6.2.2.6.1 Anaphylaxis and Serious Allergic Reactions

Anaphylaxis will be defined according to the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria. [42] In the event of anaphylactic reaction or severe/serious hypersensitivity/allergic reaction, the patient must discontinue IP and emergency resuscitation measures implemented. In case of other mild to moderate hypersensitivity reaction, depending on the severity, the Investigator may manage in accordance with the standard-of-care.

Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

- Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus, or flushing, swollen lips-tongue-uvula) and at least 1 of the following:
  a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
  b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
- Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
  a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
  b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  c. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
  d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
- Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
  a. Systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from the patient's baseline

6.2.2.6.2 Injection Site Reactions

Injection site reactions are to be captured and reported as AEs. These will include Grades 2 to 5 injection site erythema, pain, and induration (see Appendix 6), which are also captured as Adverse Events of Special Interest (see Section 6.2.2.6). The Investigator should provide a clear description of the observed or reported AE including location and severity. All concomitant treatments used to treat injection site reactions should be recorded and captured in the eCRF, together with the AE of injection site reactions.

6.2.2.6.3 Potential Drug-Induced Liver Injury

Abnormal values in AST and/or ALT levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of DILI, and as potential Hy's Law cases, and should always be considered important medical events. If symptoms compatible with DILI precede knowledge of serum chemical test abnormalities, liver enzyme measurements should be made immediately, regardless of when the next visit or monitoring interval is scheduled. In some cases, symptoms may be an early sign of injury and although typically less sensitive than serum enzyme elevations, they may indicate a need for prompt serum testing. An increase in liver enzymes should be confirmed by a repeated test within 48 to 72 hours following the initial test, prior to reporting of a potential DILI event. Patients will continue to have weekly or biweekly liver enzyme measurements until resolution or levels return to baseline.

All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.2.2.7.2 for reporting details).

Potential DILI is defined as:

1. ALT or AST elevation > 3 × ULN

AND

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

AND

3. No other immediately apparent possible causes of ALT or AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

The patient should return to the investigational site and be evaluated as soon as possible, include laboratory tests, detailed history, and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, CK, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/International Normalized Ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

Study drug discontinuation is considered if there is marked serum AST or ALT elevation or evidence of functional impairment (as indicated by rising bilirubin or INR, which represent substantial liver injury) that is related to study drug. Discontinuation of treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks

Discontinuation of treatment must occur if:

- ALT or AST > 3 × ULN and (total bilirubin > 2 × ULN or INR > 1.5)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

6.2.2.6.4 Malignancy

The identification of a malignancy event will be made by the study site and communicated to the sponsor or designee. AEs should be reported as serious per the criteria in Section 6.2.2.5.

After the first dose of study drug, when there is a decision to biopsy a potentially malignant tumor, lymph node, or other tissue (with the exception of suspected basal cell/squamous cell), the Investigator and/or consultant(s) should contact the sponsor clinicians or designee to discuss the issue and any decisions as soon as possible. Basal cell carcinoma or squamous cell carcinoma of skin is not considered an AE of special interest.

6.2.2.6.5 Specific Infections

Any diagnosis or suggested diagnosis of opportunistic infections such as disseminated histoplasmosis, cryptococcosis, disseminated herpes simplex, disseminated tuberculosis, *Aspergillus* sp., *Candida albicans*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Cytomegalovirus*, *Histoplasma capsulatum*, *Isospora belli*, or *Polyomavirus JC polyomavirus* will be recorded as AEs of special interest.

Cryptosporidiosis is also considered an AE of special interest. Patients will be evaluated for cryptosporidium in the stool at screening, and as clinically indicated (e.g., watery diarrhea) during the study. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

6.2.2.7 Reporting of Adverse Events

AE reporting will be carried out in accordance with applicable local regulations, including regulatory agency and IRB reporting requirements.

Each AE is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate, and is further outlined in Section 6.2.2.7.2.

6.2.2.7.1 Reporting of Pregnancy

As information is available, a pregnancy diagnosed during the study will be reported within 24 hours to the sponsor via the Pregnancy Notification and Outcome Form, including pregnancy in female patients who received study drug and female partners of male study patients who received study drug. The pregnancy should be followed to term and/or outcome and this outcome should also be reported to the sponsor via the Pregnancy Notification and Outcome Form. Pregnancy itself is not regarded as an AE or SAE unless there is complication.

In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an AE or SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the Investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the Investigator assesses the neonatal death as related or possibly related to exposure to investigational product.

6.2.2.7.2 Reporting of Serious Adverse Events

The principal Investigator is responsible for providing notification to the sponsor of any SAE via the Safety Adverse Event Form, whether deemed study drug related or not, that a patient experiences during their participation in this study within 24 hours of becoming aware of the event.

If an SAE is fatal or life threatening, notification to the sponsor must be made aware immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding cases. In the rare event that the Investigator does not become aware of the occurrence of an SAE immediately (e.g., if an outpatient study patient initially seeks treatment elsewhere), the Investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

The principal Investigator will review each SAE and evaluate the intensity and the causal relationship of the event to the study drug. All SAEs will be recorded from the time of first dose of study drug through the safety follow-up period (up to Day 270).

SAEs occurring after the final follow-up visit and coming to the attention of the principal Investigator must be reported only if there is (in the opinion of the principal Investigator) reasonable causal relationship with the study drug.

As a minimum requirement, the initial notification should provide the following information:

- Study number
- Patient number
- Details of the SAE (verbatim details are sufficient for immediate notification)
- Criterion for classification as 'serious'
- Causality assessment (which may be updated in a follow-up report when sufficient information is available to make this classification)

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (e.g., hospital reports, consultant reports, autopsy reports, etc), with the study patient's personal identifiers removed. All relevant information obtained by the principal Investigator through review of these documents will be recorded and submitted to the sponsor within 24 hours of receipt of the information. If a new Safety Adverse Event Form is submitted, then the principal Investigator must sign and date the form. The sponsor may also request additional information on the SAE, or clarification of omitted or discrepant information from the initial notification, which the principal Investigator or an authorized delegate should submit to the sponsor within 24 hours of the request as possible.

6.2.2.7.3 Reporting of Adverse Events of Special Interest

AEs of special interest will be reported to safety immediately or within 24 hours of the site becoming aware of the event and recorded as such on the Adverse Events eCRF and Safety Adverse Event Form.

Potential DILI will be reported based on specifications mentioned in Section 6.2.2.6.3.

Each AE of special interest is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate, and is further outlined in Section 6.2.2.7.2.

6.2.2.8 Follow Up of Adverse Events

All AEs will be followed up through the safety follow-up visits. All SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the event has resolved, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the principal Investigator and medical monitor, until there is a satisfactory explanation for the changes observed, or until the patient is lost to follow-up.

See Section 6.2.2.7.1 for details related to follow-up of pregnancy. See Section 6.2.2.6.3 for details related to follow-up of potential DILI. See Section 6.2.2.6.4 for details related to follow-up of malignancy.

6.2.3 Vital Signs

Vital signs (blood pressure, heart rate, and body temperature) will be assessed as specified in the Schedule of Assessments (Table 1 and Table 4). Vital signs will be assessed on Day 0 at predose and at Day 0, 1 and 2 hours (± 15 minutes) postdose, as well as on each of the scheduled visit days during the study (excluding PK-only site visits). Supine BP and heart rate recordings will be made after the patient has been recumbent and at rest ≥ 5 minutes. When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

6.2.4 12-Lead Electrocardiograms

ECG will be assessed as specified in the Schedule of Assessments (Table 1 and Table 4). ECG recording will initiate after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws, though timing will be such that PK draws are collected on their scheduled times where possible.

The ECG will include all 12 standard leads and a Lead II rhythm strip on the bottom of the tracing. The ECG will be recorded at a paper speed of 25 mm/second. The following ECG parameters will be collected: PR interval, QRS interval, RR interval, QT interval, and QT interval corrected for heart rate using Fridericia's formula (QTcF).

All ECGs must be evaluated by a qualified physician or qualified designee for the presence of abnormalities and will be captured electronically and retained for future evaluation if required, up to the time of the clinical study report (CSR) completion.

6.2.5 Physical Examinations

The full physical examination will be completed at screening and Day 0. It includes an assessment of general appearance and evaluation of head, eyes, ears, nose, mouth, throat, neck, thyroid, lymph nodes, and extremities, and dermatologic, respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurologic, and psychiatric systems.

The targeted (limited) physical examination will be completed at all other visits as indicated in the Schedule of Assessments (Table 1 and Table 4). It includes evaluation of patient complaints and SLE disease-related issues, and will exclude the genitourinary system.

6.2.6 C-SSRS

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed by Columbia University researchers for the National Institute of

Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment. It is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening.[43]

The C-SSRS evaluation will be performed as specified in the Schedule of Assessments (Table 1 andTable 4). Patients with recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4, or 5 is exclusionary at screening will be excluded from the study. Patients with recent or active suicidal ideation or behavior at subsequent study visits will have responses to the C-SSRS reviewed in detail to assess patient risk, and appropriate consultative mental health services will be provided.

6.2.7 Injection Site Reactions

Patients will be monitored for local injection site reactions as specified in the Schedule of Assessments (Table 1 and Table 4). Local injection site reactions will be assessed at 2 hours postdose at baseline, and predose for each injection after baseline. Injection site reactions should be managed according to the standard of care. Injection site reactions, Grades 2 to 5, are to be reported as AEs of special interest (see Section 6.2.2.7.3).

6.2.8 Immunogenicity

The serum samples to measure the presence of ADA will be collected as specified in the Schedule of Assessments (Table 1 and Table 4). Blood samples (4 mL) to provide approximately 1.5 mL of plasma for anti BOS161721 antibody analysis will be collected into appropriately labeled tubes containing K_2EDTA. The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods. Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only analyzed by a central lab if the patient had a positive ADA on Day 90.

After the first dose, if a patient tests positive in the validated confirmatory ADA assay, a sample from this patient will be further analyzed in the neutralizing antibody (nAb) assay by a central lab.

6.3 Efficacy Assessments

All efficacy assessments will be performed at times defined in the Schedule of Assessments (Table 1 and Table 4).

6.3.1 SLEDAI-2K

The SLEDAI-2K is a validated instrument that measures disease activity in SLE patients at the time of the visit and in the previous 30 days. It is a global index and includes 24 clinical and laboratory variables that are weighted by the type of manifestation, but

not by severity. The total score falls between 0 and 105, with higher scores representing increased disease activity. The SLEDAI-2K has been shown to be a valid and reliable disease activity measure in multiple patient groups. A SLEDAI -2K of 6 or more generally represents moderately to severely active disease.[44]

6.3.2 BILAG 2004

The BILAG-2004 index is an organ-specific 97-question assessment based on the principle of the doctor's intent to treat. Only clinical features attributable to SLE disease activity are to be recorded and based on the patient's condition in the last 4 weeks compared with the previous 4 weeks. It will be scored as not present (0), improved (1), the same (2), worse (3), or new (4). Disease activity is graded separately for 9 body systems to 5 different grades (A to E) as follows: A ("Active") is very active disease, B ("Beware") is moderate activity, C ("Contentment") is mild stable disease, D ("Discount") is inactive now but previously active, and E ("Excluded") indicates the organ was never involved.[44] A shift from BILAG-2004 Grade A or B to a lower grade indicates a clinically relevant change in disease activity as the BILAG-2004 grades mirror the decision points for treatment interventions.

Only Investigators that complete BILAG-2004 training will be allowed to perform the BILAG-2004 assessments. Preferably, the same Investigator should evaluate the patient at each BILAG-2004 assessment from screening to study completion. The Investigator must maintain documentation with descriptive details supporting the BILAG-2004 scoring (e.g., chart, worksheet, clinic notes, and labs) at each visit.

See Appendix 5 for detailed specifications.

6.3.3 PGA of Disease Activity

The PGA is used to assess Investigator's general impression on the patient's overall status of SLE disease activity via visual analogue scale (100 mm) with 0 being "very good, asymptomatic and no limitation of normal activities" with 100 mm being "most severe possible disease ever seen in all SLE patients". PGA worsening is defined as an increase of $\geq$ 30 mm from baseline.

When scoring the PGA, the assessor should always look back at the score from the previous visit.

6.3.4 Composite Endpoints: SRI-4, SRI-5, SRI-6, and BICLA Response

6.3.4.1 SRI-4 Response

The SRI-4 is a composite index of SLE disease improvement that consists of scores derived from the SLEDAI-2K and the BILAG 2004 Index. Response based on the SRI-4 is defined by:

1) ≥ 4-point reduction in SLEDAI-2K global score; 2) no new severe disease activity (BILAG A organ score) or more than 1 new moderate organ score (BILAG B); and 3) no

deterioration from baseline in the PGA by ≥ 30 mm. The SRI-4 response in patients with moderate to severe SLE is associated with broad improvements in clinical and patient-reported outcomes.[45]

6.3.4.2 SRI-5 and SRI-6 Response

Like the SRI-4, the SRI-5 and SRI-6 are composite indices of SLE disease improvement that consists of scores derived from the SLEDAI-2K and the BILAG 2004 Index. However, the SRI-5 and SRI-6 are computed with a minimal five-point or six-point improvement in SLEDAI-2K being required, respectively.[46]

6.3.4.3 BICLA Response

The BICLA is a responder index developed to measure response to therapy, and it includes scores from the BILAG, SLEDAI-2K, and PGA. BICLA response is defined as: 1) at least 1 gradation of improvement in baseline BILAG 2004 scores in all body systems with moderate disease activity at entry (e.g., all B [moderate disease] scores falling to C [mild], or D [no activity]); 2) no new BILAG A or more than 1 new BILAG B scores; 3) no worsening of total SLEDAI-2K score from baseline; 4) ≤ 10% deterioration in PGA score; and 5) no treatment failure.[44] It is driven primarily by the BILAG, and has been used in phase 2 and 3 mAb studies.[47]

For the endpoints of BICLA response at Days 210, 240, and 270, patient scores will be completed and response determined.

6.3.5 CLASI Response

The CLASI is a comprehensive tool for assessment of disease activity and damage in cutaneous lupus, shown to be valid, reliable, and sensitive to changes in disease activity.[48] Response is defined as 50% improvement from baseline in “A” or “B” scores. This assessment will be applied to all patients who have cutaneous disease activity.

For the secondary efficacy endpoint of CLASI response at Day 210, patient scores on MAD and POC studies will be compared with baseline for 50% improvement.

6.3.6 ACR-28 Joint Count

The ACR-28 joint count will evaluate the number of tender and swollen joints in the shoulder, elbow, wrist, hand, knee joints. Joints of the feet are excluded.

6.4 Other Variables

6.4.1 SLICC/ACR Damage Index

The SLICC/ACR damage index is a validated instrument to assess damage, defined as irreversible impairment, continuously persistent for 6 months (ascertained by clinical assessment), occurring since the onset of lupus, and it is based on a weighted scoring system. This index records damage occurring in patients with SLE regardless of cause,

with demonstrated content, face, criterion, and discriminant validity.[49] It will be performed on Days 0 and 180.

6.4.2 PROs

Patients should be encouraged to complete the PROs at the clinic at the beginning of the study visit prior to any clinical assessments. A member of the staff should be available if a patient requires further instruction and to review the PRO questionnaires for completeness prior to leaving the clinic. The PROs include the CCI and the CCI and will be assessed as specified in the Schedule of Assessments (Table 1 and Table 4).

CCI .[50]

CCI .

6.5 Pharmacokinetic Assessments

During the MAD phase 1b (all sites) and POC phase 2 (select sites only) parts of the study, blood samples for PK analysis of BOS161721 or placebo concentration will be collected according to Table 4 and Table 1.

Plasma concentrations of BOS161721 will be measured using a validated immunoassay. The PK parameters will be calculated from the plasma concentration actual time profiles.

6.6 Pharmacodynamic Assessments

Blood samples for PD parameters (plasma) will be collected at times indicated in the Schedule of Assessments (Table 1 and Table 4) for each of the following parameters:

- pSTAT3 (predose [trough] samples only phase 1b)
- Antibodies: CCI
- Plasma complement (CCI)
- Plasma CCI and CCI
- Whole blood for leukocyte immunophenotype (for MAD patients only)

6.7 Pharmacokinetic/Pharmacodynamic Relationship

Evidence of any PK/PD relationships will be evaluated between BOS161721 plasma concentrations and the available PD endpoints and biomarkers.

6.8 Protocol Deviations

Protocol deviations will be documented during the study.

7 STUDY DRUG MANAGEMENT

7.1 Description

7.1.1 Formulation

CCI [redacted]

CCI [redacted]

Additional information regarding dose preparation will be provided in a separate Pharmacy Manual.

7.1.2 Storage

All supplies of BOS161721 or placebo must be stored in accordance with the manufacturer's instructions. BOS161721 or placebo will be stored in a securely locked area, accessible to authorized persons only, until needed for dosing.

Information regarding storage and dose preparation will be provided in a separate Pharmacy Manual.

7.2 Packaging and Shipment

Investigational medicinal products will be supplied by Boston Pharmaceuticals, Inc. Investigational medicinal products will be packaged and labeled according to applicable local and regulatory requirements.

7.3 Dose and Administration

Details of dosing are provided in Section 3.1.

Each unit dose will be prepared by a qualified staff member. The vials of investigational product (IP) will appear identical and will have a "blinded" label on the vials that will state CCI mg or placebo. When the site goes into the IWRS to request the patient kit(s), the IWRS will assign the appropriate number of kits (regardless of assignment to placebo or active treatment) per the dose (i.e., CCI [redacted]). If a patient is randomized to the placebo arm, they will receive the matching number of kits.

The designated staff member (or designee under the direction of the designated staff member) will dispense BOS161721 or placebo for each patient according to the protocol, randomization list, and Pharmacy Manual, if applicable.

After receiving sponsor approval in writing, the investigational site is responsible for returning all unused or partially used BOS161721 or placebo to the sponsor or designated third party or for preparing BOS161721 or placebo for destruction via incineration.

Further details are found in a separate Pharmacy Manual.

7.4 Accountability

The Principal Investigator or designee is responsible for maintaining accurate accountability records of BOS161721 or placebo throughout the clinical study. The drug accountability log includes information such as, randomization number, amount dispensed, and amount returned to the pharmacy (if any). Used investigational product returned to the pharmacy may be maintained in an ambient condition. Unused product should follow the instructions in the Pharmacy Manual. The used product that is returned should be marked as ‘returned’ and kept separate from the products not yet dispensed.

All dispensing and accountability records will be available for sponsor review after database lock procedures are completed. During safety monitoring, the drug accountability log will be reconciled with the products stored in the pharmacy.

7.5 Prohibited Concomitant Therapy

Prohibited concomitant medications are discussed in Section 4.6 and Appendix 4 will be listed as protocol violations if taken when not permitted.

7.6 Compliance

Dosing will be performed by trained, qualified personnel designated by the principal Investigator. The date and time of dosing will be documented on each dosing day. Comments will be recorded if there are any deviations from the planned dosing procedures.

8 STATISTICS

The following analyses are planned:

- An IA will be performed during the last cohort of the MAD portion to determine dose selection for the POC part of the study.
- An additional analysis may be performed for the MAD portion of the study when all MAD patients have completed the safety follow-up or withdrawn from the study, and

prior to final analysis. Data from the POC part of the study will be excluded from this additional analysis.

- The final analysis will be performed when all patients have completed the POC safety follow-up or withdrawn from the study.
- Safety analyses will be performed for DMC reviews throughout the study to evaluate dose escalation decisions and accumulating safety data. The frequency and details of the content and format of the safety review meetings will be described in the SAP and/or DMC charter.

All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9 or higher.

The following standards will be applied for the analysis unless otherwise specified. Data will be summarized descriptively by treatment and overall for each study portion. For the MAD part of the study, BOS161721 will be summarized overall and by each dose level, and placebo patients from each cohort will be combined. Select parameters may be summarized using patients from both study parts. Statistical testing will be performed on data from the phase 2 portion only.

Continuous data will be summarized using number, mean, standard deviation (SD), 25th and 75th percentiles, minimum, median, and maximum. Categorical data will be summarized by treatment group using frequency tables (number and percentage). Time to event data will be summarized using counts, medians, 25th and 75th percentiles, and standard error. All data will be listed for all patients.

Statistical inference will be based on a 2-tailed test with an overall 0.10 level of significance, unless stated otherwise.

The effects of noncompliance, background therapy use, treatment discontinuations, premature withdrawal from study and covariates will be assessed to determine the impact on the general applicability of results from this study. Exploratory analyses of the data will be conducted as deemed appropriate. Any deviations from the planned analyses will be described and justified in the final integrated CSR.

Protocol deviations and prohibited medications that define medication failures will be fully assigned and documented before database lock and unblinding.

Further details of the analysis, including the handling of missing data, transformations and other data handling procedures will be provided in the SAP.

8.1 Sample Size

Sample size in the phase 1b part of the study is based on operational consideration.

The sample size in the phase 2 portion is based on the primary endpoint, SRI-4 Response at Day 210. Based on efficacy data from a recently completed study with Ustekinumab[51], where the primary endpoint was also SRI-4, the sample size in the phase 2 part of the BOS161721-02 study is set at 96 evaluable patients. In the

Ustekinumab study of 102 patients, a statistically significant difference in SRI-4 response was shown in favor of Ustekinumab (62% of Ustekinumab treated patients achieved SRI-4 response vs. 33% in patients receiving placebo). The Ustekinumab phase 2 study is an appropriate comparator to BOS161721-02 because both studies share the same primary endpoint of SRI-4 response and BOS161721 and Ustekinumab have overlapping mechanisms of action (T follicular helper and Th17 cell biology).

Approximately 110 additional patients will be randomized in a 2:1 ratio to BOS161721 versus placebo to achieve approximately 96 evaluable patients in the FAS of the phase 2 portion. This assumes 14 patients will drop prior to having received treatment or having completed a post-baseline efficacy measure. Enrollment and randomization will be monitored in a blinded fashion and may be increased if needed to ensure at least 96 evaluable patients are randomized into the FAS.

A total of 96 evaluable patients randomized provides 80% power to detect a treatment difference of 29% in SRI-4 response rates at Day 210, based on a targeted 2-sided significance level of 10% and using a 2-sided Pearson's chi-squared test. This assumes a response rate of 62% for BOS161721 and 33% for placebo.

8.2 Statistical Methods

8.2.1 Analysis Populations

The primary efficacy analysis will be based on the FAS, defined as all patients who receive at least 1 dose (partial or complete) of study treatment and have at least 1 evaluable post-baseline efficacy evaluation. FAS analyses will be conducted on the basis of the randomized treatment.

A per protocol (PP) analysis set may be defined to exclude major protocol violations from the efficacy analysis. The PP Population will include all patients from the FAS except those with major violations to the protocol deemed to impact the analysis of the primary endpoint. These violations will be identified based on blinded data prior to study unblinding. PP analyses will be conducted on the basis of the randomized treatment.

Safety analyses will be based on the safety analysis set (SS), defined as all patients who receive at least 1 dose (partial or complete) of study treatment. Safety analyses will be conducted on the basis of actual treatment received.

Pharmacokinetic analysis will be conducted on the PK analysis set, defined as the FAS with sufficient concentration data for the calculation of PK parameters.

8.2.2 Demographics and Baseline Characteristics

Baseline and patient characteristics will be summarized using all randomized patients.

8.2.3 Primary Efficacy Endpoint(s)

The proportion of patients who achieve a SRI-4 response at Day 210 will be assessed via Pearson's chi-squared analysis. The primary efficacy endpoint will be analyzed using the FAS and if needed repeated in the PP analysis set. Missing values will be addressed by employing a last observation carried forward (LOCF) analysis. Other imputation methods may be employed as a sensitivity analysis and will be described in the SAP. Analyses based on observed values may also be performed.

Exploratory subgroup analyses assessing impact of baseline factors such as baseline disease severity, background therapy, race, geography, baseline serologic activity and other characteristics may be performed. Additional exploratory analyses of disease activity endpoints may be performed based on emerging data.

Patients that received prohibited medications or unallowable CS usage as described in Section 4.6 will be considered "medication failures" and will be treated as statistical non-responders at time points on or following the first date of prohibited medication or unallowable CS usage for the primary efficacy analysis. The determination of medication failures will be reviewed using blinded data and finalized prior to unblinding.

The superiority of BOS161721 relative to placebo will be evaluated. If the proportion of SRI-4 responders for the selected POC dose in BOS161721 arm is higher than that of the placebo arm, then BOS161721 will be considered superior to placebo if the 2-sided p-value is < 0.10. Secondary and exploratory endpoints for this POC portion will be evaluated based on the same statistical hypothesis.

8.2.4 Secondary Efficacy Endpoint(s)

Binary efficacy endpoints will be assessed via Pearson's chi-squared analysis. Continuous efficacy endpoints will be assessed via analysis of variance (ANOVA) or analysis of covariance (ANCOVA) and treatment will be compared using the F-test. Repeated measures mixed models may be performed to evaluate data collected at each visit and overall. Time-to-event endpoints will be assessed via Kaplan-Meier methodology and treatment will be compared using the log-rank test. The secondary efficacy endpoints will be analyzed on the FAS and if needed repeated in the PP analysis set. Details including handling of missing data and "medication failures" will be available in the SAP.

8.2.5 Analysis of Safety

8.2.5.1 Safety Analysis

Safety analyses will be performed on the SS. AE data will be coded to system organ class and preferred term using MedDRA. The number and percentage of patients experiencing any treatment-emergent AE, overall, and by system organ class and preferred term, will be tabulated. Treatment-emergent AEs will also be summarized by severity and relationship.

Concomitant medications will be coded using the WHO Drug dictionary. Observed values and changes from baseline in vital signs, ECG readings, and hematology and clinical chemistry parameters will be summarized at each individual visit.

8.2.6 Pharmacokinetic and Pharmacodynamic Data

8.2.6.1 Analysis of Pharmacokinetic Data

PK parameters will be calculated from concentration data collected during the MAD phase 1b portion of the study using non-compartmental analysis and include the following:

- C_{max}, T_{max}, AUC, $t_{½}$, CL, V_d

The PK parameter data will be listed and summarized descriptively in tabular format.

If data permit, the following analyses will be performed for plasma BOS161721 concentration data:

- A listing of all plasma BOS161721 concentrations by patient at actual times post dose;
- A descriptive summary of plasma BOS161721 concentrations. Summary statistics of geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum will be tabulated by study days with PK assessments.

8.2.6.2 Analysis of Pharmacodynamic Data

The PD parameter data will be listed and summarized descriptively in tabular format.

Exploratory analyses examining the relationship between PD parameters and PK concentration and PK parameters will be performed.

8.2.6.3 Population Pharmacokinetic Analysis or PK/PD Modeling

Plots of individual patient values for each relevant PD parameter on Y-axis and each relevant PK parameter on X-axis will be examined for relationship. If relationships are revealed by these diagnostic plots, PK and PD data from this study may be analyzed using modeling approaches to describe the relationship and may also be pooled with data from other studies to investigate any association between BOS161721 exposure and biomarkers or significant safety endpoints.

8.3 Interim Analysis and Power

One IA is planned for this study and will be conducted at the time of the POC decision for dose selection.

Since there is no IA during the POC part of the study, there is no impact on the type 1 error.

9 ETHICS AND RESPONSIBILITIES

9.1 Good Clinical Practice

The procedures set out in this protocol are designed to ensure that the sponsor and the principal Investigator abide by the principles of the International Council for Harmonisation (ICH) guidelines on GCP and the Declaration of Helsinki (Version 2013). The clinical study also will be carried out in the keeping with national and local legal requirements (in accordance with US IND regulations [21 CFR 56]).

9.2 DMC

This study will use an external DMC. The DMC is an independent committee established to provide oversight of safety considerations in study and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of enrolled patients and those yet to be recruited to the trial as well as for the continuing validity and scientific merit of the study results. The DMC is charged with assessing such actions in light of an acceptable benefit/risk profile for BOS161721. The recommendations made by the DMC (i.e., dose escalation, etc.) will be forwarded to the sponsor for final decision. The sponsor will forward such decisions, which may include summaries of safety data which are not endpoints, to regulatory authorities, as appropriate.

The sponsor will appoint a DMC for the periodic review of available study data. The DMC is an independent group of experts that advises the sponsor and the study Investigators. The members of the DMC serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DMC are to (1) periodically review and evaluate the accumulated study data for participant safety, study conduct, and progress, (2) make recommendations to the sponsor concerning the continuation, modification, or termination of the study and (3) suggest dose for POC portion of the study as described in Section 3.1.1.3.

The DMC considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. The DMC is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking (unblinding), and voting procedures prior to initiating any data review. The DMC is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

The DMC will have access to unblinded treatment information during the clinical trial. Details regarding management and process of this committee are found in the DMC Charter.

The DMC may recommend termination of BOS161721 treatment arm or the entire BOS161721 MAD/POC trial for any safety concern that is felt to outweigh potential

benefits. The recommendation must be supported by the sponsor as indicated in the DMC Charter.

9.3 Institutional Review Board/Independent Ethics Committee

Independent Ethics Committees/IRB must meet the guidelines set out by the U. S. Food and Drug Administration (FDA) and conform to local laws and customs where appropriate. Written IRB/IEC approval for the protocol and the signed ICF must be obtained and transmitted to Boston Pharmaceuticals or representative before the study can be initiated. The IRB/IEC must be informed of and approve all protocol amendments. The Investigator will ensure that this study is conducted in full conformance with all applicable local and regional laws and regulations. The complete text of the World Medical Association Declaration of Helsinki is given in Appendix 2.

9.4 Informed Consent

Before each patient undergoes any protocol required assessments or procedure, the written informed consent will be obtained according to the regulatory and legal requirements of the participating country. As part of this procedure, the principal Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study patient should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. The principal Investigator or designee will provide the sponsor with a copy of the IRB-approved ICF prior to the start of the study.

The informed consent document must be signed and dated; 1 copy will be handed to the patient and the principal Investigator will retain a copy as part of the clinical study records. The principal Investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

If the informed consent document is revised, it must be reviewed and approved by the responsible IRB/IEC. Patients currently enrolled may need to sign this revision (based on IRB/IEC requirements) and all future patients enrolled in the clinical study will be required to sign this revised ICF.

9.5 Records Management

The principal Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The principal Investigator or designee will cooperate with the sponsor’s representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The principal Investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each patient receiving BOS161721 or placebo.

The principal Investigator will allow sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB to have direct access to all documents pertaining to the study.

Electronic case report forms are required and should be completed for each randomized patient. It is the principal Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported on the patients' eCRF. Electronic case report forms should be completed in a timely fashion to support the study timelines. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status. The principal Investigator or designated representative should complete and the principal Investigator should verify the source documents as the information is collected. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The principal Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes.

9.6 Source Documentation

The documents that will form the source data for the clinical study (e.g., patient charts, laboratory reports) must be defined and documented in the in-house study master file prior to the start of the study. Data on the eCRFs which will be checked against source data during monitoring visits must also be defined and documented in the in-house study master file including the percentage of each of the source data to be verified and the percentage of patients' eCRFs to be monitored.

9.7 Study Files and Record Retention

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of BOS161721. However, these documents should be retained for a longer period if required by the applicable legal requirements.

10 AUDITING AND MONITORING

Throughout the course of the study, the study monitor will make frequent contacts with the Investigator. This will include telephone calls and on-site visits. The study will be routinely monitored to ensure compliance with the study protocol and the overall quality of data collected. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor may periodically request review of the Investigator study file to assure the completeness of documentation in all respects of clinical study conduct. The study monitor will verify that each patient has proper consent documentation from the patient and/or patient's authorized representative for study procedures and for the release of medical records to the sponsor, FDA, other regulatory authorities, and the IRB. The study monitor will also verify that assent was obtained for patients not capable of providing informed consent or that documentation is provided by the Investigator explaining why the patient was unable to provide assent. The Investigator or appointed delegate will receive the study monitor during these on-site visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the Investigator will permit inspection of the study files by authorized representatives of the regulatory agencies. On completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

Throughout the course of the study, the medical monitor will determine eligibility of all screened patients, will address any medical issues that might arise, clarify medical questions, review patient safety data (e.g., AE/SAE, laboratory, and ECG), and partner with the study team in the overall study management. The study medical monitoring plan will document additional details of the study medical oversight and monitoring.

11 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by Boston Pharmaceuticals. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the Investigator must await approval before implementing the changes. Boston Pharmaceuticals will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the Investigator, and/or Boston Pharmaceuticals, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the patient and/or has an impact on the patient's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for patients enrolled in the study before continued participation.

12 STUDY REPORT AND PUBLICATIONS

Boston Pharmaceuticals is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

By signing the protocol, the principal Investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the competent authorities will be notified of the principal Investigator's name, address, qualifications, and extent of involvement.

The principal Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted and obtained approval from the sponsor in advance.

13 STUDY DISCONTINUATION

Both Boston Pharmaceuticals and the principal Investigator reserve the right to terminate the study at the Investigator's site at any time. Should this be necessary, Boston Pharmaceuticals or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the principal Investigator will inform the IRB/IEC of the same. In terminating the study Boston Pharmaceuticals and the principal Investigator will assure that adequate consideration is given to the protection of the patients' interests.

14 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Boston Pharmaceuticals, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial or to comply with regulatory requirements. However, authorized regulatory officials, IRB/IEC personnel, Boston Pharmaceuticals, and its authorized representatives are allowed full access to the records.

Identification of patients and eCRFs shall be by initials, birthdate, or patient number. Documents that identify the patient (e.g., the signed informed consent document) must be maintained in confidence by the principal Investigator. If required, the patient's full name may be made known to an authorized regulatory agency or other authorized official.

15 REFERENCES

1 Urowitz MB, Gladman DD. How to improve morbidity and mortality in systemic lupus erythematosus. Rheumatology 2000;39:238-44.

2 Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Morbidity and Mortality in Systemic Lupus Erythematosus During a 10-Year Period. Medicine 2003;82(5):299-308.

3 Pons-Estel GJ, Alarcón GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. Semin Arthritis Rheum. 2010;39(4):257. Epub 2009 Jan 10.

4 Kanta H, Mohan C. Three Checkpoints in lupus development: central tolerance in adaptive immunity, peripheral amplification by innate immunity, and end-organ inflammation. Genes and Immunity 2009;10:390-6.

5 Dall'Aqua WF, Kiener PA, Wu H. Properties of Human IgG1s Engineered for Enhanced Binding to the Neonatal Fc Receptor (FcRn). J Biol Chem. 2006 Aug 18, 281(33):23514-24.

6 Spolski R, Leonard WJ. The Yin and Yang of interleukin-21 in allergy, autoimmunity and cancer. Curr Opin Immunol. 2008a;20:295-301.

7 Asao H, Okuyama C, Kumaki S, Ishii N, Tsuchiya S, Foster D, et al. Cutting edge: the common gamma-chain is an indispensable subunit of the IL-21 receptor complex. J Immunol. 2001;167:1-5.

8 Habib T, Senadheera S, Weinberg K, Kaushansky K. The common gamma chain (gamma c) is a required signaling component of the IL-21 receptor and supports IL-21-induced cell proliferation via JAK3. Biochemistry. 2002;41:8725-31.

9 Spolski R, Leonard WJ. Interleukin-21: basic biology and implications for cancer and autoimmunity. Annu Rev Immunol. 2008b;26:57-79.

10 Puga I, Cols M, Barra CM, He B, Cassis L, Gentile M, et al. B-cell-helper neutrophils stimulate the diversification and production of immunoglobulin in the marginal zone of the spleen. Nat Immunol. 2011;13(2):170-80.

11 Costanzo A, Chimenti MS, Botti E, Caruso R, Sarra M, Monteleone G. IL-21 in the pathogenesis and treatment of skin diseases. J Dermatol Sci. 2010;60(2):61-6.

12 Avery DT, Bryant VL, Ma CS, de Waal Malefy R, Tangye SG. IL-21-induced isotype switching to IgG and IgA by human naive B cells is differentially regulated by IL-4. J Immunol. 2008;181:1767-79.

13 Rasmussen TK, Andersen T, Bak, RO, Yiu G, Sorensen CM, Stengaard-Pedersen K, et al. Overexpression of microRNA-155 increases IL-21 mediated STAT3 signaling and IL-21 production in systemic lupus erythematosus. Arthritis Research & Therapy 2015;17(154)

14 Ettinger R, Kuchen S, Lipsky PE. The role of IL-21 in regulating B-cell function in health and disease. Immunol Rev. 2008;223:60-86.

15 Caprioli F, Sarra M, Caruso R, Stolfi C, Fina D, Sica G, et al. Autocrine regulation of IL-21 production in human T lymphocytes. J Immunol. 2008;180(3):1800-7.

16 Yang L, Anderson DE, Baecher-Allan C, Hastings WD, Bettelli E, Oukka M, et al. IL-21 and TGF-beta are required for differentiation of human T(H)17 cells. Nature. 2008;454(7202):350-2.

17 Tangye SG, Ma CS, Brink R, Deenick EK. The good, the bad and the ugly - TFH cells in human health and disease. Nat Rev Immunol. 2013;13(6):412-26.

18 Fantini MC, Rizzo A, Fina D, Caruso R, Becker C, Neurath MF, et al. IL-21 regulates experimental colitis by modulating the balance between Treg and Th17 cells. Eur J Immunol. 2007;37(11):3155-63.

19 Peluso I, Fantini MC, Fina D, Caruso R, Boirivant M, MacDonald TT, et al. IL-21 counteracts the regulatory T-cell-mediated suppression of human CD4+ T lymphocytes. J Immunol. 2007;178(2):732-9.

20 Hippen KL, Bucher C, Schirm DK, Bearl AM, Brender T, Mink KA, et al. Blocking IL-21 signaling ameliorates xenogeneic GVHD induced by human lymphocytes. Blood. 2012;119(2):619-28.

21 Davis ID, Skrumsager BK, Cebon J, Nicholaou T, Barlow JW, Moller NP, et al. An open- label, two-arm, phase I trial of recombinant human interleukin-21 in patients with metastatic melanoma. Clin Cancer Res. 2007;13:3630-6.

22 Frederiksen KS, Lundsgaard D, Freeman JA, Hughes SD, Holm TL, Skrumsager BK, et al. IL-21 induces in vivo immune activation of NK cells and CD8(+) T-cells in patients with metastatic melanoma and renal cell carcinoma. Cancer Immunol Immunother. 2008;57(10):1439-49.

23 Karrich JJ, Jachimowski LC, Nagasawa M, Kamp A, Balzarolo M, Wolkers MC, et al. IL-21- stimulated human plasmacytoid dendritic cells secrete granzyme B, which impairs their capacity to induce T-cell proliferation. Blood. 2013;121(16):3103-11.

24 Lindner S, Dahlke K, Sontheimer K, Hagn M, Kaltenmeier C, Barth TF, et al. Interleukin-21-induced granzyme B-expressing B-cells infiltrate tumors and regulate T-cells. Cancer Res. 2013;73(8):2468-79.

25 Monteleone G, Caruso R, Fina D, Peluso I, Gioia V, Stolfi C, et al. Control of matrix metalloproteinase production in human intestinal fibroblasts by interleukin 21. Gut. 2006;55(12):1774-80.

26 Nakou M, Papadimitraki ED, Fanouriakis A, Bertsias GK, Choulaki C, Goulidaki N, et al. Interleukin-21 is increased in active systemic lupus erythematosus patients and contributes to the generation of plasma B-cells. Clin Exp Rheumatol. 2013;31(2):172-9.

27 Li Q, Liu Z, Dang E, Jin L, He Z, Yang L, et al. Follicular helper T-cells (Tfh) and IL-21 involvement in the pathogenesis of bullous pemphigoid. PLoS One. 2013;8(7):e68145.

28 Liu R, Wu Q, Su D, Che N, Chen H, Geng L, et al. A regulatory effect of IL-21 on T follicular helper-like cell and B-cell in rheumatoid arthritis. Arthritis Res Ther. 2012;14(6):R255.

29 Kang KY, Kim HO, Kwok SK, Ju JH, Park KS, Sun DI, et al. Impact of interleukin-21 in the pathogenesis of primary Sjögren's syndrome: increased serum levels of interleukin-21 and its expression in the labial salivary glands. Arthritis Res Ther. 2011;13(5):R179.

30 Terrier B, Geri G, Chaara W, Allenbach Y, Rosenzwajg M, Costedoat-Chalumeau N, et al. Interleukin-21 modulates Th1 and Th17 responses in gianT-cell arteritis. Arthritis Rheum. 2012a;64(6):2001-11.

31 Terrier B, Costedoat-Chalumeau N, Garrido M, Geri G, Rosenzwajg M, Musset L, et al. Interleukin 21 correlates with T-cell and B-cell subset alterations in systemic lupus erythematosus. J Rheumatol. 2012b;39(9):1819-28.

32 International Conference on Harmonisation. Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6 (R1). 2011.

33 Wang W, Wang EQ, Balthasar JP. Monoclonal Antibody Pharmacokinetics and Pharmacodynamics. Clin Pharm & Ther 2008; 84(5):548-58.

34 Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. Journal of Allergy and Clinical Immunology 2006;117:391–7.

35 Elsaesser H, Sauer K, Brooks DG. IL-21 is required to control chronic viral infection. Science. 2009;324(5934):1569-72.

36 Kotlarz D, Zietara N, Uzel G, Weidemann T, Braun CJ, Diestelhorst J, et al. Loss-of-function mutations in the IL-21 receptor gene cause a primary immunodeficiency syndrome. J Exp Med. 2013;210(3):433-43.

37 Hunter PR, Nichols G. Epidemiology and clinical features of Cryptosporidium infection in immunocompromised patients. Clinical microbiology reviews. 2002;15(1):145-54.

38 Desjardins M, Mazer BD. B-cell memory and primary immune deficiencies: interleukin-21 related defects. Curr Opin Allergy Clin Immunol. 2013;13(6):639-45.

39 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron.1976;16(1):31-41.

40 Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, US: http://www. cdc. gov/mmwr/preview/mmwrhtml/rr5415a4. htm.

41 NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, available at https://evs. nci. nih. gov/ftp1/CTCAE/About. html.

42 Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. Journal of Allergy and Clinical Immunology 2006;117:391–7.

43 Posner K, Melvin G a, Stanley B, Oquendo M a, Gould M. Factors in the assessment of suicidality in youth. CNS Spectr. 2007;12(2):156-162.

44 Castrejon I, Tani C, Jolly M, Huang A, Mosca M. Indices to assess patients with systemic lupus erythematosus in clinical trials, long-term observational studies, and clinical care. Clin Exp Rheumatol 2014; 32(85):S85-95.

45 Furie R, Wang L, Drappa J, Illei G. Systemic Lupus Erythematosus (SLE) Responder Index [SRI(4)] Response Is Associated with Global Benefit in Patients with Moderate to Severe SLE [abstract]. Arthritis Rheumatol. 2016; 68 (suppl 10).

46 Thanou A, Chakravarty E, James JA, Merrill JT. Which outcome measures in SLE clinical trials best reflect medical judgment? Lupus Science & Medicine 2014;1:e000005. doi:10.1136/lupus-2013-000005.

47 Wallace DJ, Kalunian K, Petri MA, Strand V, Houssiau FA, Pike M,et al. Efficacy and safety of epratuzumab in patients with moderate/severe active systemic lupus erythematosus: results from EMBLEM, a phase IIb, randomised, double-blind, placebo-controlled, multicentre study. Ann Rheum Dis 2014;73:183-90.

48 Albrecht J, Taylor L, Berlin JA, Dulay S, Ang G, Fakharzadeh S. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): An Outcome Instrument for Cutaneous Lupus Erythematosus. J Invest Derm. 2005;125(5):889-94.

49 Stoll T, Seifert B, Isenberg DA. SLICC/ACR Damage Index is Valid, and Renal and Pulmonary Organ Scores are Predictors of Sever Outcome in Patients with Systemic Lupus Erythematosus. Br J Rheumatol.1996;35:248-54.

50 CCI [redacted]

51 Van Vollenhoven RF, Hahn BH, Tsokos GC, et al. Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study. Lancet. 2018;392(10155):1330-1339.

16 APPENDICES

16.1 Appendix 1: Names of Study Personnel

Sponsor:	Boston Pharmaceuticals 55 Cambridge Parkway Suite 400 Cambridge, MA 02142, USA
Medical Monitor:	PPD
Clinical Research Organizations:	PPD
Bioanalytical Laboratory:	PPD
Central Laboratory:	PPD

16.2 Appendix 2: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles For Medical Research Involving Human Subjects.

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

It is the duty of the physician to promote and safeguard the health of the people. The physician’s knowledge and conscience are dedicated to the fulfillment of this duty.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subject".

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic, and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility, and quality.

In current medical practice and in medical research, most prophylactic, diagnostic, and therapeutic procedures involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Research Investigators should be aware of the ethical, legal, and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal, or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the Investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any SAEs. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a subject of the research, even though the subject has given consent.

Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

The subjects must be volunteers and informed participants in the research project.

The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the subject’s information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the Investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the Investigator must obtain that assent in addition to the consent of the legally authorized representative.

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

Both authors and publishers have ethical obligations. In publication of the results of research, the Investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic, or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the subjects who are research subjects.

The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists.

At the conclusion of the study, every subject entered into the study should be assured of access to the best-proven prophylactic, diagnostic, and therapeutic methods identified by the study.

The physician should fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study must never interfere with the subject-physician relationship.

In the treatment of a subject, where proven prophylactic, diagnostic, and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the subject, must be free to use unproven or new prophylactic, diagnostic, and therapeutic measures, if in the physician’s judgment it offers hope of saving life, re-establishing health, or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases,

new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

16.3 Appendix 3: Commonly Used Corticosteroid Equivalents

Medication	Prednisone Dose Equivalence
Prednisone	1 mg
Cortisone	5 mg
Hydrocortisone	4 mg
Prednisolone	1 mg
Methylprednisolone	0.8 mg
Triamcinolone	0.8 mg
Budesonide	0.25 mg
Dexamethasone	0.16 mg
Bethamethasone	0.16 mg

16.4 Appendix 4: Medication Washout Periods

WASHOUT TIMES OF MEDICATIONS BASED ON 5 HALF-LIVES

Medication	Discontinuing Prior to Signing Consent
Abatacept (CTLA4Ig)	24 weeks
Alefacept	12 weeks
AMG 623 (blisibimod)	24 weeks
Anifrolumab	12 weeks
Atacicept (TACI-Ig)	12 weeks
Belimumab	24 weeks
Cyclophosphamide	24 weeks
Cyclosporine (except for CSA eye drops)	4 weeks for oral and 8 weeks for topical
Danazol	4 weeks
Dapsone	4 weeks
Eculizumab	12 weeks
Efalizumab	12 weeks
Epratuzumab	24 weeks
Intravenous globulin	4 weeks
Leflunomide	8 weeks (4 weeks for washout with cholestyramine)
Lenalidomide with cholestiramine	8 weeks
Lupuzor	12 weeks
Memantine	4 weeks
Natalizumab	24 weeks
Ocrelizumab	48 weeks (or 24 weeks with recovery of B cell)
Pimecrolimus	4 weeks
Plasmapheresis	24 weeks
Retinoids (oral or topical)	4 weeks
Rituximab	48 weeks (or 24 weeks with recovery of B cell)
Sirolimus	4 weeks
Tacrolimus	4 weeks
Thalidomide	8 weeks
Tocilizumab	12 weeks

16.5 Appendix 5: BILAG-2004 (Study-Specific Modified Criteria)

CCI

16.6 Appendix 6: Injection Site Reaction Grading Scale

Adverse event Injection site reaction	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; Lipodystrophy; Edema; phlebitis	Ulceration or necrosis; Severe tissue damage; Operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	-
Rash maculopapular/Erythema/Induration Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally, and associated with pruritus.	Macules/papules covering < 10% BSA with or without symptoms (e.g., pruritus, burning, tightness) Erythema covering < 10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10% - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL; Erythema 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering > 30 % BSA with or without associated symptoms; limiting self-care ADL Erythema covering > 30 % BSA with or without associated symptoms; limiting self-careADL	-	-

ADL = active daily living

16.7 Appendix 7: Opioid Oral Morphine mg Equivalents of Commonly Used Opioids

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

Note that this list is not comprehensive. If an opioid is being used which is not in this list, please see the appropriate conversion factor below.

Opioid Oral Morphine Equivalent Conversion Factors[a,b]

Type of Opioid (strength in units)	MME Conversion Factor
Buprenorphine film/table[c] (mg)	30
Buprenorphine patch[d] (mcg/hr)	12.6
Buprenorphine film (mcg)	0.03
Butorphanol (mg)	7
Codeine (mg)	0.15
Dihydrocodeine (mg)	0.25
Fentanyl buccal or SL tablets, or lozenge/troche[e] (mcg)	0.13
Fentanyl film or oral spray[f] (mcg)	0.18
Fentanyl nasal spray[g] (mcg)	0.16
Fentanyl patch[h] (mcg)	7.2
Hydrocodone (mg)	1
Hydromorphone (mg)	4
Levorphanol tartrate (mg)	11
Meperidine hydrochloride (mg)	0.1
Methadone[i] (mg)	3
> 0, ≤ 20	4
> 20, ≤ 40	8
> 40, ≤ 60	10
> 60	12
Morphine (mg)	1
Opium (mg)	1
Oxycodone (mg)	1.5
Oxymorphone (mg)	3
Pentazocine (mg)	0.37
Tapentadol[j] (mg)	0.4
Tramadol (mg)	0.1

CDC = Centers for Disease Control; CMS = Centers for Medicare and Medicaid Services; FDA = Food and Drug Administration; MAT = Medication Assisted Treatment; MME = morphine mg equivalent; OMS = Overutilization Monitoring System.

[a] The MME conversion factor is intended only for analytic purposes where prescription data is used to calculate daily MME. It is to be used in the formula: Strength per Unit × (Number of Units/Days Supply) × MME conversion factor = MME/Day. This value does not constitute clinical guidance or recommendations for converting patients from one form of opioid analgesic to another. Please consult the manufacturer's full prescribing information for such guidance. Use of this file for the purposes of any clinical decision-making warrants caution.

[b] National Center for Injury Prevention and Control. CDC compilation of benzodiazepines, muscle relaxants, stimulants, zolpidem, and opioid analgesics with oral morphine mg equivalent conversion factors, 2016 version. Atlanta, GA: Centers for Disease Control and Prevention; 2016. Available at https://www.cdc.gov/drugoverdose/media/. For more information, send an email to Mbohm@cdc.gov.

[c] Buprenorphine formulations with a FDA approved indication for MAT are excluded from Medicare's Overutilization Monitoring System's opioid overutilization reporting.

[d] The MME conversion factor for buprenorphine patches is based on the assumption that 1 mg of parenteral buprenorphine is equivalent to 75 mg of oral morphine and that one patch delivers the dispensed micrograms per hour over a 24 hour day. Example: 5 µg/hr buprenorphine patch × 24 hrs = 120 µg/day buprenorphine = 0.12 mg/day = 9 mg/day oral MME. In other words, the conversion factor not accounting for days of use would be 9/5 or 1.8.

However, since the buprenorphine patch remains in place for 7 days, we have multiplied the conversion factor by 7 (1.8 × 7 = 12.6). In this example, MME/day for 4 5 µg/hr buprenorphine patches dispensed for use over 28 days would work out as follows: Example: 5 µg/hr buprenorphine patch × (4 patches/28 days) × 12.6 = 9 MME/day. Please note that because this allowance has been made based on the typical dosage of 1 buprenorphine patch per 7 days, you should first change all Days Supply in your prescription data to follow this standard, i.e., Days Supply for buprenorphine patches = number of patches x 7.

[e] The MME conversion factor for fentanyl buccal tablets, sublingual tablets, and lozenges/troche is 0.13. This conversion factor should be multiplied by the number of micrograms in a given tablet or lozenge/troche.

[f] The MME conversion factor for fentanyl film and oral spray is 0.18. This reflects a 40% greater bioavailability for films compared to lozenges/tablets and 38% greater bioavailability for oral sprays compared to lozenges/tablets.

[g] The MME conversion factor for fentanyl nasal spray is 0.16, which reflects a 20% greater bioavailability for sprays compared to lozenges/tablets.

[h] The MME conversion factor for fentanyl patches is based on the assumption that 1 mg of parenteral fentanyl is equivalent to 100 mg of oral morphine and that 1 patch delivers the dispensed micrograms per hour over a 24 hour day. Example: 25 µg/hr fentanyl patch × 24 hrs = 600 ug/day fentanyl = 60 mg/day oral morphine mg equivalent.

In other words, the conversion factor not accounting for days of use would be 60/25 or 2.4.

However, since the fentanyl patch remains in place for 3 days, we have multiplied the conversion factor by 3 (2.4 × 3 = 7.2). In this example, MME/day for 10 25 µg/hr fentanyl patches dispensed for use over 30 days would work out as follows:

Example: 25 µg/hr fentanyl patch × (10 patches/30 days) × 7.2 = 60 MME/day. Please note that because this allowance has been made based on the typical dosage of 1 fentanyl patch per 3 days, you should first change all Days Supply in your prescription data to follow this standard, i.e., Days Supply for fentanyl patches = number of patches × 3.

[i] The CDC MME conversion factor to calculate morphine mg equivalents is 3. CMS uses this conversion factor when analyzing Medicare population opioid use. CMS uses the graduated methadone MME conversion factors to calculate MME within the OMS for identifying and reporting potential opioid overutilizers. https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf.

[j] Tapentadol is a mu receptor agonist and norepinephrine reuptake inhibitor. Oral MMEs are based on degree of mu-receptor agonist activity, but it is unknown if this drug is associated with overdose in the same dose-dependent manner as observed with medications that are solely mu receptor agonists.

16.8 Appendix 8: Schedule of Assessments - Phase 1b Multiple Ascending Dose

Table 4. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
GENERAL ASSESSMENTS																
Informed consent	X															
Inclusion/Exclusion criteria	X															
Medical history	X															
Demographics	X															
SLICC Criteria for SLE	X															
Concomitant medication[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[c]		X														
BOS161721 or placebo dosing		X			X		X	X	X	X	X					
SAFETY ASSESSMENTS																
Full physical exam	X	X														

[a] Screening assessments will be performed over more than 1 visit.

[b] Concomitant use of oral corticosteroids: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). See Section 4.6.1 for further details.

[c] Randomization should occur after patient eligibility has been confirmed by central eligibility review.

Table 4. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
Chest x-ray[d]	X															
C-SSRS	X	X						X			X					
AEs and SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	X	X			X			X								X
Injection site reaction assessment		X[f]	X		X		X	X	X	X	X	X	X	X	X	X
Targeted physical examination				X	X	X	X	X	X	X	X			X	X	X
Vital signs (BP, HR, and temperature)[g]	X	X		X	X	X	X	X	X	X	X			X	X	X
EFFICACY ASSESSMENTS																
BILAG-2004 Index	X	X			X		X	X	X	X	X			X	X	X

[d] If patients have had a TB test and chest x ray within 3 months prior to screening, then these assessments do not need to be repeated during screening. The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

[e] ECGs will be performed after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws.

[f] Injection site reaction assessments to be performed at 2 hours postdose.

[g] Vital signs will be assessed after the patient has been supine and at rest ≥ 5 minutes. Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours (±15 minutes) postdose, as well as on each of the scheduled outpatient days in the table above (excluding PK-only site visits at Days 7, 187, and 195). When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection

Table 4. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
SLEDAI-2K[h]	X	X			X		X	X	X	X	X			X	X	X
PGA of disease activity	X	X			X		X	X	X	X	X			X	X	X
ACR-28 joint count	X	X			X		X	X	X	X	X			X	X	X
CLASI	X	X			X		X	X	X	X	X			X	X	X
CCI [redacted]		X			X		X	X	X	X	X			X	X	X
SLICC/ACR Damage Index		X									X					
CCI [redacted]		X			X		X	X	X	X	X			X	X	X
LABORATORY ASSESSMENTS																
CD4+ count	X	X		X	X	X		X			X					
Clinical laboratory assessments (hematology and clinical chemistry)[i]	X	X			X	X	X	X	X	X	X			X	X	X
Coomb's test direct[j]	X	X			X		X	X	X	X	X			X	X	X
Total IgG and IgM	X	X		X	X	X		X			X					
Plasma CCI [redacted]	X	X			X		X	X	X	X	X			X	X	X
Plasma CCI [redacted] & CCI [redacted]		X		X	X		X	X			X					

[h] SLEDAI-2K should be done before randomization and dosing on Day 0 as SLEDAI-2K < 6 is exclusionary

[i] Clinical laboratory assessments will include a fasting glucose and lipid panel, with exception of screening (Visit 1) which will be non-fasting

[j] When clinically indicated for hemolytic anemia

Table 4. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
Whole blood for leukocyte immunophenotype		X		X	X		X	X			X					
ADA[k]		X		X	X		X	X			X					X
nAb[l]								X			X					
pSTAT3[m]		X			X	X	X	X								
CCI [redacted]		X		X				X			X					X
CCI [redacted]		X														
CCI [redacted]	X	X			X		X	X	X	X	X			X[n]	X[n]	X[n]
CRP	X							X								X
Serum pregnancy test (women)	X															

[k] Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients, but only assayed (analyzed) if the patient had a positive ADA on Day 90

[l] nAb is collected for all patients, though will only be analyzed by central lab if patient is positive for ADA at Day 90

[m] Predose (trough) samples only

[n] Antibodies and autoantibodies (CCI [redacted]) will not be analyzed during safety follow-up visits

Table 4. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
FSH (postmenopausal women)	X															
Urine pregnancy test (women)[o]		X			X		X	X	X	X	X					X
TB test (QuantiFERON®-TB Gold In-Tube)[d]	X															
Serology (hepatitis B and C, HIV-1/2 combination)	X															
Stool sample[p]	X															
Spot urine for protein/creatinine ratio	X	X			X		X	X	X	X	X			X	X	X
Urinalysis	X	X			X		X	X	X	X	X			X	X	X
PK Labs																
Predose		X			X		X	X	X	X	X					
Predose PK Window		60 m			± 3 d		± 3 d	± 3 d	± 3 d	± 3 d	± 3 d					
Postdose		X[q]	X	X	X[q]						X[q]	X	X	X	X	X

[o] Urine pregnancy test will be collected on WOCBP prior to study drug administration on dosing visits

[p] Cryptosporidium test is required at screening. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium

[q] Postdose samples will be collected at 4, 8, and 24 hours after study drug administration on Days 0, 30, and 180

Table 4. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
Postdose PK Window		4 h ± 30 m 8 h ± 45 m 24 h ± 60 m	± 1d	± 3 d	4 h ± 30 m 8 h ± 45 m 24 h ± 60 m						4 h ± 30 m 8 h ± 45 m 24h ± 60 m	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d

Abbreviations: ACR = American College of Rheumatology; ADA= anti-drug antibody; AE = adverse event; APL = antiphospholipid; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; CD4+ = cluster of differentiation 4; CLASI = Cutaneous Lupus Area and Severity Index; CRP = C-reactive protein; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; CCI [redacted]; FSH = follicle stimulating hormone; HR = heart rate; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IL-21 = interleukin 21; nAb = neutralizing antibody; PGA = Physician's Global Assessment; PK = pharmacokinetic; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; SAE = serious adverse event; CCI [redacted]; SLEDAI-2K = SLE Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; CCI [redacted] CCI [redacted]; TB = tuberculosis.

16.9 Appendix 9: Protocol Summary of Changes

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has necessitated social distancing and shelter-in-place type practices and limited transportation globally. A contingency plan was implemented in anticipation of disruptions to study visits and study assessments. This amendment summarizes the measures implemented during the COVID-19 pandemic to protect patient safety and data integrity.

- Safety oversight: In case a patient cannot return to the study site for the scheduled visit, the site staff will contact the patient remotely for safety follow up, for example, via telephone or video conferencing.
- Central Laboratory: In the case that there are courier issues that will prevent the protocol-required laboratory specimens to be sent to the study core laboratory, the site should have the safety laboratory specimens (Table 2: Hematology, Chemistry, and Urinalysis) sent to their local laboratory for analysis and review by the study physician.
- Investigational Product Dosing: In cases when dosing cannot be performed during the protocol-designated windows, the Investigator should discuss each case with the Sponsor to determine whether it is a missed visit or whether the dosing can be performed outside protocol windows (as a protocol deviation). A minimum of 2 weeks must be maintained between consecutive doses. Patients who miss more than 2 doses of the study drug (whether consecutive or not) will be discontinued from the study and will undergo assessments as outlined in Section 5.5 (Premature Discontinuation).

Additional changes in this amendment include:

1. Sample size recalculation based on data from the Ustekinumab Phase 2 study in SLE.

2. Revisions to secondary and exploratory endpoints based on precedence in other successful clinical trials and to account for SLE disease heterogeneity.

3. Additional options for acceptable contraception methods.

Significant changes are described in the table below. Changed text is displayed for the first major occurrence only. Deleted text is presented in strikethrough format, and added text is presented in bold format.

Section	Description of Changes	Rationale
Global	Replace: Protocol Date and Version: 23 July 2019; V6.0 With: Protocol Date and Version: 30 April 2020; V7.0	Administrative
Global	Change:	Administrative

Section	Description of Changes	Rationale
	Changed Version number from V6.0 (Amendment 5) to V7.0 (Amendment 6) and Version date from 23 July 2019 to 30 April 2020.	
Global	Made administrative and editorial (formatting, typographical, and grammatical) updates.	Administrative
CLINICAL PROTOCOL APPROVAL FORM	Replace: Name and Title PPD , MD, PhD Chief Medical Officer Boston Pharmaceuticals With: Name and Title PPD , MD, PhD Chief Medical Officer Boston Pharmaceuticals	New CMO.
CLINICAL PROTOCOL APPROVAL FORM	Replace: Name and Title PPD , PhD Senior Vice President Clinical Development and Head of Clinical Operations Boston Pharmaceuticals With: Name and Title PPD , MD Vice President Clinical Development Boston Pharmaceuticals	New clinical lead for the program.
PROTOCOL SUMMARY, Objectives and Endpoints, POC Phase 2, Secondary	Replace: Results and changes from baseline in: With: Changes and percent changes from baseline in:	SLE is a very heterogeneous disease. As a result, baseline data could vary considerably from patient to patient. Percent change from baseline enables

Section	Description of Changes	Rationale
Endpoints, Bullet 2 (sub-bullet 2)		comparison between treatment arms despite baseline variability.
PROTOCOL SUMMARY, Objectives and Endpoints, POC Phase 2, Secondary Endpoints, Bullet 2 (sub-bullet 2)	Replace: The Results and changes from baseline in: CLASI With: The Changes and percent changes from baseline in: CLASI PGA	PGA is added as an important disease activity score in SLE.
PROTOCOL SUMMARY, Objectives and Endpoints, POC Phase 2, Secondary Endpoints, Bullet 6	Remove: Time to first SRI-4 response	This endpoint is removed since the SRI-4 response is not always stable and could disappear from one visit to next.
PROTOCOL SUMMARY, Objectives and Endpoints, POC Phase 2, Exploratory Endpoints	Insert: CCI • CCI • CCI • CCI	CCI
PROTOCOL SUMMARY, Objectives and Endpoints, POC phase 2, Exploratory Endpoints, second row, second column, Bullet 2	Replace: CCI	CCI
INTRODUCTION AND RATIONALE, Section 1.2.5, Potential Risks, Sub-section	Replace: Since the risk of opportunistic cryptosporidium infection increases with low levels of CD4+ T-cells, patients with a CD4+ count < 500 cell/mm^3 were	The text is made consistent with the revised eligibility criteria for CD4+ count in POC.

Section	Description of Changes	Rationale
1.2.5.4, Infections, Paragraph 7.	excluded from the Phase 1 SAD study (BOS161721-01), and CD4+ < 350 cells/mm^3 will be excluded from the MAD/POC parts of the study. With: Since the risk of opportunistic cryptosporidium infection increases with low levels of CD4+ T-cells, patients with a CD4+ count < 500 cell/mm^3 were excluded from the phase 1 SAD study (BOS161721-01). Patients with CD4+ count < 350 cells/mm^3 and CD4+ count < 150 cells/mm^3 will be excluded from the MAD and POC parts of the study, respectively.	
STUDY OBJECTIVES AND ENDPOINTS, Section 2.2, phase 2 Proof of Concept, Secondary Endpoints, Bullet 2.	Replace: Results and changes from baseline in: With: Changes and percent changes from baseline in:	SLE is a very heterogeneous disease. As a result, baseline data could vary considerably from patient to patient. Percent change from baseline enables comparison between treatment arms despite baseline variability.
STUDY OBJECTIVES AND ENDPOINTS, Section 2.2, phase 2 Proof of Concept, Secondary Endpoints, Bullet 2.	Replace: The Results and changes from baseline in: CLASI With: The Changes and percent changes from baseline in: CLASI PGA	PGA is added as an important disease activity score in SLE.
STUDY OBJECTIVES AND ENDPOINTS, Section 2.2, phase 2 Proof of Concept, Secondary Endpoints, Bullet 6.	Remove: Time to first SRI-4 response	This endpoint is removed since the SRI-4 response is not always stable and could disappear from one visit to next.

Section	Description of Changes	Rationale
STUDY OBJECTIVES AND ENDPOINTS, Section 2.2, phase 2 Proof of Concept, Exploratory Endpoints	Insert: CCI • CCI • CCI • CCI	CCI
STUDY OBJECTIVES AND ENDPOINTS, Section 2.2, phase 2 Proof of Concept, Exploratory Endpoints, second row, second column, Bullet 2	Replace: CCI	CCI
STUDY PLAN, Section 3.1.1, Multiple Ascending Dose Phase 1b,	Replace: All doses selected for the MAD part of the study are projected not to exceed the mean exposure of that achieved in the SAD study. With: All doses selected for the MAD part of the study are projected not to exceed the mean exposure of that achieved at the highest dose in the SAD study.	Clarification is made as to the approach to dose selection.
STUDY PLAN, Section 3.1.2.2, POC Study Design	Replace: For the POC part of the study, approximately 156 additional patients will be randomized to active or placebo groups in a 2:1 ratio. With: For the POC part of the study, approximately 110 additional patients will be randomized to active or placebo groups in a 2:1 ratio.	Efficacy data from a Phase 2 SLE study of SRI-4 response to Ustekinumab, which has a partially overlapping mechanism of action on T cells, became available[51] and was therefore used to reassess power calculations in this study of BOS-161721 of SRI-4 response in SLE. Ustekinumab produced a

<table>
<tr><th>Section</th><th>Description of Changes</th><th>Rationale</th></tr>
<tr><td></td><td></td><td>statistically significant difference in SRI-4 response in favor of Ustekinumab (62% Ustekinumab vs. 33% placebo) with 102 patients. Therefore, sample size was reduced in BOS161721-02 from 156 to 96 evaluable patients.</td></tr>
<tr><td>STUDY PLAN, Section 3.2, Randonization and Blinding</td><td>Replace:<table><tr><td>Phase 2</td><td>156*</td><td>2:1</td></tr></table>With:<table><tr><td>Phase 2</td><td>Approximately 110</td><td>2:1</td></tr></table></td><td>Efficacy data from a Phase 2 SLE study of SRI-4 response to Ustekinumab, which has a partially overlapping mechanism of action on T cells, became available[51] and was therefore used to reassess power calculations in this study of BOS-161721 of SRI-4 response in SLE. Ustekinumab produced a statistically significant difference in SRI-4 response in favor of Ustekinumab (62% Ustekinumab vs. 33% placebo) with 102 patients. Therefore, sample size was reduced in BOS161721-02 from 156 to 96 evaluable patients.</td></tr>
<tr><td>STUDY PLAN, Section 3.4, Schedule of Assessments</td><td>Replace:
Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours postdose, as well as on each of the scheduled outpatient days in the table above (excluding PK-only site visits at Days 187 and 195).
With:
Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours (± 15 minutes) postdose, as well as on each of the scheduled outpatient days in the table above (excluding PK-only site visits at Days 187 and 195).</td><td>Flexible language is introduced for the timing of the vital signs.</td></tr>
<tr><td>STUDY PLAN, Section 4.2, Number of Patients</td><td>Replace:
Approximately 186 male and female patients are planned for enrollment, but may be adjusted upward according to the dropout (noncompliance) rate,</td><td>Sample size re-calculation was performed based on recent data from the</td></tr>
</table>

Section	Description of Changes	Rationale
	which will be monitored in a blinded fashion in an ongoing basis. Approximately 30 patients will be randomized for the MAD Phase 1b portion, and approximately 156 additional patients will be randomized in the POC Phase 2 portion. Note that approximately 24 dropouts are assumed. With: Approximately 140 male and female patients are planned for enrollment, but may be adjusted upward according to the dropout (noncompliance) rate, which will be monitored in a blinded fashion in an ongoing basis. Approximately 30 patients will be randomized for the MAD phase 1b portion, and approximately 110 additional patients will be randomized in the POC phase 2 portion. Note that approximately 14 dropouts are assumed in the POC phase 2 portion.	Ustekinumab phase 2 study. Please see Section 8.1.
STUDY PLAN, Section 4.7.2, Contraception	Replace: Patients must agree to either complete abstinence, defined as a complete avoidance of heterosexual activity, or the use of 2 methods of highly effective contraception from the following: • Male condoms with spermicide • Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by patients who are WOCBP or a male patient's WOCBP partner. Women who are partner of men who are patients participating in the study may use hormone-based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug • IUDs, such as ParaGard® • Vasectomy • Note: Women who are abstinent while participating in the study must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the patient chooses to forego complete abstinence • Azoospermic men and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP must still undergo pregnancy testing With:	As many patients with SLE are unable to tolerate hormonal contraception, additional effective methods of contraception (diaphragm with spermicide, cervical cap with spermicide and hormonal patches) were introduced to provide more flexibility for study participants.

Section	Description of Changes	Rationale
	Patients must agree to either complete abstinence, defined as a complete avoidance of heterosexual activity, or the use of 2 methods of effective contraception from the following: • Male condoms with spermicide • Diaphragm with spermicide • Cervical cap with spermicide • Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, patches, and intrauterine devices (IUDs) such as Mirena® by patients who are WOCBP or a male patient's WOCBP partner. Women who are partner of men who are patients participating in the study may use hormone-based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug • IUDs, such as ParaGard® • Vasectomy • Note: Women who are abstinent while participating in the study must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the patient chooses to forego complete abstinence • Azoospermic men and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP must still undergo pregnancy testing	
STUDY PLAN, Section 5.2, Enrollment/Randomization and Day 0 Treatment	Replace: • Vital signs (prior to PK blood draw, predose, and at 1 and 2 hours postdose on Day 0) With: • Vital signs (prior to PK blood draw, predose, and at 1 and 2 hours [± 15 minutes] postdose on Day 0)	Flexible language is introduced for the timing of the vital signs.
STUDY PLAN, Section 5.6, Contingency Plans During the COVID-19 Pandemic	Inserted: • Safety oversight: In case a patient cannot return to the study site for the scheduled visit, the site staff will contact the patient remotely for safety follow up, for example, via telephone or video conferencing. • Central Laboratory: In the case there are courier issues that will prevent the protocol-required laboratory specimens to be sent to the study core laboratory, the site should have the safety	During the COVID-19 pandemic, due to social distancing and shelter-in-place type practices and limitations in transportation, measures were implemented to protect patient safety and data integrity.

Section	Description of Changes	Rationale
	laboratory speciments (Table 2: Hematology, Chemistry, and Urinalysis) sent to their local laboratory for analysis and review by the study physician. • Investigational Product Dosing: In cases when dosing cannot be performed during the protocol-designated windows, the Investigator should discuss each case with the Sponsor to determine whether it is a missed visit or whether the dosing can be performed outside protocol windows (as a protocol deviation). A minimum of 2 weeks must be maintained between consecutive doses. Patients who miss more than 2 doses of the study drug (whether consecutive or not) will be discontinued from the study and will undergo assessments as outlined in Section 5.5 (Premature Discontinuation).	
ASSESSMENTS, Section 6.2.3, Vital Signs	Replace: Vital signs will be assessed on Day 0 at predose and at Day 0, 1 and 2 hours postdose, as well as on each of the scheduled visit days during the study (excluding PK-only site visits). With: Vital signs will be assessed on Day 0 at predose and at Day 0, 1 and 2 hours (± 15 minutes) postdose, as well as on each of the scheduled visit days during the study (excluding PK-only site visits).	Flexible language is introduced for the timing of the vital signs.
ASSESSMENTS, Section 6.3.5, CLASI Response, Paragraph 1.	Replace: This assessment will be applied to all patients as all are required to have cutaneous disease activity. With: This assessment will be applied to all patients who have cutaneous disease activity.	Inclusion criteria could be met without presence of mucocutaneous disease.
STATISTICS, Section 8.1, Sample Size	Replace: The sample size in the Phase 2 portion is based on the primary endpoint, SRI-4 Response at Day 210. Approximately 156 additional patients will be randomized in a 2:1 ratio to BOS161721 versus placebo to achieve 132 evaluable patients in the FAS. This assumes 24 patients will drop prior to having received treatment and an evaluable post-baseline efficacy measure. Enrollment and randomization will be monitored in a blinded fashion and increased if needed to ensure at least 132 patients are randomized into the FAS. A total of 132 patients randomized provides more than 80% power to detect a treatment difference of 25% in SRI-4 response rates at Day 210, based on a targeted 2-sided significance level of 10% and	Efficacy data from a Phase 2 SLE study of SRI-4 response to Ustekinumab, which has a partially overlapping mechanism of action on T cells, became available[51] and was therefore used to reassess power calculations in this study of BOS-161721 of SRI-4 response in SLE. Ustekinumab produced a statistically significant difference in SRI-4 response in favor of

Section	Description of Changes	Rationale
	using a 2-sided Pearson's chi-squared test. This assumes of a response rate of 65% for BOS161721 and 40% for placebo, where missing data at Day 210 is carried forward from most recent non-missing result and patients are treated as a non-responder if a prohibited medication defined as a medication failure occurs. With: The sample size in the phase 2 portion is based on the primary endpoint, SRI-4 Response at Day 210. Based on efficacy data from a recently completed study with Ustekinumab, where the primary endpoint was also SRI-4, the sample size in the phase 2 part of the BOS161721-02 study is set at 96 evaluable patients. In the Ustekinumab study of 102 patients, a statistically significant difference in SRI-4 response was shown in favor of Ustekinumab (62% of Ustekinumab treated patients achieved SRI-4 response vs. 33% in patients receiving placebo). The Ustekinumab phase 2 study is an appropriate comparator to BOS161721-02 because both studies share the same primary endpoint of SRI-4 response and BOS161721 and Ustekinumab have overlapping mechanisms of action (T follicular helper and Th17 cell biology). Approximately 110 additional patients will be randomized in a 2:1 ratio to BOS161721 versus placebo to achieve approximately 96 evaluable patients in the FAS of the phase 2 portion. This assumes 14 patients will drop prior to having received treatment or having completed a post-baseline efficacy measure. Enrollment and randomization will be monitored in a blinded fashion and may be increased if needed to ensure at least 96 evaluable patients are randomized into the FAS. A total of 96 evaluable patients randomized provides 80% power to detect a treatment difference of 29% in SRI-4 response rates at Day 210, based on a targeted 2-sided significance level of 10% and using a 2-sided Pearson's chi-squared test. This assumes a response rate of 62% for BOS161721 and 33% for placebo.	Ustekinumab (62% Ustekinumab vs. 33% placebo) with 102 patients. Therefore, sample size was reduced in BOS161721-02 from 156 to 96 evaluable patients.
STATISTICS, Section 8.2.1, Analysis Populations, Paragraph 1 and 3	Inserted: (partial or complete)	Words partial or complete are added for further clarity.
STATISTICS, Section 8.2.3, Primary Efficacy	Replace: The proportion of patients who achieve a SRI-4 response at Day 210 will be assessed via Pearson's chi-squared analysis. The primary efficacy endpoint	Flexible language is introduced to perform additional analyses or apply additional

Section	Description of Changes	Rationale
Endpoint(s), Paragraph 1 and 2.	will be analyzed using the FAS and if needed repeated in the PP analysis set. Missing values will be addressed by employing a last observation carried forward (LOCF) analysis. Other imputation methods may be employed as a sensitivity analysis and will be described in the SAP. Additional analyses exploring impact of baseline factors such as baseline disease severity, race, and other characteristics may be performed. With: The proportion of patients who achieve a SRI-4 response at Day 210 will be assessed via Pearson's chi-squared analysis. The primary efficacy endpoint will be analyzed using the FAS and if needed repeated in the PP analysis set. Missing values will be addressed by employing a last observation carried forward (LOCF) analysis. Other imputation methods may be employed as a sensitivity analysis and will be described in the SAP. Analyses based on observed values may also be performed. Exploratory subgroup analyses assessing impact of baseline factors such as baseline disease severity, background therapy, race, geography, baseline serologic activity, and other characteristics may be performed. Additional exploratory analyses of disease activity endpoints may be performed based on emerging data.	impuation methodology based on emerging data.
APPENDICIES, Section 16.8, Appendix 8, Table 4 Schedule of Assessments - Phase 1b Multiple Assceding Dose	Replace: Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours postdose, as well as on each of the scheduled outpatient days in the table above (excluding PK-only site visits at Days 7, 187, and 195). With: Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours (±15 minutes) postdose, as well as on each of the scheduled outpatient days in the table above (excluding PK-only site visits at Days 7, 187, and 195).	Flexible language is introduced for the timing of the vital signs.

Certificate Of Completion

Envelope Id: PPD
Status: Completed
Subject: Please DocuSign: BOS161721-02_Protocol_Amendment 6_V 7 0_Clean_30Apr2020.docx
Source Envelope:
Document Pages: 130
Signatures: 3
Envelope Originator:
Certificate Pages: 5
Initials: 0
PPD
AutoNav: Enabled
PPD
EnvelopeId Stamping: Disabled
PPD
Time Zone: (UTC-05:00) Eastern Time (US & Canada)
PPD
PPD

Record Tracking

Status: Original
5/5/2020 1:46:10 PM
Holder: PPD
PPD
Location: DocuSign

Signer Events	Signature	Timestamp
PPD PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 5/5/2020 1:50:48 PM Viewed: 5/6/2020 7:06:37 AM Signed: 5/6/2020 7:07:11 AM
Electronic Record and Signature Disclosure: Accepted: 5/6/2020 7:06:37 AM ID: PPD		
PPD PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 5/5/2020 1:50:48 PM Viewed: 5/6/2020 9:57:01 AM Signed: 5/6/2020 9:57:24 AM
Electronic Record and Signature Disclosure: Accepted: 5/6/2020 9:57:01 AM ID: PPD		

Signer Events	Signature	Timestamp
PPD PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 5/5/2020 1:50:48 PM Viewed: 5/5/2020 3:46:16 PM Signed: 5/5/2020 3:46:47 PM
Electronic Record and Signature Disclosure: Accepted: 5/5/2020 3:46:16 PM ID: PPD		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	5/5/2020 1:50:48 PM
Certified Delivered	Security Checked	5/6/2020 9:57:01 AM
Signing Complete	Security Checked	5/6/2020 9:57:24 AM
Completed	Security Checked	5/6/2020 9:57:24 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, MMS Holdings Inc. (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through your DocuSign, Inc. (DocuSign) Express user account. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to these terms and conditions, please confirm your agreement by clicking the 'I agree' button at the bottom of this document.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. For such copies, as long as you are an authorized user of the DocuSign system you will have the ability to download and print any documents we send to you through your DocuSign user account for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. To indicate to us that you are changing your mind, you must withdraw your consent using the DocuSign 'Withdraw Consent' form on the signing page of your DocuSign account. This will indicate to us that you have withdrawn your consent to receive required notices and disclosures electronically from us and you will no longer be able to use your DocuSign Express user account to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through your DocuSign user account all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact MMS Holdings Inc.:
You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:

To advise MMS Holdings Inc. of your new e-mail address
To let us know of a change in your e-mail address where we should send notices and disclosures electronically to you, you must send an email message to us at PPD and in the body of such request you must state: your previous e-mail address, your new e-mail address. We do not require any other information from you to change your email address..
In addition, you must notify DocuSign, Inc to arrange for your new email address to be reflected in your DocuSign account by following the process for changing e-mail in DocuSign.

To request paper copies from MMS Holdings Inc.
To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an e-mail to PPD and in the body of such request you must state your e-mail address, full name, US Postal address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with MMS Holdings Inc.
To inform us that you no longer want to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your DocuSign account, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;
ii. send us an e-mail to PPD and in the body of such request you must state your e-mail, full name, IS Postal Address, telephone number, and account number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

Operating Systems:	Windows2000? or WindowsXP?
Browsers (for SENDERS):	Internet Explorer 6.0? or above
Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
Email:	Access to a valid email account
Screen Resolution:	800 x 600 minimum
Enabled Security Settings:	•Allow per session cookies •Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

** These minimum requirements are subject to change. If these requirements change, we will provide you with an email message at the email address we have on file for you at that time providing you with the revised hardware and software requirements, at which time you will have the right to withdraw your consent.

Acknowledging your access and consent to receive materials electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please verify that you were able to read this electronic disclosure and that you also were able to print on paper or electronically save this page for your future reference and access or that you were able to e-mail this disclosure and consent to an address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format on the terms and conditions described above, please let us know by clicking the 'I agree' button below.
By checking the 'I Agree' box, I confirm that:

- I can access and read this Electronic CONSENT TO ELECTRONIC RECEIPT OF ELECTRONIC RECORD AND SIGNATURE DISCLOSURES document; and

- I can print on paper the disclosure or save or send the disclosure to a place where I can print it, for future reference and access; and

- Until or unless I notify MMS Holdings Inc. as described above, I consent to receive from exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to me by MMS Holdings Inc. during the course of my relationship with you.

A RANDOMIZED DOUBLE-BLIND PHASE 1b/2 COMBINED STAGGERED MULTIPLE DOSE ESCALATION STUDY OF BOS161721 IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS ON A BACKGROUND OF LIMITED STANDARD OF CARE

SPONSOR	Boston Pharmaceuticals, Inc. 55 Cambridge Parkway, Suite 400 Cambridge, MA 02142 United States of America (USA)
INVESTIGATIONAL COMPOUND:	BOS161721
PROTOCOL NUMBER:	BOS161721-02
PHASE	Phase 1b/2
INVESTIGATIONAL NEW DRUG (IND) NUMBER:	131796
ORIGINAL PROTOCOL DATE:	06 October 2017
VERSION NUMBER:	V6.0 (Amendment 5)
VERSION DATE:	23 July 2019

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care **Study Number: BOS161721-02**	
Version	**Date**
Original Protocol	06 October 2017
Protocol Version 2.0 (Amendment 1)	14 November 2017
Protocol Version 3.0 (Amendment 2)	21 March 2018
Protocol Version 4.0 (Amendment 3)	27 July 2018
Protocol Version 5.0 (Amendment 4)	23 January 2019
Protocol Version 6.0 (Amendment 5)	23 July 2019

This study protocol was subject to critical review and has been approved by sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (APPENDIX 2), and principles of Good Clinical Practices (GCP) as described in 21 Code of Federal Regulations (CFR) parts 50, 54, 56 and 312 and according to applicable local requirements.

The investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

I agree with these statements and indicate my approval by signature for this protocol:

Name and Title	**Signature and Date**
PPD, MD, PhD Chief Medical Officer Boston Pharmaceuticals	PPD
PPD, PhD Senior Vice President Clinical Development and Head of Clinical Operations Boston Pharmaceuticals	PPD
PPD Clinical Operations Lead Boston Pharmaceuticals	PPD

BOS161721-02

A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to BOS161721 are the confidential and proprietary information of Boston Pharmaceuticals, Inc., and except as may be required by federal, state, or local laws or regulation, may not be disclosed to others without prior written permission of Boston Pharmaceuticals, Inc.

I have read the protocol (Version 6.0, dated 23 July 2019), including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Council for Harmonisation (ICH) guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Boston Pharmaceuticals, Inc., or specified designees. I will discuss the material with them to ensure that they are fully informed about BOS161721 and the study.

_____ _____

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

PROTOCOL SUMMARY

Title:	A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care
Indication	Adults with moderately to severely active SLE
Background and Rationale	SLE is a chronic systemic autoimmune disease with considerable heterogeneity in clinical manifestations and disease course. There is evidence that B- and T-cells are critical to the development of the disease, and that T-cell-derived cytokines such as interleukin-21 (IL-21) are involved in the SLE-associated inflammatory pathological response. BOS161721 is a humanized immunoglobulin G1 (IgG1) triple mutation monoclonal antibody (mAb) intended to have an extended terminal elimination half-life ($t_{½}$) that selectively binds to and neutralizes IL-21, which acts on multiple cell types that drive inflammation and autoimmunity. *In vivo*, BOS161721 inhibits T-cell dependent antigen responses of B-cells and is being developed as a potential treatment for adults with moderately to severely active SLE. Nonclinical studies have evaluated the toxicity, pharmacodynamics (PD), toxicokinetics (TK), pharmacokinetics (PK), and immunogenicity of BOS161721 administered intravenously (IV) and subcutaneously (SC). The no observed adverse effect level (NOAEL) in Cynomolgus monkeys was determined to be 100 mg/kg (SC and IV), the highest dose tested. There were no injection site reactions in animals dosed subcutaneously. In a Phase 1 single ascending dose (SAD) study, BOS161721 was administered IV and SC to healthy male and female adult subjects. This double-blind, placebo-controlled study evaluated 8 ascending dose levels (1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg) for safety, tolerability, PK, PD and immunogenicity. Overall, there were no clinically significant safety or tolerability findings from this study. Results from the Phase 1 SAD study informed the dose regimens used for the multiple ascending doses (MAD) Phase 1b portion of this trial. The MAD portion will involve 3 cohorts. The Phase 2 portion will be a proof of concept (POC) part, where dose selection will be based on the data monitoring committee (DMC) and sponsor's assessment of safety, tolerability, immunogenicity, and PK and PD data from the MAD portion of 30 patients treated with BOS161721/placebo. The purpose of the study is to establish a safe and effective dosage for adult patients with moderately to severely active SLE.

Objectives and Endpoints:

MAD Phase 1b

OBJECTIVES	ENDPOINTS
Primary	
• To assess safety, tolerability, and immunogenicity of repeat doses of BOS161721 (20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment, in order to estimate the optimal dose.	Safety Endpoints • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • Columbia Suicide Severity Rating Scale (C-SSRS) • 12-lead electrocardiograms (ECGs) parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from baseline • Physical examinations changes from baseline • Anti-drug antibodies (ADAs) • Study drug exposure/compliance
Secondary	
• To characterize the PK of BOS161721 and select the optimal dose of BOS161721 based on safety, PK, and PD effects in patients with moderately to severely active SLE.	Pharmacokinetic Endpoints • BOS161721 concentration by visit and time point • Maximum observed concentration (C_{max}), first time to maximum concentration (T_{max}), area under the concentration-time curve (AUC), $t_{½}$, systematic clearance (C_L), volume of distribution (V_d) Pharmacodynamic Endpoints • Results and changes (or shifts) from baseline to each visit in phosphorylated signal transducer and activator of transcription 3 (pSTAT3), C3 and C4 levels, and leukocyte immunophenotype • Results and changes (or shifts) from baseline in anti-double-stranded DNA (dsDNA), antinuclear antibodies (ANA), anti-Sjögren syndrome A and B (SSA, SSB), Smith (Sm), and antiphospholipid (APL) autoantibodies at each visit • Results and changes (or shifts) from baseline in abrogation of IL-21 gene signature at each indicated visit

Exploratory	
• CCI	CCI • CCI - CCI • CCI • CCI
• CCI	• CCI
• CCI	• CCI

POC Phase 2

OBJECTIVES	ENDPOINTS
Primary	
• To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on the SLE Responder Index 4 (SRI-4)	Primary Efficacy Endpoint • The proportion of patients with a SRI-4 response at Day 210 (see Section 6.3.4.1)
Secondary	
• To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on clinical indicators of SLE activity, in adult patients with moderately to severely active SLE on limited background standard of care treatment	Secondary Efficacy Endpoints • The proportion of patients with: - SRI-4 response at each visit - SRI-5 and SRI-6 response at each visit (Section 6.3.4.2) - a sustained reduction from baseline of oral corticosteroid (CS) (≤ 7.5 mg/day and < Day 0 dose) between Day 150 and Day 210 - new or recurrent BILAG flares (≥ 1 qualifying BILAG A or > 1 qualifying BILAG B) through Day 210 - PGA worsening - a BICLA response - a CLASI response - medication failures • Results and changes from baseline in: - CLASI - Total number of swollen joints, tender joints, and active joints (swelling and tenderness in the same joint) in the ACR-28 joint count - SLEDAI-2K - SLICC/ACR damage index • Time to medication failure • Group mean percent reduction in corticosteroid administration from baseline Day 0 dose through Day 210 in patients receiving ≥ 7.5 mg/day prednisone equivalent at Day 0 • Duration of longest SRI-4 response • Time to first SRI-4 response • Time to first BILAG flare (≥ 1 new or recurrent BILAG A or > 1 new or recurrent BILAG B) relative to baseline through Day 210
Safety	
• To assess safety and tolerability of repeat doses of BOS161721 at the chosen dose administered SC in	Safety Endpoints • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs),

adult patients with moderately to severely active SLE on limited background standard of care treatment	related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • C-SSRS • 12-lead ECGs parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from baseline • Physical examinations changes from baseline • ADAs • Study drug exposure/compliance
Exploratory	
• CCI [redacted]	CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

Study Design: This is a Phase 1b/2 combined, randomized, multicenter, double-blind, placebo-controlled trial to study the clinical efficacy, safety, and PK of multiple SC doses of BOS161721 in adult patients with moderately to severely active SLE. After successfully completing a screening phase, eligible patients will be randomized to a specified dose of BOS161721 or placebo. The dosing schedule will be monthly. The trial will consist of 2 double-blinded portions: MAD Phase 1b and POC Phase 2. Patients may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180, followed by safety follow-up visits at Days 210, 240, and 270.

The MAD Phase 1b portion of the study design will consist of 3 cohorts, with

Cohort 1 containing 6 patients, where 5 of these patients will receive BOS161721 (active), and 1 will receive placebo. Cohorts 2 and 3 will each contain 12 patients, including 9 active and 3 placebo patients. Dose selection for each cohort is based on 90-day safety, tolerability, PK, and PD data review from the Phase 1 SAD study (BOS161721-01) in healthy subjects. Each of the 3 doses (20, 60, and 120 mg) selected for the MAD portion are projected not to exceed the mean exposure of that achieved in the SAD study following the single 240 mg SC dose. Each patient may receive a total of 7 SC monthly doses on Days 0, 30, 60, 90, 120, 150, and 180.

The MAD portion design is staggered, where after the 6 patients in Cohort 1 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 2 begins dosing (after the DMC evaluates the safety and tolerability data from Cohort 1). Similarly, after 8 of the 12 patients in Cohort 2 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 3 begins dosing after the DMC evaluation of the safety and tolerability data from Cohort 2 and Cohort 1. Thirty days after the last patient in Cohort 3 receives the third dose, the DMC and Boston Pharmaceuticals will conduct a data review to determine which dose will be carried forward into the POC part of the study. This dose will not exceed doses tested during the MAD portion.

For the POC portion, approximately 156 additional patients will be randomized to active or placebo groups in a 2:1 ratio. As in the MAD portion, each patient in the POC portion may receive a total of 7 SC monthly doses on Days 0, 30, 60, 90, 120, 150, and 180.

A maximum stable (for at least 6 weeks prior to Day 0) daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study. One oral CS "burst" for increased SLE disease activity may occur during the study between Day 0 and Day 120. Tapering of steroids during the course of the study will be highly encouraged and should be evaluated during the protocol-allowed tapering windows (Day 0 through Day 150) with the target of achieving a CS daily dose of $\leq$ 7.5 mg and < Day 0 dose between Day 150 and Day 210. Between Day 150 and Day 210, oral CS doses must be held constant due to the Day 210 endpoint evaluations.

DMC safety reviews will be conducted periodically throughout the study as described in the DMC charter.

Main Criteria for Inclusion and Exclusion

Inclusion Criteria:

1. Men and women, ages 18 to 70 years, inclusive

2. Patients must be mentally capable of giving consent and there must be evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study

3. Patients must have SLE as defined by meeting 4 of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE (with at least 1 clinical and 1 immunologic criterion OR Lupus nephritis as the sole clinical criterion in the presence of antinuclear antibodies [ANA] or anti- double-stranded deoxyribonucleic acid [dsDNA] antibodies), either sequentially or simultaneously

4. At screening, patients must have at least 1 of the following:

   a. Elevated ANA ≥ 1:80 via immunofluorescent assay at the central laboratory

   b. Positive anti-dsDNA or anti-Smith (Sm) above the normal level as determined by the central laboratory

5. At screening, the total SLEDAI-2K score must be ≥ 8, including points from at least 1 of the following clinical components:

   a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis

   Note: Points from lupus headache and organic brain syndrome will also be excluded from qualifying total and clinical SLEDAI-2K scores at screening and Day 0.

6. A clinical SLEDAI-2K score of ≥ 6 at screening at Day 0. Clinical SLEDAI-2K score is defined as follows:

   a. Contains points from arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, or vasculitis

   b. Excludes parameters which require central laboratory results: hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia

   Note: Points from lupus headache and organic brain syndrome will also be excluded from qualifying total and clinical SLEDAI-2K scores at screening and Day 0.

7. Patients must have at least 1 qualifying A or 2Bs from the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer:

    a. BILAG A or B score in the mucocutaneous body system. If a BILAG B score is due to BILAG number 6, mild skin eruption, the CLASI activity score including erythema and scale/hypertrophy must be ≥ 3 excluding points from mucosal ulcers and alopecia.

    b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis as defined in the protocol Section 4.4

    Note: Hips, shoulders, back, neck, and temporomandibular joints do not count towards the total number of joints with active synovitis.

    If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in at least 1 other body system for a total of 2 "B" BILAG body system scores.

8. Patients must be currently receiving at least 1 of the following:

    a. Administration for a minimum of 12 weeks, and a stable dose for at least 56 days (8 weeks prior to Day 0) of the following permitted steroid-sparing agents:

        i. Azathioprine (AZA), mycophenolate mofetil or mycophenolic acid, chloroquine, hydroxychloroquine, or methotrexate (MTX)

    b. If AZA, myocophenolate mofetil, mycophenolic acid, hydroxychloroquine, or MTX were discontinued prior to screening, the washout period must be ≥ 12 weeks.

    c. Corticosteroids (prednisone or prednisone-equivalent) at a stable dose of up to 30 mg/day for at least 6 weeks prior to Day 0 (see APPENDIX 3)

        i. For patients whose only SLE treatment is CSs, the stable CS dose must be ≥ 10 mg/day for at least 6 weeks prior to Day 0 and no more than 30 mg/day at the time of randomization.

        ii. Topical steroids may be used, but the dose must be stable for at least 6 weeks prior to Day 0. PRN topical steroids are not permitted.

9. Women of childbearing potential (WOCBP; see Section 4.7 for full information regarding WOCBP, definition of menopause, and

contraception):

a. Must have a negative serum pregnancy test at screening. Urine pregnancy test must be negative prior to first dose

b. Must not be breastfeeding

c. Must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 52 weeks

10. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 52 weeks

11. Patients must demonstrate willingness and ability to comply with the scheduled study visits, treatment plans, laboratory tests, and other procedures

Exclusion Criteria

Patients presenting with any of the following will not be included in this study:

1. Drug-induced SLE, rather than "idiopathic" SLE
2. Other systemic autoimmune disease (eg, erosive arthritis, rheumatoid arthritis [RA], multiple sclerosis [MS], systemic sclerosis, or vasculitis not related to SLE)
   a. RA-Lupus overlap (Rupus), and secondary Sjögren syndrome are allowed
3. Any major surgery within 6 weeks of study drug administration, (Day 0), or any elective surgery planned during the course of the study
4. Any history or risk for tuberculosis (TB), specifically those with:
   a. Current clinical, radiographic, or laboratory evidence of active TB
   b. History of active TB
   c. Latent TB defined as positive QuantiFERON-TB Gold In-Tube (QFT-G) or other diagnostic test in the absence of clinical manifestations. Latent TB is not excluded if the patient has documented completion of adequate course of prophylactic treatment with regimen recommended by local health authority guideline, or the patient has started treatment with isoniazid, or other regimen recommended by local health authority guidelines for at least 1 month before Day 0 and continues to receive the prophylactic treatment during study until the treatment course is completed
5. Active or unstable lupus neuropsychiatric manifestations, including but

not limited to any condition defined by BILAG A criteria, with the exception of mononeuritis multiplex and polyneuropathy, which are allowed

6. Severe proliferative lupus nephritis, (WHO Class III, IV), which requires or may require induction treatment with cytotoxic agents or high dose CS
7. Concomitant illness that, in the opinion of the investigator or the sponsor or their designee, is likely to require additional systemic glucocorticosteroid therapy during the study, (eg, asthma), is exclusionary
    a. However, treatment for asthma with inhalational CS therapy is allowed
8. Use or planned use of concomitant medication outside of standard of baseline treatment for SLE from Day -1 or for any time during the study
9. Active and clinically significant infection (bacterial, fungal, viral, or other) within 60 days prior to first dose of study drug. Clinically significant is defined as requiring systemic parenteral antibiotics or hospitalization
10. A history of opportunistic infection, or a history of recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years
11. Chronic viral hepatitis including hepatitis B (HBV) and hepatitis C (HCV) unless patient received curative treatment for HCV and has a documented negative viral load, known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness
12. Cryptosporidium in the stool sample at screening
13. White blood cells (WBC) < 1,200/mm^3 (1.2×10^9/L) at screening
14. Absolute neutrophil count (ANC) < 500/mm^3 at screening
15. CD4+ count < 150/µL at screening
16. Platelets < 50,000/mm^3 (50×10^9/L) or < 35,000/ mm^3 (35×10^9/L) if related to SLE, at screening
17. Hemoglobin < 8 g/dL or < 7 g/dL at screening if related to SLE
18. Proteinuria > 3.0 g/day (3000 mg/day) at screening or equivalent level of proteinuria as assessed by protein/creatinine ratio (3 mg/mg or 339 mg/mmol)
19. Serum creatinine > 2.0 mg/dL at screening or creatinine clearance (CrCL) < 40 ml/minute based on Cockcroft-Gault calculation
20. Serum alanine aminotransferase (ALT) and/or serum aspartate aminotransferase (AST) > 2 × the upper limit of normal (ULN) at screening, unless explicitly related to lupus based on the investigator's judgment

21. Creatinine kinase (CK) > 3.0 × ULN at screening unless related to lupus myositis
22. Total bilirubin > 1.5 × ULN at screening (unless related to Gilbert's syndrome)
23. Any other laboratory test results that, in the opinion of the Investigator or the sponsor or sponsor's designee, might place a patient at unacceptable risk for participating in this study
24. History of allergic or anaphylactic reaction to any therapeutic or diagnostic mAb (eg, IgG protein) or molecules made of components of mAbs
25. History substance and/or alcohol abuse, or dependence within the past 1 year, at the investigator's judgment
26. History of cancer within the last 5 years (except for cutaneous basal cell or squamous cell cancer, or cervical cancer in situ resolved by excision)
27. Any other severe acute or chronic medical or psychiatric condition, including recent (within the past year) medical conditions (eg, cardiovascular conditions, respiratory illnesses) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, sponsor or sponsor's designee, would make the patient inappropriate for entry into this study
28. Investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or patients who are employees of the sponsor or directly involved in the conduct of the trial
29. Currently participating in, or who have participated in other interventional (drug or device) clinical study within 30 days or 5 half-lives of baseline, whichever is longer
30. Recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4, or 5 on the C-SSRS
31. Current or pending incarceration
32. Current or pending compulsory detainment for treatment of either a psychiatric or physical (eg, infectious disease) illness
33. Currently taking a total daily dose of > 30 mg morphine or morphine equivalent (see APPENDIX 7)
34. Body mass index (BMI) ≥ 40.0

Statistical Considerations

Below is a summary of the statistical methods. Further details can be found in Section 8.

Two analyses are planned: 1) an interim analysis to select the POC dose based on the MAD data, and 2) a final analysis at study completion.

Additionally, DMC safety analyses will be performed for each MAD cohort and throughout the POC to monitor patient safety as described in the DMC charter. An additional analysis may be performed for the MAD portion of the study when all MAD patients have completed the safety follow-up, or withdrawn from the study, and prior to the final analysis. Data from the POC part of the study will be excluded from this additional analysis.

Unless stated otherwise, statistical testing will only be performed on the POC data and will be done using 2-sided overall alpha of 0.10. Data will be summarized descriptively by treatment and overall for each study phase. For the MAD portion, BOS161721 will be summarized overall and by each dose level and placebo patients from each cohort will be combined.

The descriptive summaries for the categorical data will include number and percentage. The descriptive summaries for the continuous data will include number, mean, median, standard deviations (SD), 25^{th} and 75^{th} percentiles, minimum, median, and maximum. Counts, medians, 25^{th} and 75^{th} percentiles, and standard error will be presented for time-to-event data.

All safety analyses will be performed using the safety analysis set (SS), defined as all patients who receive at least 1 dose of study treatment. All efficacy analyses will be performed using the full analysis set (FAS), defined as all patients who receive at least 1 dose of study treatment and have at least 1 evaluable post-baseline efficacy evaluation. Select efficacy analyses may also be performed on the per protocol (PP) set.

Binary efficacy endpoints, including the primary efficacy endpoint, will be assessed via Pearson's chi-squared analysis.

Continuous efficacy endpoints will be assessed via analysis of variance (ANOVA) or analysis of covariance (ANCOVA) when applicable, adjusting for the baseline value. Repeated measures mixed models may be performed to evaluate data collected at each visit and overall. Time-to-event endpoints will be assessed via Kaplan-Meier methodology and treatment will be compared using the log-rank test.

Adverse event data will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients experiencing any treatment-emergent AE, overall, and by system organ class and preferred term will be tabulated. Treatment-emergent AEs will also be summarized by severity and relationship.

Concomitant medications will be summarized, based on coded terms, using frequency and percentage of patients. Observed values and changes from baseline in vital signs, ECG readings, and hematology and clinical chemistry parameters, will be summarized at each individual visit.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANC	absolute neutrophil count
ANOVA	analysis of variance
ANCOVA	analysis of covariance
APL	antiphospholipid
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AZA	azathioprine
BICLA	BILAG-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
BW	body weight
C	complement
C-SSRS	Columbia Suicide Severity Rating Scale
CD	cluster of differentiation
CK	creatine kinase
C_L	systematic clearance
CLASI	Cutaneous Lupus Erythematosus Area and Severity Index
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CS	corticosteroids
CSR	clinical study report
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
dsDNA	double-stranded deoxyribonucleic acid
ECG	electrocardiogram
EOT	end of treatment
eCRF	electronic case report form
F	female
CCI	[redacted]

FAS	full analysis set
Fc	fragment crystallizable
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
eGFR	estimated glomerular filtration rate
GLP	Good Laboratory Practice
GWAS	genome-wide association studies
γc	gamma chain
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCl	hydrochloride
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IL	interleukin
IL-21R	interleukin 21 receptor
IM	intramuscular
IFNγ	interferon gamma
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
IVRS	interactive voice response system
JAK	Janus kinase
kg	kilogram
KLH	keyhole limpet hemocyanin
LOCF	last observation carried forward
M	male
mAb	monoclonal antibody
MAD	multiple ascending dose
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary of Regulatory Activities
MS	multiple sclerosis

MTX	methotrexate
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIAID/FAAN	National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network
NK	natural killer
NOAEL	no observed adverse event level
NO	nitric oxide
NSAID	nonsteroidal anti-inflammatory drug
OTC	over-the-counter
PD	pharmacodynamics
PEF	peak expiratory flow
PGA	Physician's Global Assessment
PK	pharmacokinetics
POC	proof of concept
PP	per protocol
PR	(interval) from onset of the p-wave to the end of the r-wave
pSS	primary Sjögren's syndrome
pSTAT3	phosphorylated signal transducer and activator of transcription 3
PT	preferred term
QRS	(interval) from the onset of the q-wave to the end of the s-wave
QT	(interval) from onset of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
QFT-G	QuantiFERON-TB Gold In-Tube
RA	rheumatoid arthritis
RR	(interval) from the onset of the r-wave to the onset of the next consecutive r-wave
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SDMT	safety data monitoring board
CCI [redacted]	[redacted]
SLE	systemic lupus erythematosus
SLEDAI-2K	SLE Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
Sm	Smith
SOC	system organ class
SRI-4	SLE Responder Index 4
SRI-5	SLE Responder Index 5
SRI-6	SLE Responder Index 6
SS	safety analysis set

SSA	Sjögren syndrome-A (Ro)
SSB	Sjögren syndrome-B (La)
STAT3	signal transducer and activator of transcription 3
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
TB	tuberculosis
TDAR	T-cell dependent antibody response
Tfh	T-follicular helper
Th	T-helper
TK	toxicokinetics
T_{max}	first time to maximum concentration
Treg	regulatory T-cell
ULN	upper limit of normal
US	United States
Vd	volume of distribution
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
YTE	triple mutation

1. INTRODUCTION AND RATIONALE

1.1 Indication

BOS161721 is a humanized monoclonal antibody (mAb), which binds to and inhibits interleukin-21 (IL-21) bioactivity, and is being developed for the treatment of moderately to severely active systemic lupus erythematosus (SLE) in adults.

1.2 Background and Rationale

1.2.1 Overview of the Disease State

SLE is a chronic inflammatory autoimmune disease that has variable manifestations in multiple organ systems and follows a relapsing and remitting course. The disease process includes abnormal immune responses mediated by tissue-binding autoantibodies and immune complex deposition, giving rise to tissue damage often resulting in end organ disease and even mortality. Survival of SLE has improved due to earlier detection, improved overall medical care, and standardized SLE treatment with corticosteroids (CS), immunosuppressants, and cytotoxic agents.[1] However, some of the morbidity in patients with SLE is related to its treatment. Comparison of early and late outcomes in patients with SLE demonstrate that death in early disease is most commonly due to infections and active SLE causing multi-system organ damage, while thromboses were the most common cause of death during later disease.[2]

The reported prevalence of SLE in the United States (US) is 20 to 70 cases per 100,000 people.[3] More than 90% of cases of SLE occur in women, frequently starting at childbearing age. Women of color are disproportionately affected by SLE. This suggests multiple genetic and environmental factors are at play. Accordingly, a multifactorial view of the immunopathogenesis of SLE suggests more than 1 area of interest, including breach in central tolerance in the adaptive arm of the immune system, peripheral amplification of the autoimmune response by the innate immune system, and local processes in the target organ that facilitate end-organ disease.[4]

1.2.2 BOS161721 Development

Boston Pharmaceuticals is developing BOS161721 for the treatment of SLE. BOS161721 is a humanized immunoglobulin G1 (IgG1) mAb with extended half-life directed against human IL-21.

Murine mAb 19E3, the progenitor of BOS161721, was generated using mouse hybridoma technology. 19E3 has subpicomolar (pM) affinity to human IL-21 and was selected for its potent neutralization of IL-21 bioactivity. BOS161721 was generated by the humanization of mAb 19E3 where its complementarity-determining regions were grafted onto a human IgG1 kappa backbone. The fragment crystallizable (Fc) portion of BOS161721 contains a YTE (M252Y/S254T/T256E triple mutation) in the constant domain of the IgG1 heavy chain that was introduced into the parental molecule, 19E3, intended to prolong the *in vivo* terminal elimination half-life ($t_{½}$) of the mAb.[5] Thus, BOS161721 retains sub-pM binding to IL-21 and prevents IL-21 from binding to the IL-21 receptor (IL-21R), inhibiting IL-21 bioactivity.

BOS161721 binds to human IL-21 and Cynomolgus monkey IL-21, which are highly homologous, and neutralizes the bioactivity of both. BOS161721 is specific for IL-21 as it does not bind to or inhibit the other gamma-chain (γc) family of cytokines, and acts to specifically neutralize the IL-21 pathway. In *in vitro* studies, BOS161721 inhibited downstream IL-21-induced signaling, IL-21-induced plasma cell differentiation, and IL-21-induced natural killer (NK) cell activation. In *in vivo* studies, BOS161721 significantly inhibited the T-cell dependent antibody response (TDAR) to immunization with a protein antigen as well as B-cell expansion following a second protein antigen immunization in Cynomolgus monkeys.

1.2.2.1 Interleukin-21

IL-21 is an inflammatory cytokine, which belongs to a family of cytokines that also includes IL-2, IL-4, IL-7, IL-9, and IL-15, all of which bind to private receptors in complex with the common cytokine receptor γc.[6] Most cytokines in this family are critically important for both the maintenance and function of T-cell and B-cell responses. IL-21 signals through a receptor complex consisting of its own private receptor, the IL-21R and γc.[6,7] Engagement of the IL-21R/γc complex leads to the activation of several signaling pathways, including the Janus kinase/signal transducer and activator of transcription, mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase pathways.[8] IL-21 is produced mainly by T-cells and NK T-cells, but neutrophils have also been reported to produce IL-21.[9,10] The IL-21R is expressed on a broad array of cell types, including B-cells, T-cells, NK-cells, macrophages and dendritic cells, as well as other hematopoietic and nonhematopoietic cells such as fibroblasts, keratinocytes, and intestinal epithelial cells.[9,11] Activation of signal transducer and activator of transcription 3 (STAT3) via phosphorylation is critical in regulating human B-cell responses to IL-21[12]; phosphorylated STAT3 (pSTAT3) forms a homodimer, which translocates to the nucleus where it initiates transcription of the IL-21 gene, forming an autocrine loop for IL-21 production via STAT3 phosphorylation.[13] In addition, IL-21 has been shown to upregulate expression of its own receptor[14] and induces an autocrine feedback loop.[15]

IL-21 modulates various aspects of immune function. It promotes cluster of differentiation 4 (CD4+) T-cell differentiation and promotes the generation of T-helper (Th)17[16] and T-follicular helper (Tfh) cells.[15,17] In mice, IL-21 has been shown to regulate the balance between Th17 and regulatory T-cell (Treg), in that it increases Th17, while inhibiting Treg differentiation.[18] Less is understood with regards to human Tregs, although IL-21 has been reported to counteract Treg suppression of human effector T-cells[19] and blockade of IL-21 promotes Treg generation in a murine model of graft versus host disease induced by human T-cells.[20] IL-21 upregulates CD8+ T-cell and NK-cell expansion and cytolytic activity by increasing granzyme B and perforin.[21,22] IL-21 also has been reported to increase granzyme B in plasmacytoid dendritic cells and B-cells resulting in inhibition of T-cell responses.[23,24] IL-21 also has a variety of effects on nonhematopoietic cells, such as stromal cells and induces inflammation through matrix metalloproteinase release by gut intestinal fibroblasts.[25]

One principal non-redundant role of IL-21 is the promotion of B-cell activation, differentiation, or death during humoral immune responses.[14] Furthermore, increased IL-21 production is characteristic of several autoimmune diseases and is likely to contribute to autoantibody production as well as pathologic features of autoimmune disease.[26] The critical role of IL-21 in promoting humoral and other immune responses makes it an important focus of potential

therapeutic interventions in conditions characterized by overproduction of pathogenic autoantibodies. IL-21 production by Tfh cells in humans is believed to play a major role in driving the autoantibody production through its role in plasma cell differentiation. Importantly, Tfh cell populations are expanded in patients with autoimmune diseases such as lupus, bullous pemphigoid, rheumatoid arthritis (RA) and primary Sjögren's syndrome (pSS) and have been reported to correlate with IL-21 levels, autoantibodies, and disease severity.[26,27,28,29] Furthermore, loss of number and functionality of Tregs has been associated with autoimmune diseases such as SLE and giant cell arteritis, which IL-21 is expected to modulate.[30,31] Thus, neutralization of IL-21 in settings of autoimmunity is expected to impact several cell populations believed to be involved in the pathogenesis of autoimmune disorders including SLE.

BOS161721 selectively binds IL-21 with high affinity to neutralize IL-21, and due to its pleiotropic nature, neutralization of IL-21 is expected to impact several cell populations believed to be involved in the pathogenesis of SLE. Importantly, patients with SLE have elevated IL-21 plasma levels that correlate with the severity of the disease. Recently, genome-wide association studies (GWAS) have provided convincing evidence that the chromosomal 4q 27 region harbors the IL-21 genes and is associated with chronic inflammatory disorders, including SLE.[29]

1.2.2.2 Preclinical Studies

The pharmacokinetics (PK) of BOS161721 were characterized following single-dose intravenous (IV) administration of BOS161721 (0.01 to 30 mg/kg) in male Cynomolgus monkeys or repeat, every 2 weeks IV administration (15 to 100 mg/kg) and subcutaneous (SC) administration (50 mg/kg) in male and female Cynomolgus monkeys. Systemic exposure was approximately dose-proportional within the tested dose range. SC bioavailability was determined to be 64.3%. CCI [redacted]

Two single-dose (IV) non-good laboratory practice (GLP) studies conducted in Cynomolgus monkeys evaluated the toxicity, pharmacodynamics (PD), toxicokinetics (TK), and immunogenicity of BOS161721. Following a single IV administration (slow bolus), there were no BOS161721-related adverse changes, resulting in a no-observed-adverse-effect-level (NOAEL) value of 30 mg/kg, the highest dose tested among 2 studies. CCI [redacted]

In a repeat-dose GLP toxicology study in Cynomolgus monkeys, BOS161721 was administered every 2 weeks by IV or SC (50 mg/kg) administration for 3 months (a total of 7 doses). CCI [redacted]

CCI [redacted] The NOAEL was determined to be 100 mg/kg (SC and IV), the highest dose tested.

An additional GLP, repeat-dose toxicity study was conducted in Cynomolgus monkeys (4 males and 4 females per dose group) following every 2 weeks (Q2W) administration by SC (10, 30, and 100 mg/kg) injection for a total of 14 doses. CCI [redacted] There were no BOS161721-related effects on survival, clinical signs, male body weights, ophthalmologic parameters, electrocardiogram (ECG) findings, clinical pathology, macroscopic observations, organ weights, or microscopic observations. CCI [redacted]

The 100 mg/kg/dose was the NOAEL CCI [redacted].

1.2.2.3 Clinical Studies

BOS161721-01 was a double-blind, Phase 1, single ascending dose (SAD) study to assess the safety, PK, and PD of BOS161721 in healthy subjects. The primary objective of the study was to characterize the safety and tolerability of IV and SC SADs of BOS161721 in an otherwise healthy subject population without concomitant illnesses, immune abnormalities, or concomitant medications. Secondary objectives included characterization of the PK and immunogenicity of BOS161721, and exploratory objectives included the evaluation of the effect of BOS161721 on TDAR to keyhole limpet hemocyanin (KLH) (primary and secondary immunizations) in healthy subjects, the effects of BOS161721 on plasma levels of IL-21 (free and bound), and the evaluation of the effect of BOS161721 on IL-21 gene expression (via gene signature) in blood. This study consisted of 8 cohorts. Subjects were randomized in a 3:1 ratio (BOS161721: placebo) and received either a single dose of BOS161721 (1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg) or placebo, with safety follow-up. For the first cohort, after the first 2 subjects were dosed (1 active and 1 placebo), there was a minimum gap of 48 hours before the remaining subjects from that cohort were dosed, to allow for an initial review of any emerging safety and tolerability data. For all cohorts, escalation to the next dose was not sooner

than 8 days after all the subjects in the prior cohort had been dosed and were based on a review of at least 7 days of safety and tolerability data by the Safety Data Monitoring Team (SDMT).

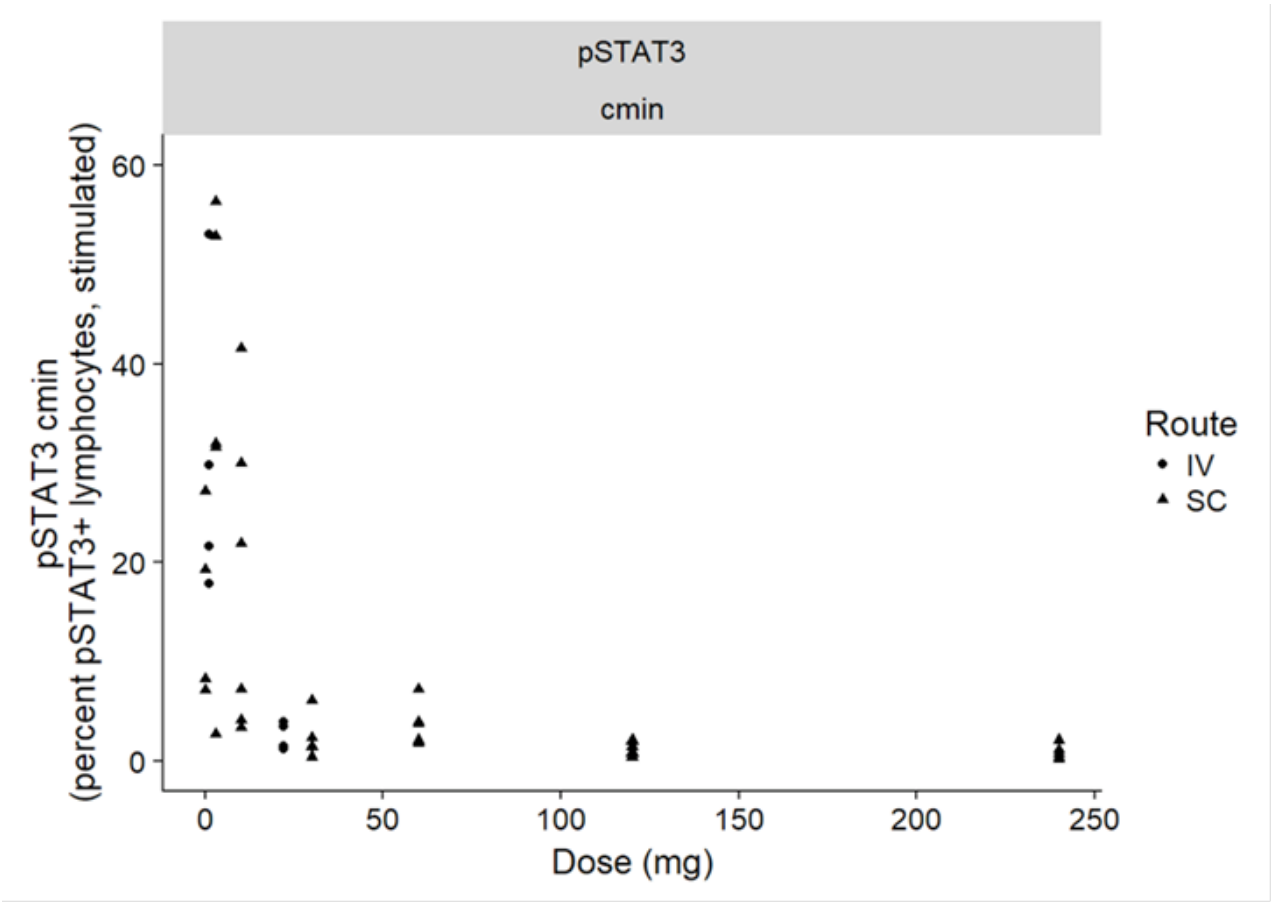
Blood samples were collected at every in-house study visit for BOS161721 concentration determinations. Blood samples were also collected for determination of IL-21 plasma levels (free and total). Safety was assessed based on the occurrence of treatment-emergent AEs, hepatic function abnormality, and acute and delayed hypersensitivity reactions. Other safety variables included ECGs, vital signs (blood pressure [BP], heart rate, and temperature), safety laboratory assessments, blood sampling for ADAs, total IgG and immunoglobulin M (IgM) levels, CD4+ count, and full and targeted physical examinations. Overall, there were no clinically significant findings from this study. Adverse events reported as related to the study drug, particularly infections, were expected for the compound, and there were no clinically relevant changes in laboratory and ECG results or vital signs. There was 1 serious adverse event (SAE; death due to pulmonary embolism) that occurred 127 days after a single administration of 240 mg SC dose of BOS161721. The causality of this single SAE was not attributed to study drug and further information can be found in the Investigator's Brochure. Final PK data from the SAD study demonstrates BOS161721 has a mean $t_{½}$ ranging from 80 to 87 days for doses of ≥ 30 mg in healthy subjects.

1.2.3 Study Dose Selection

Doses have been selected for the multiple ascending dose (MAD) Phase 1b portion based on a 90-day safety, tolerability, PK, and PD data review from the Phase 1 SAD study (BOS161721-01); the SDMT reviewed the blinded safety data from subjects for each dose cohort (8 cohorts, evaluating 1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg), along with the accumulated safety and available PK/PD data from all subjects in the previous dose cohorts, to make a decision on whether to proceed to the next higher dose level, repeat a dose level, or stop dose escalation. Overall, there were no clinically significant safety or tolerability findings from this study.

Based on the Day-90 interim cut of the PK and biomarker data in the BOS161721-01 study, the recommended doses for evaluation in the MAD portion of this study are 20, 60, and 120 mg SC monthly. This dose recommendation is supported by evidence of linear PK with BOS161721 resulting in a median first time to maximum concentration (T_{max}) of 6 days and an apparent terminal half-life of 44 days. Furthermore, pSTAT3 suppression, a marker of IL-21 target engagement, follows a similar time course of the mAb levels, with maximal and sustained suppression apparent with doses greater than 30 mg SC (Figure 1).

Figure 1. Individual pSTAT3 C_{min} Levels Versus Dose



IV = intravenous, pSTAT3 = phosphorylated signal transducer and activator of transcription 3; SC = subcutaneous

All doses selected for the MAD portion are projected not to exceed the mean exposure of that achieved following the highest single dose of 240 mg SC administered in the Phase 1 SAD study. Cohort 1 will include randomized treatment to the 20 mg dose. Based on the staggered study design, the data monitoring committee (DMC) will perform a scheduled review of safety data and sequentially consider dose escalation for Cohorts 2 and 3. In addition, the DMC and Boston Pharmaceuticals will conduct a data review to determine which dose will be carried forward into the proof of concept (POC) Phase 2 portion. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2 and 3 from the MAD portion (see Section 3.1.2.1 for the chosen POC dose and justification).

1.2.4 Risk-Benefit Assessment

The available preclinical data on BOS161721, the findings in clinical study BOS161721-01, and existing clinical information on IL-21 inhibitors suggest that the present clinical study has an acceptable risk-benefit ratio. In this study, the risk-benefit assessment of BOS161721 in adult patients with moderately to severely active SLE will be ongoing, with step-wise evaluations during the staggered MAD portion. The DMC used in this study is charged with assessing such actions in light of an acceptable benefit-risk profile for BOS161721 as an anti-IL-21 mAb.

Formal DMC monitoring meetings will occur as described in the DMC Charter. Two weeks after Cohort 1 has received a second dose of study drug, the DMC will evaluate the safety and tolerability data from Cohort 1 to determine the recommended dose for Cohort 2. Two weeks after 8 patients in Cohort 2 receive a second dose, the DMC will determine if dose escalation to Cohort 3 can proceed. Thirty days after the last patient in Cohort 3 receives the third dose, the DMC and Boston Pharmaceuticals will conduct a data review to determine which dose will be carried forward into the POC part of the study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2 and 3 during the MAD part of study. Thereafter, DMC safety reviews will be conducted periodically throughout the study as described in the DMC charter. With the agreement of the DMC and sponsor, this schedule may be modified depending on the rate of patient accrual. Additional details can be found in the DMC Charter.

The benefit of participation for all patients in this study is close monitoring of their medical condition and safety of their treatment. Those randomized to the active treatment arm may potentially experience improvement in their SLE disease. Those randomized to the placebo (in combination with standard of care) arm are not expected to obtain any additional benefit, beyond those of their background treatment, though close monitoring of their medical condition and safety may itself be associated with improving their SLE.

1.2.5 Potential Risks

Potential risks based on the mechanism of action of BOS161721 include infections, risks associated with the administration of any foreign protein or biologic agent, including injection site reaction, anaphylaxis, serious allergic reaction, and development of ADAs. ADAs could result in immune complex disease (with manifestations such as arthralgias, serum-sickness, and vasculitis), or altered BOS161721 levels or activity. Further details can be found in the current Investigator's Brochure (IB) for BOS161721, which contains comprehensive toxicology, preclinical and clinical information on BOS161721.

Two investigational drug products are considered to be in the same pharmacological class as BOS161721 based on interruption of signaling through the IL-21 signaling pathway. No potential risk generalizable across the class has been observed with these investigational products. Based on the clinical Phase 1 SAD study (BOS161721-01), AEs reported as related to the study drug, particularly infections (flu-like symptoms, etc.), were expected for the compound, and there were no clinically relevant changes in laboratory and ECG results or vital signs.

The majority of IgG elimination occurs via intracellular catabolism, following fluid-phase or receptor-mediated endocytosis. This type of endocytosis and elimination is a form of target-mediated disposition where the interaction of the drug and its pharmacological target (eg, a target receptor) serves as a significant contributor to the kinetics of antibody distribution and elimination. Renal elimination, which is a primary pathway of clearance of small-molecule drugs, is relatively unimportant for IgG, as its large size prevents efficient filtration through the glomerulus. Secretion into the bile is an important pathway of elimination of IgA antibodies, but this route is not a significant contributor to the elimination of IgG antibodies. Thus, risk to renal and hepatic systems due to metabolism of BOS161721 is low.[33]

1.2.5.1 Anaphylaxis and Serious Allergic Reactions

As with the administration of any foreign protein and/or other biological agents, acute hypersensitivity reactions, including acute anaphylactic/hypersensitivity, severe allergic, and anaphylactoid reactions may follow infusion of mAbs and can be caused by various mechanisms. These acute hypersensitivity reactions may be severe and result in death.

Anaphylaxis will be defined according to the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria,[34] and are discussed in Section 6.2.2.6.1.

Based on the Phase 1 SAD study (BOS161721-01), anaphylaxis and serious allergic reactions in subjects who received BOS161721 was not observed.

Patients with a known history of allergy or severe hypersensitivity reaction to any component of BOS161721 formulation or patients with a history of anaphylaxis to any other biological therapy such as mAbs will be excluded from studies with BOS161721. In addition, appropriate drugs and medical equipment to treat acute hypotensive, bronchoconstrictive, or anaphylactic reactions will be immediately available at the unit and study personnel will be trained to recognize and treat these reactions.

1.2.5.2 Injection Site Reactions

In a repeat-dose GLP toxicology study in Cynomolgus monkeys, BOS161721 was administered every 2 weeks by IV or SC for 3 months (a total of 7 doses). There were no injection site reactions in animals dosed subcutaneously. Further, there were no reports of injection site reactions in the 26-week GLP toxicology study in Cynomolgus monkeys.

Based on the Phase 1 SAD study (BOS161721-01), incidence of injection site reactions in subjects who received BOS161721 was similar to placebo.

Patients will be monitored for local injection site reactions in this study. See Section 6.2.7.

1.2.5.3 Immune Complex Disease

The potential risk of immune complex disease for BOS161721 is theoretical, based on the known risks associated with mAbs. The administration of a mAb can result in the formation of ADAs. Administration of the mAb in the presence of ADA may result in the formation of circulating antibody-antigen complexes potentially resulting in altered BOS161721 levels or activity or deposition of the complexes in microvasculature. Complement is frequently involved in the latter setting, and the breakdown products of complement attract polymorphonuclear leukocytes to the site of deposition where they can provoke local tissue damage through specific or nonspecific release of enzymes. Two of the more common end-organ targets are the blood vessels (vasculitis) and kidney (nephritis). These clinical manifestations represent immune complex disease or Type III hypersensitivity. Although BOS161721 is a humanized mAb, ADAs may develop; however, the likelihood of occurrence of immune complex disease with BOS161721 is low. The findings of immune complex disease are typically reversible when mAb administration stops and the antibody-antigen complexes are cleared from the body.

Based on the Phase 1 SAD study (BOS161721-01), immune complex disease in subjects who received BOS161721 was not observed.

1.2.5.4 Infections

BOS161721 is expected to diminish the activity of T-cell, B-cell and NK-cell lines. Like other medications modulating immune response, BOS161721 may increase the potential risk for infection, including serious infections. IL-21 produced by CD4+ Th cells is required to sustain the anti-viral function of CD8+ T-cells against chronic viral infections. Nonclinical evidence suggests that the risk of chronic viral infection recurrence or increased severity may occur with IL-21 inhibition.[35]

These conditions will be fully characterized with clinical descriptions and routine laboratory and/or specialty testing and treated where indicated with appropriate local standard of care.

Patients with a history of opportunistic infection, including recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years, or any other underlying pathology predisposing to serious infection, are excluded from studies with BOS161721 (for further details please refer to the current IB for BOS161721).

Patients will be assessed for hepatitis B, and C, and HIV-1/2 combination, at screening.

Cryptosporidium Infection

Cryptosporidium infection was noted in patients with an IL-21 receptor loss-of-function gene mutation and similar findings of cryptosporidium infection have been observed in immunosuppressed liver transplant and human immunodeficiency virus patients.[36,37] Since BOS161721 is expected to diminish the immunosurveillance activity of T-cell, B-cell, and NK-cell lines, a similar risk is biologically plausible with prolonged exposure to BOS161721.

Since the risk of opportunistic cryptosporidium infection increases with low levels of CD4+ T-cells,[37] patients with a CD4+ count < 500 cell/mm^3 were excluded from the Phase 1 SAD study (BOS161721-01), and CD4 + < 350 cells/mm^3 will be excluded from the MAD/POC parts of the study. Patients exposed to investigational product who develop diarrhea during the course of the study should immediately undergo an assessment for opportunistic infection including stool for ova and parasites and stool examination for cryptosporidium. Positive cryptosporidium in stool sample at screening is an exclusion. Treatment by the investigator where indicated should be guided by findings and be consistent with local standard of care.

Based on the Phase 1 SAD study (BOS161721-01), infections in subjects who received BOS161721 was not observed.

1.2.5.5 Malignancy

The stimulatory effect of IL-21 on NK cells and CD8+ T-cells suggests the cytokine may have anti-tumor activity. Nonclinical studies have demonstrated significant anti-tumor effects of IL-21 in a number of tumor models. IL-21 therapy of human metastatic melanoma and renal cell carcinoma has demonstrated POC with significant increases in levels of perforin, granzyme B,

and interferon gamma (IFNγ) expression in CD8+ T-cells and NK T-cells. Clinical response has been limited in these generally unmanageable diseases.

The impact of treatment with anti-IL-21 therapy on the development or growth of malignancies is not known; however, as with other immunomodulatory biologic agents, treatment with BOS161721 may result in an increase in the risk of malignancies. NK cell suppression by IL-21 neutralization may represent a biological mechanism for a potential risk for malignancy. Patients with a history or current diagnosis of cancer within the past 5 years, with the exception of non-melanoma skin cancer or cervical cancer in situ treated with apparent success with curative therapy, are excluded from the study.

Based on the Phase 1 SAD study (BOS161721-01), malignancy in subjects who received BOS161721 was not observed.

1.2.5.6 Hepatic Function Abnormality

There is no substantial evidence suggesting BOS161721 is associated with liver function abnormality. However, as a precaution, patients with a history of abnormal alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), or bilirubin at screening (ALT/AST > 2 × upper limit of normal [ULN]; total bilirubin > 1.5 × [ULN] and judged by the investigator to be clinically significant) were excluded from the Phase 1 SAD study (BOS161721-01), and will be excluded from this trial. Patients with a positive hepatitis B or C test or a history of alcohol dependence will also be excluded.

Based on the Phase 1 SAD study (BOS161721-01), hepatic function abnormality in subjects who received BOS161721 was not observed.

1.2.5.7 Failure of Vaccination

IL-21 is a key cytokine in development of B-cells into immunoglobulin-secreting plasma cells. Abnormal signaling through the IL-21R/Janus Kinase (JAK)3/signal transducer and activator of transcription (STAT3) pathway leads to defective humoral immune responses to both T-dependent and T-independent antigens and impairs the establishment of long-lasting B-cell memory. Abnormal signaling through the pathway has been related to decreased specific antibody responses following vaccination, and to increased susceptibility to encapsulated bacterial infections.[38]

The effect of BOS161721 was evaluated in *in vivo* single dose studies in Cynomolgus monkey in which the animals received vaccination to T-cell dependent KLH antigen to stimulate a TDAR. These *in vivo* studies demonstrated that BOS161721 significantly inhibited B-cell proliferation and IgG antibody responses to the KLH protein antigen in a dose-dependent fashion; however, BOS161721 administration did not affect anti-tetanus toxoid antibody data for IgM, IgG, IgG1, or immunoglobulin E (IgE) during the dosing phase in the same study.

1.2.5.8 Potential for Drug-Drug Interactions

Drug-drug interactions were not evaluated in the Phase 1 SAD study (BOS161721-01), which included only healthy adult subjects. Use of prescription medications (with the exceptions of

oral contraceptives), and over-the-counter (OTC) treatments including herbal supplements such as St John's Wort (except multivitamins), in the 2 weeks prior to screening was prohibited in the SAD study.

See Section 4.5 for other specific exclusion criteria which support lowered risk of interactions, and Section 4.6.1 for corticosteroid (CS) dosing. In addition, Section 1.2.5.6 describes considerations for hepatic function for this study.

1.2.5.9 Potential Risk to Fetal Development

No data on preclinical reproductive toxicity are available at the time of this study.

2 STUDY OBJECTIVES AND ENDPOINTS

This trial has separate objectives and endpoints for the MAD Phase 1b and POC Phase 2 portions of the study. The primary, secondary, and exploratory objectives for each phase, as applicable, are described below with their corresponding endpoints.

2.1 Phase 1b Multiple Ascending Dose

OBJECTIVES	ENDPOINTS
Primary	
• To assess safety, tolerability, and immunogenicity of repeat doses of BOS161721 (20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment, in order to estimate the optimal dose.	Safety Endpoints • Incidence and severity of AEs and SAEs, related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • Columbia Suicide Severity Rating Scale (C-SSRS) • 12-lead ECGs parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from baseline • Physical examinations changes from baseline • ADAs • Study drug exposure/compliance
Secondary	
• To characterize the PK of BOS161721 and select the optimal dose of BOS161721 based on safety, PK, and PD effects in patients with moderately to severely active SLE.	Pharmacokinetic Endpoints • BOS161721 concentration by visit and time point • Maximum observed concentration (C_{max}), T_{max}, area under the concentration-time curve (AUC), terminal elimination half-life ($t_{½}$), systematic clearance (C_L), volume of distribution (V_d) Pharmacodynamic Endpoints • Results and changes (or shifts) from baseline to each visit in phosphorylated signal transducer and activator of transcription 3 (pSTAT3), C3 and C4 levels, and leukocyte immunophenotype • Results and changes (or shifts) from baseline in anti-double-stranded DNA (dsDNA), antinuclear antibodies (ANA), anti-Sjögren syndrome A and B (SSA, SSB), Smith (Sm), and antiphospholipid (APL) autoantibodies at each visit • Results and changes (or shifts) from baseline in abrogation of IL-21 gene signature at each indicated visit

Exploratory	
• CCI	CCI - CCI • CCI • CCI
• CCI	• CCI
• CCI	• CCI

2.2 Phase 2 Proof of Concept

OBJECTIVES	ENDPOINTS
Primary	
• To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on the SRI-4	Primary Efficacy Endpoint • The proportion of patients with a SRI-4 response at Day 210 (see Section 6.3.4.1)
Secondary	
To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on clinical indicators of SLE activity, in adult patients with moderately to severely active SLE on limited background standard of care treatment	Secondary Efficacy Endpoints • The proportion of patients with: - SRI-4 response at each visit - SRI-5 and SRI-6 response at each visit (Section 6.3.4.2) - a sustained reduction from baseline of oral corticosteroid (CS) (≤ 7.5 mg/day and < Day 0 dose) between Day 150 and Day 210 - new or recurrent BILAG flares (≥ 1 qualifying BILAG A or > 1 qualifying BILAG B) through Day 210 - PGA worsening - a BICLA response - a CLASI response - medication failures • Results and changes from baseline in: - CLASI - Total number of swollen joints, tender joints, and active joints (swelling and tenderness in the same joint) in the ACR-28 joint count - SLEDAI-2K - SLICC/ACR damage index • Time to medication failure • Group mean percent reduction in CS administration from baseline Day 0 dose through Day 210 in patients receiving ≥ 7.5 mg/day prednisone equivalent at Day 0 • Duration of longest SRI-4 response • Time to first SRI-4 response • Time to first BILAG flare (≥ 1 new or recurrent BILAG A or > 1 new or recurrent BILAG B) relative to baseline through Day 210
Safety	
• To assess safety and tolerability of repeat doses of BOS161721 at the chosen dose administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment	Safety Endpoints • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • C-SSRS • 12-lead ECGs parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline

	• Clinical laboratory results and change from baseline • Physical examinations changes from baseline • ADAs • Study drug exposure/compliance

Exploratory	
• CCI [redacted]	CCI [redacted] CCI [redacted] [redacted] [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

3 STUDY PLAN

3.1 Study Design

This is a Phase 1b/2 combined, randomized, multicenter, double-blind, placebo-controlled trial to study the clinical efficacy, safety, and PK of SC doses of BOS161721 in adult patients with moderately to severely active SLE. After successfully completing a screening phase, eligible patients will be randomized to a specified dose of BOS161721 or placebo. The dosing schedule will be monthly.

The trial will consist of 2 double-blinded portions: MAD Phase 1b and POC Phase 2. Patients may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180, followed by safety follow-up visits at Days 210, 240, and 270.

SLE disease activity assessment data will be centrally reviewed by medical monitor and sponsor to ensure the scores are clinically meaningful and compliant with specific definition. The scope of responsibility includes, but is not limited to, review and confirmation of "A" and "B" BILAG system organ disease, confirmation of clinical components of the SLEDAI-2K score at screening and during the study, and cross-validation of the instruments used in this study to assess the disease activity. Further details on the content and methods of data reports by the medical

monitor and sponsor will be outlined in the Medical Data Review Plan along with the processes and procedures that will be followed.

3.1.1 Multiple Ascending Dose Phase 1b

The MAD portion will consist of 3 cohorts:

- Cohort 1 (20 mg SC) will include 6 patients
    - 5 patients will receive BOS161721 (active group) and 1 patient will receive placebo (placebo group)
- Cohorts 2 (60 mg SC) and 3 (120 mg SC) will include 12 patients each
    - 9 patients in the active group and 3 in the placebo group

Doses selected for each of the 3 cohorts is based on a 90-day safety, tolerability, PK and PD data review from the Phase 1 SAD study (BOS161721-01) in healthy subjects. All doses selected for the MAD part of the study are projected not to exceed the mean exposure of that achieved in the SAD study.

3.1.1.1 Dose Escalation for the MAD Portion

The MAD portion of the study design is staggered, where after the 6 patients in Cohort 1 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 2 begins dosing (after the DMC evaluation of the safety and tolerability data from Cohort 1). Similarly, after 8 of the 12 patients in Cohort 2 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 3 begins dosing after the DMC evaluation of the safety and tolerability data from Cohorts 1 and 2. Each cohort will continue at their assigned dose level through their respective 6-month treatment periods (See Study Schematic, Section 3.1). If patients discontinue the study in a cohort prior to adequate safety follow-up, he/she may be replaced.

Criteria for dose escalation are further described in the DMC Charter. See Section 3.1.1.2 for additional details about DLTs.

3.1.1.2 Dose Limiting Toxicity (DLT)

Severity of adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. For the purpose of dose escalation, any of the following AEs occurring after study drug administration, which are attributable to the study drug, will be considered DLTs:

Hematologic:

- Grade 4 neutropenia
- Grade 3 neutropenic infection

- Grade 3 thrombocytopenia with bleeding
- Grade 4 thrombocytopenia

Non-Hematologic:

- Grade 3 or above toxicities, persisting after optimal treatment with standard medical therapy (eg, anti-emetics, anti-diarrheals)
- Drug-induced liver injury ([DILI], Hy's Law), as defined in Section 6.2.2.6.3

Investigators should always manage their patients according to their medical judgment which may include interruption of study drug based on the particular clinical circumstances.

3.1.1.3 DMC Recommendations

During scheduled meetings, the DMC will review relevant study data for safety or benefit-risk concern. During the MAD part of the study, the DMC may provide the following recommendations to the sponsor:

- Expanding a cohort at a specific dosing level, or repeating a lower dose in a subsequent cohort
- Continuing a dose level for a given cohort
- Escalating a dose level for a subsequent cohort
- Termination of current or previous cohort(s)

Further dosing in a given cohort will be halted if 2 or more DLTs are identified intra- and inter-patients dosed. For the POC portion, the DMC and Boston Pharmaceuticals will conduct a data review to determine which dose will be carried forward into the POC Phase 2 part of the study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2, and 3; this dose will not exceed doses tested during the MAD portion. The DMC will be reviewing all relevant data from Cohorts 1, 2, and 3 that is available 30 days after the last patient from Cohort 3 receives the third dose. Details are provided in the DMC Charter.

3.1.2 POC Phase 2

3.1.2.1 BOS161721 POC Dose Selection and Justification

The dose for the POC portion of the study is 120 mg administered SC monthly (a total of 7 doses). The rationale for the BOS161721-02 Phase 2 POC dose selection was based on cumulative safety, tolerability, immunogenicity, PK, and PD data available from an interim analysis (IA) performed during the MAD Phase 1b portion of the trial.

The data cut-off for this IA occurred on CCI and included all 6 patients and 7 doses from Cohort 1 (20 mg), 12 patients and 6 doses from Cohort 2 (60 mg), and 12 patients and 4 doses from Cohort 3 (120 mg).

The safety analysis focused on incidence and severity of all AEs, SAEs, and pre-determined adverse events of special interest (see Section 6.2.2.6). The DMC and designated unblinded Boston Pharmaceuticals team met on CCI and did not identify any untoward safety signals at any BOS161721 dose levels.

Because there were no safety, tolerability, or immunogenicity trends observed at the time of the IA, the Phase 2 POC dose selection was made based on available PK and PD data. pSTAT3 levels were assessed as the primary PD biomarker of IL-21R signaling levels. This is because IL-21R signaling, upon IL-21 binding, initially involves phosphorylation of JAK1/JAK3 which dissociate from the receptor complex, and phosphorylate STAT3 which translocates to the nucleus and drives IL-21-regulated gene expression. CCI .

The 120 mg dose was communicated to site investigators participating in the POC Phase 2 portion, and to Institutional Review Boards (IRBs) and the Independent Ethics Committee (IEC).

3.1.2.2 POC Study Design

For the POC part of the study, approximately 156 additional patients will be randomized to active or placebo groups in a 2:1 ratio.

As in the MAD part of the study, each patient in the POC portion may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180. Assessments will be completed according to the Schedule of Assessments (Table 1 and Table 4).

DMC safety reviews will be conducted periodically throughout the study as described in the DMC charter.

3.2 Randomization and Blinding

This is a randomized, double-blind study.

Patients meeting all inclusion and exclusion criteria will be centrally randomized to either placebo or BOS161721 using an IWRS according to a randomization list generated by an independent, non-study statistician. Randomization will be performed separately for each study portion and separately for each cohort in the Phase 1b and 2 portions as follows:

Phase/Cohort	Number of Patients	Randomization Ratio BOS161721:Placebo
Phase 1b/Cohort 1	6	5:1
Phase 1b/Cohort 2	12	3:1
Phase 1b/Cohort 3	12	3:1
Phase 2	156*	2:1

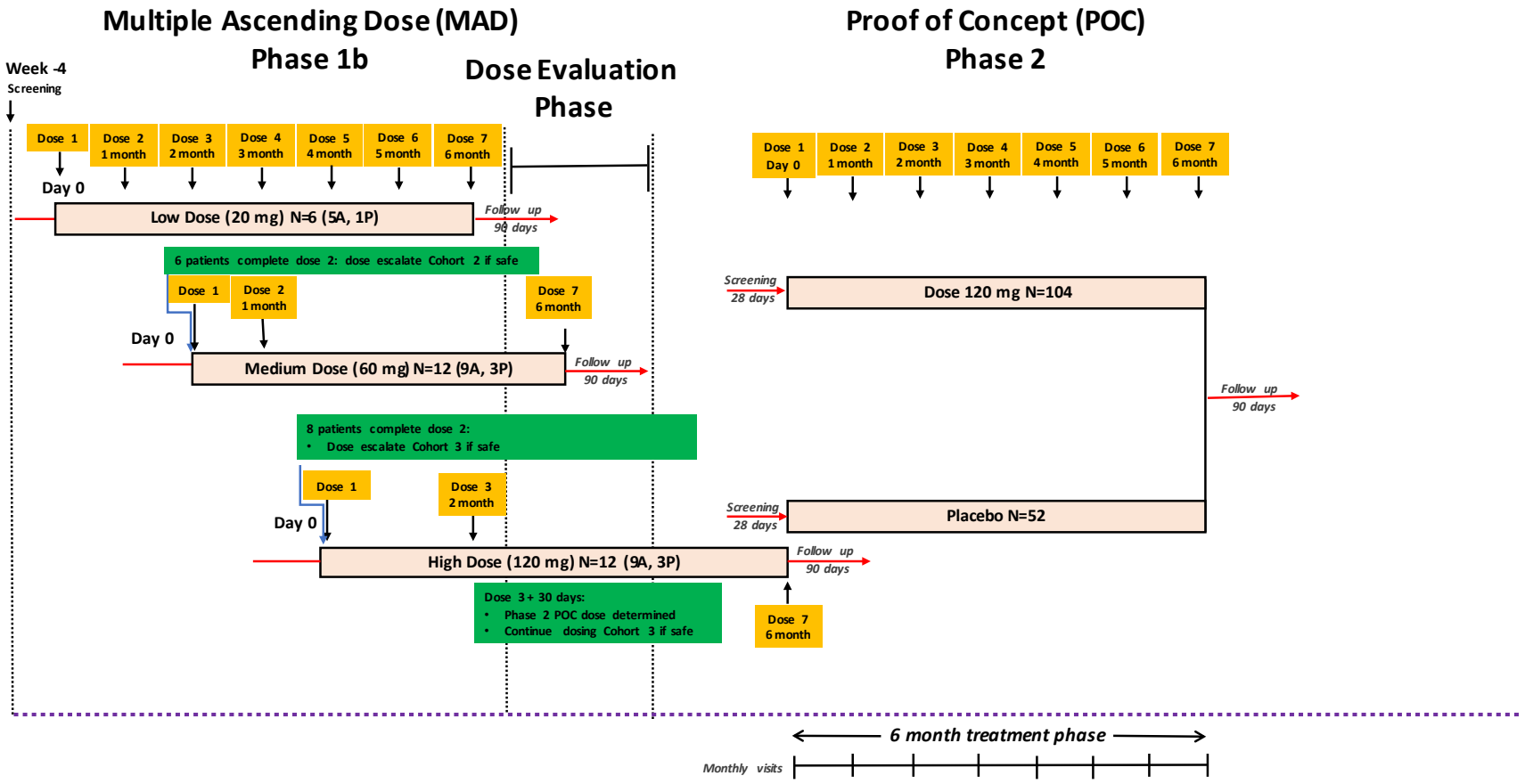
*Additional patients may be enrolled to ensure sufficient numbers of patients are in the full analysis set (FAS).

Eligible patients will be assigned to the study portion which is active at time of enrollment. Similarly, patients in the Phase 1b MAD will be assigned to the cohort which is active. Each patient will be assigned a unique randomization number which will not be reused.

All patients, investigators, and study team participants will be blinded to treatment assignment. An independent biostatistician not otherwise involved on the study will be unblinded and prepare materials for the IA, ad hoc analyses as needed, and the DMC safety reviews. The DMC will review unblinded data during safety reviews and the IA. A limited team at Boston Pharmaceuticals will review unblinded results from the Phase 1b MAD portion during the IA to determine the dose that will be used for the Phase 2 POC portion of the study. Details regarding maintenance of the blinding and content of data reviews will be described in the DMC charter or related study documentation.

3.3 Study Schematic

Figure 2. Study Diagram for MAD Phase 1b and POC Phase 2



A = active drug (BOS161721); P = placebo

3.4 Schedule of Assessments

Table 1. Schedule of Assessments - Phase 2 Proof of Concept (POC)

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187[b] (± 3)**	**195[b] (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
GENERAL ASSESSMENTS														
Informed consent	X													
Inclusion/Exclusion criteria	X													
Medical history	X													
Demographics	X													
SLICC Criteria for SLE	X													
Concomitant medication[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[d]		X												
BOS161721 or placebo dosing		X		X	X	X	X	X	X					
SAFETY ASSESSMENTS														
Full physical exam	X	X												
Chest x-ray[e]	X													
C-SSRS	X	X				X			X					
AEs and SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[f]	X	X		X		X								X
Injection site reaction assessment		X[g]		X	X	X	X	X	X	X	X	X	X	X
Targeted physical examination			X	X	X	X	X	X	X			X	X	X
Vital signs (BP, HR, and temperature)[h]	X	X	X	X	X	X	X	X	X			X	X	X
EFFICACY ASSESSMENTS														
BILAG-2004 Index	X	X		X	X	X	X	X	X			X	X	X
SLEDAI-2K	X	X[i]		X	X	X	X	X	X			X	X	X
PGA	X	X		X	X	X	X	X	X			X	X	X
ACR-28 joint count	X	X		X	X	X	X	X	X			X	X	X
CLASI	X	X		X	X	X	X	X	X			X	X	X
CCI		X		X	X	X	X	X	X			X	X	X

Table 1. Schedule of Assessments - Phase 2 Proof of Concept (POC)

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187[b] (± 3)**	**195[b] (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
SLICC/ACR Damage Index		X							X					
CCI		X		X	X	X	X	X	X			X	X	X
LABORATORY ASSESSMENTS														
CD4+ count	X	X	X	X		X			X					
Clinical laboratory assessments (hematology and clinical chemistry)[j]	X	X		X	X	X	X	X	X			X	X	X
Coomb's test direct[k]	X	X		X	X	X	X	X	X			X	X	X
Total IgG and IgM	X	X	X	X		X			X					
Plasma CCI	X	X		X	X	X	X	X	X			X	X	X
Plasma CCI & CCI		X	X	X		X			X					
ADA[l]		X	X	X	X	X			X					X
nAb[m]						X			X					
CCI		X	X			X			X					X
CCI		X												
CCI	X	X		X	X	X	X	X	X			X[n]	X[n]	X[n]
CRP	X					X								X
Serum pregnancy test (women)	X													
FSH (postmenopausal women)	X													
Urine pregnancy test (women)[o]		X		X	X	X	X	X	X					X
TB test (QuantiFERON-TB Gold In-Tube)[e]	X													
Serology (hepatitis B and C, HIV-1/2 combination)	X													
Stool sample[p]	X													

Table 1. Schedule of Assessments - Phase 2 Proof of Concept (POC)

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187[b] (± 3)**	**195[b] (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
Spot urine for protein/creatinine ratio	X	X		X	X	X	X	X	X			X	X	X
Urinalysis	X	X		X	X	X	X	X	X			X	X	X
PK Labs[b]														
Predose		X		X	X	X	X	X	X					
Postdose			X							X	X	X	X	X

Abbreviations: ACR = American College of Rheumatology; ADA= anti-drug antibody; AE = adverse event; CCI [redacted]; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; C = complement; CD4+ = cluster of differentiation 4; CLASI = Cutaneous Lupus Area and Severity Index; CRP = C-reactive protein; C-SSRS = Columbia Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; CCI [redacted]; FSH = follicle stimulating hormone; h = hour; HR = heart rate; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IL-21 = interleukin 21; IV = intravenous; m = minute; nAb = neutralizing antibody; PGA = Physician's Global Assessment; PK = pharmacokinetic; SAE = serious adverse event; SC = subcutaneous; CCI [redacted]; SLEDAI-2K = SLE Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; CCI [redacted]; TB = tuberculosis; TDAR = T-cell dependent antigen response.

[a] Screening assessments will be performed over more than 1 visit.

[b] PK samples will only be collected at the investigational sites that participate in the PK portion of the study. On PK only days (ie, Day 187 and Day 195 when no laboratory assessments are scheduled) samples will be collected at the investigational sites of the selected countries that participate in the PK portion of the study. Patients not participating in PK are not required to return for investigation site visits on Days 187 and 195.

[c] Concomitant use of oral corticosteroids: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the dose must be stable for at least 6 weeks prior to Day 0 (randomization day). See Section 4.6.1 for further details.

[d] Randomization should occur after patient eligibility has been confirmed. The actual randomization procedure can be completed on Day -1 after eligibility confirmation or the morning of Day 0 prior to dosing for logistical purposes.

[e] If patients have had a TB test and chest x ray within 3 months prior to screening, then these assessments do not need to be repeated during screening. The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

[f] ECGs will be performed after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws.

[g] Injection site reaction assessments to be performed at 2 hours postdose.

[h] Vital signs will be assessed after the patient has been supine and at rest ≥ 5 minutes. Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours postdose, as well as on each of the scheduled outpatient days in the table above (excluding PK-only site visits at Days 187 and 195). When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

[i] SLEDAI-2K should be done before randomization and dosing on Day 0 as SLEDAI-2K < 6 is exclusionary.

Table 1. Schedule of Assessments - Phase 2 Proof of Concept (POC)

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187[b] (± 3)**	**195[b] (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**

j Clinical laboratory assessments will include a fasting glucose and lipid panel, with exception of screening (Visit 1) which will be nonfasting.

k When clinically indicated for hemolytic anemia.

l Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only assayed (analyzed) if the patient had a positive ADA on Day 90.

m nAb is collected for all patients, though will only be analyzed by central lab if patient is positive for ADA at Day 90.

n CCI will not be analyzed during safety follow-up visits.

o Urine pregnancy test will be collected on WOCBP prior to study drug administration on dosing visits.

p Cryptosporidium test is required at screening. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

3.5 End of Study

End of Study (Individual Patient): A patient is considered at the end of study if he/she has withdrawn, prematurely discontinued, or completed all of the study procedures including the last visit.

End of Study (End of trial): The end of the study is defined as the date of the last visit of the last patient in the study globally, or the date of which the last patient withdraws or discontinues if all prior enrolled patients have already completed/withdrawn.

4 POPULATION

4.1 Participant Recruitment

Advertisements approved by the IRB, and investigator databases, may be used as recruitment procedures for adult men and women with moderately to severely active SLE.

4.2 Number of Patients

Approximately 186 male and female patients are planned for enrollment, but may be adjusted upward according to the dropout (noncompliance) rate, which will be monitored in a blinded fashion in an ongoing basis. Approximately 30 patients will be randomized for the MAD Phase 1b portion, and approximately 156 additional patients will be randomized in the POC Phase 2 portion. Note that approximately 24 dropouts are assumed.

4.3 Patient Screening

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular individual. Patient eligibility will be reviewed and confirmed by the medical monitor or designee prior to randomization. Screening assessments (see the Schedule of Assessments [Table 1 and Table 4]) for this study must be performed between Day -28 and Day -1.

4.4 Inclusion Criteria

Patients who meet the following criteria will be considered eligible to participate in this clinical study:

1. Men and women, ages 18 to 70 years, inclusive
2. Patients must be mentally capable of giving consent and there must be evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study
3. Patients must have SLE as defined by meeting 4 of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE (with at least 1 clinical and 1

immunologic criterion or Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies), either sequentially or simultaneously

4. At screening, patients must have at least 1 of the following:
   a. Elevated ANA ≥ 1:80 via immunofluorescent assay at the central laboratory
   b. Positive anti-dsDNA or anti-Smith (Sm) above the normal level as determined by the central laboratory
5. At screening, the total SLEDAI-2K score must be ≥ 8, including points from at least 1 of the following clinical components:
   a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis

   Note: Points from lupus headache and organic brain syndrome will also be excluded from qualifying total and clinical SLEDAI-2K scores at screening and Day 0.

6. A clinical SLEDAI-2K score of ≥ 6 at screening at Day 0. Clinical SLEDAI-2K score is defined as follows:
   a. Contains points from arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, or vasculitis
   b. Excludes parameters which require central laboratory results: hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia

   Note: Points from lupus headache and organic brain syndrome will also be excluded from qualifying total and clinical SLEDAI-2K scores at screening and Day 0.

7. Patients must have at least 1 qualifying A or 2Bs from the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer:
   a. BILAG A or B score in the mucocutaneous body system. If a BILAG B score is due to BILAG number 6, mild skin eruption, the CLASI activity score including erythema and scale/hypertrophy must be ≥ 3 excluding points from mucosal ulcers and alopecia.
   b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis defined as follows:
      i. "BILAG A:" Severe Arthritis, (BILAG item number 41), manifested by observed active synovitis defined by BOTH swelling and tenderness in ≥ 6 joints with marked loss of functional range of movements and significant impairment of basic activities of daily living (ADLs) that has been present on several days (> 4 days) cumulatively over the past 30 days, including at the time of the screening visit. See APPENDIX 5 for additional detailed specifications.

         - Basic ADLs are defined as the following activities which require assistance or assistive devices, (at least 1 must be present and documented in source):

- Ambulation, toileting, grooming- including bathing and dressing; feeding oneself

ii. "BILAG B:" Moderate Arthritis, Tendonitis or Tenosynovitis, (BILAG item number 42), defined as tendonitis/tenosynovitis, or active synovitis defined by BOTH swelling and tenderness in ≥ 3 joints, (observed or through patient history), with some loss of functional range of movements manifested by effects on instrumental ADLs such as:

- Cooking, driving, using the telephone or computer, shopping, cleaning, etc., and has been present on several days over the last 30 days, and is present at the time of the screening visit

Note: Hips, shoulders, back, neck, and temporomandibular joints do not count towards the total number of joints with active synovitis.

If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in at least 1 other body system for a total of 2 "B" BILAG body system scores.

8. Patients must be currently receiving at least 1 of the following:
   a. Administration for a minimum of 12 weeks, and a stable dose for at least 56 days (8 weeks prior to Day 0) of the following permitted steroid-sparing agents:
      i. Azathioprine (AZA), mycophenolate mofetil or mycophenolic acid, chloroquine, hydroxychloroquine, or methotrexate (MTX)
   b. If AZA, myocophenolate mofetil, mycophenolic acid, hydroxychloroquine, or MTX were discontinued prior to screening, the washout period must be ≥ 12 weeks.
   c. Corticosteroids (prednisone or prednisone-equivalent) at a stable dose of up to 30 mg/day for at least 6 weeks prior to Day 0 (see APPENDIX 3)
      i. For patients whose only SLE treatment is CS, the stable CS dose must be ≥ 10 mg/day for at least 6 weeks prior to Day 0 and no more than 30 mg/day at the time of randomization.
      ii. Topical steroids may be used, but the dose must be stable for at least 6 weeks prior to Day 0. PRN topical steroids are not permitted.
9. Women of childbearing potential (WOCBP; see Section 4.7 for full information regarding WOCBP, definition of menopause, and contraception):
   a. Must have a negative serum pregnancy test at screening. Urine pregnancy test must be negative prior to first dose
   b. Must not be breastfeeding

   c. Must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 52 weeks

10. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 52 weeks
11. Patients must demonstrate willingness and ability to comply with the scheduled study visits, treatment plans, laboratory tests, and other procedures

4.5 Exclusion Criteria

Patients presenting with any of the following will not be included in this study:

1. Drug-induced SLE, rather than "idiopathic" SLE
2. Other systemic autoimmune disease (eg, erosive arthritis, rheumatoid arthritis [RA], multiple sclerosis [MS], systemic sclerosis, or vasculitis not related to SLE)
   a. RA-Lupus overlap (Rupus), and secondary Sjögren syndrome are allowed
3. Any major surgery within 6 weeks of study drug administration, (Day 0), or any elective surgery planned during the course of the study
4. Any history or risk for tuberculosis (TB), specifically those with:
   a. Current clinical, radiographic, or laboratory evidence of active TB
   b. History of active TB
   c. Latent TB defined as positive QuantiFERON-TB Gold In-Tube (QFT-G) or other diagnostic test in the absence of clinical manifestations. Latent TB is not excluded if the patient has documented completion of adequate course of prophylactic treatment with regimen recommended by local health authority guideline, or the patient has started treatment with isoniazid, or other regimen recommended by local health authority guidelines for at least 1 month before Day 0 and continues to receive the prophylactic treatment during study until the treatment course is completed.
5. Active or unstable lupus neuropsychiatric manifestations, including but not limited to any condition defined by BILAG A criteria, with the exception of mononeuritis multiplex and polyneuropathy, which are allowed
6. Severe proliferative lupus nephritis, (WHO Class III, IV), which requires or may require induction treatment with cytotoxic agents or high dose CS
7. Concomitant illness that, in the opinion of the investigator or the sponsor or their designee, is likely to require additional systemic glucocorticosteroid therapy during the study, (eg, asthma), is exclusionary
   a. However, treatment for asthma with inhalational CS therapy is allowed
8. Use or planned use of concomitant medication outside of standard of baseline treatment for SLE from Day -1 or for any time during the study. (See Section 4.6 for prohibited concomitant medication)

9. Active and clinically significant infection (bacterial, fungal, viral, or other) within 60 days prior to first dose of study drug. Clinically significant is defined as requiring systemic parenteral antibiotics or hospitalization
10. A history of opportunistic infection, or a history of recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years
11. Chronic viral hepatitis including hepatitis B (HBV) and hepatitis C (HCV) unless patient received curative treatment for HCV and has a documented negative viral load, known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness
12. Cryptosporidium in the stool sample at screening
13. White blood cells (WBC) < 1,200/mm^3 (1.2×10^9/L) at screening
14. Absolute neutrophil count (ANC) < 500/mm^3 at screening
15. CD4+ count < 150/µL at screening
16. Platelets < 50,000/mm^3 (50×10^9/L) or < 35,000/ mm^3 (35×10^9/L) if related to SLE, at screening
17. Hemoglobin < 8 g/dL or < 7 g/dL at screening if related to SLE
18. Proteinuria > 3.0 g/day (3000 mg/day) at screening or equivalent level of proteinuria as assessed by protein/creatinine ratio (3 mg/mg or 339 mg/mmol)
19. Serum creatinine > 2.0 mg/dL at screening or creatinine clearance (CrCL) < 40 ml/minute based on Cockcroft-Gault calculation[39]:

    GFR = ([1 for male] or [0.85 for female]) × (140 – Age) × BW / (72 × Creatinine)

20. Serum ALT and/or serum AST > 2 × ULN at screening, unless explicitly related to lupus based on the investigator's judgment
21. Creatinine kinase (CK) > 3.0 × ULN at screening, unless it is related to lupus myositis
22. Total bilirubin > 1.5 × ULN at screening (unless related to Gilbert's syndrome)
23. Any other laboratory test results that, in the opinion of the Investigator or the sponsor or sponsor's designee, might place a patient at unacceptable risk for participating in this study
24. History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody (eg, IgG protein) or molecules made of components of monoclonal antibodies
25. History substance and/or alcohol abuse or dependence within the past 1 year, at the investigator's judgment
26. History of cancer within the last 5 years (except for cutaneous basal cell or squamous cell cancer, or cervical cancer in situ resolved by excision)

27. Any other severe acute or chronic medical or psychiatric condition, including recent (within the past year) medical conditions (eg, cardiovascular conditions, respiratory illnesses) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, sponsor or sponsor's designee, would make the patient inappropriate for entry into this study

28. Investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or patients who are employees of the sponsor or directly involved in the conduct of the trial

29. Currently participating in, or who have participated in other interventional (drug or device) clinical study within 30 days or 5 half-lives of baseline, whichever is longer

30. Recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4 or 5 on the C-SSRS

31. Current or pending incarceration

32. Current or pending compulsory detainment for treatment of either a psychiatric or physical (eg, infectious disease) illness

33. Currently taking a total daily dose of > 30 mg morphine or morphine equivalent (see APPENDIX 7)

34. Body mass index (BMI) ≥ 40.0

4.6 Concomitant Medications

Any medicinal product, prescribed or OTC, including herbal and other nontraditional remedies, is considered a concomitant medication. Patients should stay on stable regimen (not PRN) of other concomitant medications for the treatment of SLE (eg, analgesics, nonsteroidal anti-inflammatory drugs [NSAIDs], statins, ACE inhibitors/ARBs and other antihypertensive drugs), unless changes in these treatments are clinically indicated. Patients should refrain from Tylenol, NSAIDs, and any pain medications including tramadol and other opiates for at least 12 hours before each visit, with the exception of the Screening Visit.

Use of any other drugs for non-SLE conditions, including over-the-counter medications and herbal preparations, should remain stable unless change or addition is clinically necessary. Discussion with the medical monitor prior to initiation of new medication is strongly recommended. Any concomitant therapies must be recorded on the eCRF. Prior and concomitant medication use will be recorded for the 30 days prior to screening until the last follow-up visit. In addition, historical treatment for SLE (including immunosuppressant, anti-malarial, corticosteroid, and/or biologic agent including investigational agents) will be recorded for the 48 weeks prior to screening in the eCRF.

4.6.1 Corticosteroid

Prior to randomization, oral CSs (prednisone or prednisone equivalent), may be used in accordance with the investigator's clinical judgment and best standard of care. See APPENDIX 3 for examples of equivalents.

A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study. For patients whose only SLE treatment is steroids, their stable steroid dose must be at least 10 mg/day and no more than 30 mg/day for a minimum of 6 weeks at time of randomization on Day 0.

Topical steroids may be used, but the dose must be stable for at least 6 weeks prior to Day 0, and be maintained at a constant dose throughout the study duration until the rashes resolve. PRN topical steroids are not permitted.

Once the patient has received the first dose of study drug (Day 0), tapering of oral steroids will be highly encouraged and should be continually evaluated during the protocol-allowed tapering windows (Day 0 through Day 150) with the target of achieving a CS daily dose of < 7.5 mg and < Day 0 dose between Day 150 and Day 210.

Between Day 150 and Day 210 (ie, within 60 days of primary endpoint assessments), oral CS doses must be held constant.

CS Burst for SLE-related Indications

After Day 0 (first dose of study drug), a maximum of 1 oral CS "burst" equivalent to ≤ 40 mg/day prednisone for increased SLE disease activity will be allowed between Day 0 and Day 120, which must be tapered down to the baseline (Day 0) CS dose or lower within 14 days of initiation of the "burst." Any "burst" continuing after Day 120 or occurring after Day 120 is considered a protocol deviation.

- Alternatively, a single intramuscular (IM) dose of methylprednisolone (< 40 mg) is permitted during this period.

CS Burst for Non-SLE-related Indications

A single treatment of oral prednisone equivalent of ≤ 40 mg/day for 14 days is permitted for a non-SLE indication, though it must be completed prior to Day 120. No long acting steroid injections are permitted.

Note: Treatment with inhaled CS are allowed for the treatment of non-SLE-related indications only (eg, for asthma).

Any other increase from baseline of CS dose or systemic use of CS of any kind (including intra-articular and intravenous administration) are not permitted from Day 0 through Day 210 and will result in the patient being considered a treatment failure. There is no restriction of CS usage after Day 210.

4.6.2 Other Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study drug administration and during the study are described below, and washout requirements are provided in APPENDIX 4. All medications taken within 30 days prior to screening must be recorded on the eCRF.

1. Prior exposure to BOS161721
2. Patients who have received treatment with anti-CD20 monoclonal antibodies within 24 weeks of screening
3. Patients who have received treatment with cyclophosphamide within the 24 weeks prior to screening
4. Patients who have received treatment with cyclosporine (with exception of ophthalmic use), any other calcineurin inhibitor or other immunosuppressive medication not specified in the inclusion criteria within 4 weeks for oral use or 8 weeks for topical use of screening
5. Patients who are currently receiving or are scheduled to receive plasmapheresis or lymphapheresis therapy, or have received such therapy within 24 weeks prior to screening
6. Patients who have received any live vaccines within 30 days of screening. Note: Furthermore, live vaccines should not be used during the course of the study and within the 2 months following last dose. Other inactivated vaccines such as tetanus, etc., may be used according to local guidelines during treatment period
7. Patients who are scheduled or anticipated to have elective surgery during the course of the study
8. Initiation of new immunosuppressant or anti-malarial agent is not permitted. Note: Dose reduction or replacement may be allowed due to intolerability or shortage for patients on a stable dose prior to study initiation

4.7 Women of Childbearing Potential

WOCBP is defined as any woman who has experienced menarche and who has not undergone surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) and is not postmenopausal.

See Section 4.7.2 for detailed information regarding contraceptive requirements for WOCBP.

4.7.1 Determination of Menopause

Menopause is defined as at least 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. Women under the age of 55 years must have a documented serum FSH level > 40 mIU/mL at screening to confirm menopause.

4.7.2 Contraception

WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 52 weeks, due to the mean terminal ½ life of the study drug.

Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 52 weeks, due to the mean terminal ½ life of the study drug.

Investigators shall counsel WOCBP and men who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

Investigators shall advise WOCBP and men who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

Patients must agree to either complete abstinence, defined as a complete avoidance of heterosexual activity, or the use of 2 methods of highly effective contraception from the following:

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by patients who are WOCBP or a male patient's WOCBP partner. Women who are partner of men who are patients participating in the study may use hormone-based contraceptives as 1 of the acceptable methods of contraception since they will not be receiving study drug.
- IUDs, such as ParaGard®
- Vasectomy

Note: Women who are abstinent while participating in the study must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the patient chooses to forego complete abstinence.

Azoospermic men and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP must still undergo pregnancy testing.

4.8 Deviation from Inclusion/Exclusion Criteria

Deviation from the inclusion or exclusion criteria will not be allowed. If deviation of inclusion/exclusion criteria is discovered after randomization, the investigator should contact the medical monitor for discussion. A decision will be made whether to allow a patient to continue or withdrawal from the study medication.

See Section 6.8 for additional details.

4.8.1 Patient Withdrawal and Replacement

See Section 5.5 for reasons for removal from the trial. Withdrawn patients may be replaced during the MAD part of the study after discussion between the principal investigator or designee and sponsor.

5 STUDY PROCEDURES

Refer to the eCRF completion guidelines for data collection requirements and documentation of study assessments/procedures.

5.1 Screening

Screening will be the same for both the MAD and POC portions of the study.

Screening will take place from Day -28 to Day -1, and assessments may be performed over more than 1 visit. Confirmation that the most current IRB/IEC approved informed consent form (ICF) has been signed must occur before any study-specific screening procedures are performed. Procedures that are part of standard of care are not considered study-specific procedures and may be performed prior to informed consent and used to determine eligibility.

All screened patients will be assigned a unique screening number. The screening number will include a 3-digit site number and a 4-digit sequential number to identify patients from the time of screening. Only eligible patients who are confirmed by central review as meeting the inclusion/exclusion criteria, listed in Section 4.4 and Section 4.5 respectively, will be enrolled in the study. Screened patients who drop out of the clinical study before randomization will be recorded as screen failures. If rescreening occurs, the site will assign a new screening number.

Specific procedures at the screening visit will include:

- Medical history documentation
- Review of inclusion and exclusion criteria
  - Patient medical records must contain documentation of SLE diagnosis
  - C-SSRS
- Concomitant medication documentation
- Demographics
- Full physical examination
- Vital signs
- Chest x-ray (a prior x-ray can be used if taken within 12 weeks of screening date)
- Laboratory evaluations (non-fasting):
  - Hematology and clinical chemistry
  - Serology (Hepatitis B and C; HIV-1/2 combination)
  - TB test
  - CRP
  - Direct Coomb's test (if indicated for hemolytic anemia)
  - CD4+ count, total IgG and IgM levels, plasma CCI , CCI [redacted]
  - Serum pregnancy test (WOCBP)
  - FSH (postmenopausal women under age 55 years)
  - Spot urine for protein/creatinine ratio
  - Urinalysis
  - Stool sample
- 12-lead ECG
- SLE-related indices (BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, Physician's Global Assessment (PGA) of disease activity

Screening procedures are listed in the Schedule of Assessments (Table 1 and Table 4), and details are provided in Section 6.

5.1.1 Retesting During Screening Period

A single retesting of laboratory parameters and/or other assessments during the screening period is permitted (in addition to any parameters that require a confirmatory value) only if:

- medically indicated
- there is evidence a laboratory sample was mislabeled, indeterminate, inadequately processed, and/or deteriorated in transit to the central laboratory

Any new result will override the previous result (ie, the most current result prior to randomization) and is the value by which study inclusion/exclusion will be assessed, as it represents the patient's most current clinical state. This will also apply to patients who are being rescreened.

5.2 Enrollment/Randomization and Day 0 Treatment

Randomization should occur after patient eligibility for enrollment has been confirmed by the central eligibility review. The central eligibility review team has the final decision on patient eligibility and can decide the patient is not eligible for the study based on their review of the eligibility packet.

Prior to randomization, the study site should confirm that the patient still meets inclusion/exclusion criteria (especially SLE disease activity and treatment). The site will obtain a randomization number when registering the patient in IWRS. All patients will receive BOS161721 or placebo according to the kit number assigned by the IWRS randomization scheme.

After randomization, procedures include:

- PROs: CCI
- C-SSRS
- Laboratory evaluations (fasting):
  - Hematology and clinical chemistry
  - Direct Coomb's test (if indicated for hemolytic anemia)
  - CD4+ count, total IgG and IgM levels, plasma CCI, plasma CCI and CCI, whole blood for leukocyte immunophenotype (leukocyte immunophenotype for MAD patients only)
  - ADA
  - pSTAT3 (predose [trough] samples only in Phase 1b)
  - CCI
  - CCI
  - CCI
  - See Table 4 and Table 1for details of PK sampling in the MAD and POC portions
  - Urine pregnancy test will be collected on WOCBP prior to study drug administration

  - Spot urine for protein/creatinine ratio
  - Urinalysis
- Concomitant medication documentation
- Documentation of AEs and SAEs (see Section 6.2.2.5 on SAE reporting requirements)
- Full physical examination
- Vital signs (prior to PK blood draw, predose, and at 1 and 2 hours postdose on Day 0)
- 12-lead ECG (prior to PK blood draw)
- SLE-related indices (BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, PGA)
- SLICC/ACR damage index
- Study drug administration:
  - Administration of BOS161721 or placebo will take place on-site, and is discussed in Section 7.3
- Injection site reaction assessment performed at 2 hours postdose

Procedures on Day 0 are listed in the Schedule of Assessments (Table 1 and Table 4), and details are provided in Section 6.

All patients who are enrolled, randomized, and receive study drug, or undergo study-specific procedures should reconsent with any updated versions of IRB/IEC approved informed consents during study participation as applicable and per institutional guidelines.

5.3 Treatment Period/Follow-Up Visits

The following procedures will be performed as indicated in the Schedule of Assessments (Table 1and Table 4). See Schedule of Assessment tables for allowable windows for each visit.

- Targeted physical examination
- Vital signs (prior to PK blood draw)
- Concomitant medication documentation
- Documentation of AEs and SAEs (see Section 6.2.2.5 on SAE reporting requirements)
- PROs: CCI
- Urine pregnancy tests will be collected on WOCBP prior to study drug administration
- Injection site reaction assessments will be performed predose
- Direct Coomb's test (if indicated for hemolytic anemia)
- Spot urine for protein to creatinine ratio
- Urinalysis
- CCI
- Plasma CCI
- PGA, BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, and the CLASI will be completed
- SLICC/ACR Damage Index will be completed at Day 180
- C-SSRS

- ECGs prior to PK blood draw
- See Table 4 and Table 1for details of PK sampling in the MAD and POC studies, respectively
- Fasting hematology and chemistry assessments
- The CD4+ count and total IgG and IgM levels
- Plasma CCI and CCI, ADA, and whole blood for leukocyte immunophenotype (leukocyte immunophenotype for MAD patients only)
- pSTAT3 (predose [trough] samples only Phase 1b)
- nAb will be analyzed by central lab if patient is positive for ADA
- CRP
- CCI

5.4 Safety Follow-Up Visits

Safety follow-up visits will take place at Days 210, 240, and 270. These visits will include the following assessments as indicated in the Schedule of Assessments (Table 1 and Table 4):

- PROs: CCI
- Documentation of AEs and SAEs (see Section 6.2.2.5 on SAE reporting requirements)
- Injection site reactions
- Targeted physical examination
- Vital signs (prior to PK blood draw)
- Spot urine for protein/creatinine ratio and urinalysis
- Concomitant medication documentation
- BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, and PGA
- Fasting clinical laboratory assessments (hematology and clinical chemistry)
- Direct Coomb's test (if indicated for hemolytic anemia)
- Plasma CCI
- CCI
- 12-lead ECG (prior to PK blood draw)
- CRP
- ADA
- CCI
- Urine pregnancy test
- See Table 4 and Table 1for details of PK sampling in the MAD and POC portions, respectively

5.5 Premature Discontinuation

While patients are encouraged to complete all study evaluations, they may withdraw from the study at any time and for any reason. Every effort will be made to determine why any patient

withdraws from the study prematurely. If the patient is unreachable by telephone, a registered letter, at the minimum, should be sent to the patient requesting him/her to contact the clinic.

All patients who withdraw from the study with an ongoing AE or SAE must be followed until the end of study or until the event is resolved or deemed stable, respectively.

If a patient withdraws prematurely after dosing, an end of treatment (EOT) visit should be performed (Day 180) and a last follow-up visit 90 days after dosing should be scheduled (Day 270). Safety follow-up visit procedures based on the Schedule of Assessments (see Section 5.4).

Patient participation may be terminated prior to completing the study and the reason recorded as follows:

- AE/SAE
- Protocol deviation
- Lost to follow-up
- Patient withdraws consent at their own request
- Investigator decision
- Decision by sponsor (other than AE/SAE, protocol deviation, or lost to follow-up)

Withdrawn patients may be replaced after discussion between the investigator or designee and sponsor.

6 ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, which may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and wellbeing of the patient. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. All protocol violations are entered directly into the eCRFs.

6.1 Medical History, Demographic and Other Baseline Information

The medical history comprises:

- General medical history
- Documentation of SLE diagnosis
- Historical medication therapy for SLE

The following demographic information will be recorded:

- Age

- Ethnic origin (Hispanic/Latino or not Hispanic/not Latino)
- Race (White, American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black/African American)
- Height (without shoes, in cm)
- Body weight, without shoes (kg)
- BMI [kg/m^2]

Other baseline characteristics will be recorded as follows:

- Concomitant medication documentation (see Section 4.6)
- Status of child bearing potential and contraception

6.2 Safety Assessments

6.2.1 Laboratory Assessments

Laboratory tests will be performed at times defined in the Schedule of Assessments (Table 1 and Table 4). Patient eligibility will be determined based on these tests at screening. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

A central laboratory will be used (with the exception of urine pregnancy tests) to ensure accuracy and consistency in test results. Laboratory/analyte results that could unblind the study (ie, biomarker results) will not be reported to investigative sites. Urinalysis will be performed on midstream, clean catch specimens. Some biomarkers listed above will not be drawn at some sites due to geographical logistical challenges. See the laboratory manual for details.

Endpoint analyses will be based on changes from baseline assessments at Days 120 and 210.

Table 2. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other Safety Tests
Hemoglobin	BUN	pH	Spot urine for protein/creatinine ratio
Hematocrit	Creatinine	Glucose (qual)	FSH[b]
RBC count	Glucose (fasting)	Protein (qual)	Urine pregnancy test[c]
RDW	Calcium	Blood (qual)	QuantiFERON®-TB Gold In-Tube test (QFT-G)[d]
MCV	Sodium	Ketones	
MCH	Potassium	Nitrites	Serology[d] (Hepatitis B and C; HIV-1/2 combination)
MCHC	Chloride	Leukocyte esterase	
Platelet count	Total CO_2 (bicarbonate)	Urobilinogen	Stool sample[e]
WBC count	AST, ALT	Urine bilirubin	Serum pregnancy test
CD4+ count	Total bilirubin	Microscopy[a]	
Total neutrophils (Abs)	Alkaline phosphatase		
	Creatine kinase		
Eosinophils (Abs)	Uric acid		
Monocytes (Abs)	Albumin		
Basophils (Abs)	Total cholesterol (fasting)		
Lymphocytes (Abs)			

Table 2. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other Safety Tests
	LDL-C (fasting) HDL-C (fasting) Triglycerides (fasting) Total protein PT/INR		

	Additional Tests[f] (potential Hy's Law)	Immunogenicity, PD and other Biomarker Tests
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin GGT Prothrombin time/international normalized ratio (repeat) Creatine kinase (repeat)	ADA nAb[g] pSTAT3 (predose [trough] samples only in Phase 1b) Total IgG & IgM Plasma CCI Plasma CCI & CCI Whole blood for leukocyte immunophenotype (for MAD patients only) CCI CCI CCI CRP Direct Coomb's test[h]

Abbreviations: Abs = absolute; ADA = anti-drug antibody; ALT = alanine aminotransferase; CCI ; CCI ; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C = complement; CD4+ = cluster of differentiation 4; CRP = C-reactive protein; CCI ;; FSH = follicle stimulating hormone; GGT = gamma-glutamyltransferase; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ration; IL-21 = interleukin 21; LDL-C = low-density lipoprotein cholesterol; MAD = multiple ascending doses; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = Mean corpuscular volume; nAb = neutralizing antibody; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; PT = prothrombin time; qual = qualitative; RBC = red blood cell; RDW = RBC distribution width; SAE = serious adverse event; SC = subcutaneous; CCI ; TB = tuberculosis.

a. On all urine samples.
b. At screening only, in women who are amenorrheic for at least 12 consecutive months and under 55 years old.
c. For WOCBP.
d. Screening only.
e. At screening, and if a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.
f. Additional testing for potential Hy's Law cases only (See Section 6.2.2.6.3).
g. If patient is positive for ADA.
h. If clinically indicated for hemolytic anemia.

6.2.1.1 Pregnancy testing

For WOCBP, a serum pregnancy test will be performed at screening. Following a negative serum pregnancy result at screening, appropriate contraception must be commenced or

continued and a further negative urine pregnancy test results will then be required at the baseline visit before the patient may receive the investigational product. Urine pregnancy tests will also be routinely repeated at study drug administration visits prior to study drug administration, at the last follow up visit day (Day 270) and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive pregnancy test or confirmed pregnancy, the patient will be discontinued from study drug, an EOT visit should be performed (Day 180), and a last follow-up visit 90 days after last dose should be scheduled (Day 270). Safety follow-up visit procedures (see Section 5.4) are specified in the Schedule of Assessments (see Table 1 and Table 4).

See Section 6.2.2.7.1 for information on reporting of pregnancies as AEs/SAEs during the study.

6.2.1.2 Tuberculosis Screening

During the screening period, it must be determined and documented that a patient does not have evidence of active or latent or inadequately treated TB per the exclusion criteria (Section 4.5). The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

6.2.1.2.1 Mycobacterium Tuberculosis Testing Using QuantiFERON Test[40]

QuantiFERON®-TB Gold In-Tube (QFT-G) is an *in vitro* diagnostic test using a peptide cocktail simulating ESAT-6, CFP-10, and TB 7.7 proteins to stimulate cells in heparinized whole blood. Detection of INFγ performed by enzyme-linked immunosorbent assay (ELISA) is used to identify *in vitro* responses to these peptide antigens that are associated with Mycobacterium tuberculosis infection. QFT-G is an indirect test for M. tuberculosis infection (including disease) and is intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.

Test results will be reported as positive, negative, or indeterminate. A negative QFT-G test result is required to meet the inclusion criterion. In the case of an indeterminate result, repeat tests should be permitted for the purpose of determining eligibility of patients to enroll in this study. If a repeat test is indeterminate again, the patient is a screen failure. The procedure for using this test and interpreting the results will be described fully in the laboratory manual, which will be provided to investigators.

6.2.2 Adverse Events

6.2.2.1 Definitions

An AE is defined as any untoward medical occurrence experienced by a study patient, whether or not considered drug related by the principal investigator.

AEs are unfavorable changes in a general condition, subjective or objective signs or symptoms, worsening of pre-existing concomitant disease, and clinically significant abnormality in laboratory parameters observed in a patient in the course of a clinical study.

Non-serious SLE manifestations or abnormal laboratory results related to SLE disease activity would not be recorded as AEs unless they meet the definition for SAEs (Section 6.2.2.5).

6.2.2.2 Recording of Adverse Events

AEs should be collected and recorded for each patient from the date of the first dose of study drug until the end of their participation in the study, including the safety follow up period.

AEs may be volunteered spontaneously by the study patient, or discovered by the study staff during physical examinations or by asking an open, nonleading question such as 'How have you been feeling since you were last asked?' All AEs and any required remedial action will be recorded on the Adverse Events eCRF and Safety Adverse Event Form. The details of the AE, date of AE onset, date of AE outcome, and action taken for the AE will be documented together with the principal investigator's assessment of the seriousness of the AE and causal relationship to the study drug and/or the study procedure.

All AEs should be recorded individually, using diagnostic terms where possible. If the diagnosis is not established, individual symptoms may be reported. The AEs will subsequently be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

6.2.2.3 Severity of Adverse Events

Each AE will be assessed by the principal investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03 criteria. [41] When changes in the severity (grade) of an AE occur more frequently than once a day, the maximum severity for the event should be noted for that day. Any change in severity of signs and symptoms over a number of days will be captured by recording a new AE, with the amended severity grade and the date (and time, if known) of the change.

6.2.2.4 Causality of Adverse Events

The principal investigator will assess the causal relationship between BOS161721 or placebo and the AE. One of the following categories (Table 3) should be selected based on medical judgment, considering the definitions below and all contributing factors.

Table 3. Causality Definitions

Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment (dechallenge[a]) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge[b] procedure if necessary.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (eg, concomitant disease, environmental factors, or other drugs or chemicals).

[a] Dechallenge: Upon discontinuation of a drug suspected of causing an AE, the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation (positive dechallenge), or the symptoms continue despite withdrawal of the drug (negative dechallenge). Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists (for example, as in bone marrow suppression, fixed drug eruptions, or tardive dyskinesia).

[b] Rechallenge: Upon re-administration of a drug suspected of causing an AE in a specific patient in the past, the AE recurs upon exposure (positive rechallenge), or the AE does not recur (negative rechallenge).

An unexpected adverse drug event is any adverse drug event for which the specificity or severity is not consistent with the current IP.

6.2.2.5 Seriousness of Adverse Events

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

- Results in death
- Is life threatening; this means that the patient was at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires hospitalization or prolongation in existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly or birth defect
- Is other important medical event (see below)

Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in inpatient hospitalization
- Development of drug dependency or drug abuse

Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (eg, elective surgery for a pre-existing condition that has not worsened) need not be considered SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'nonserious' according to the usual criteria.

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are associated with the use of the drug and are serious and unexpected.

6.2.2.6 Adverse Events of Special Interest

AEs of special interest in this study include the following:

1. Anaphylaxis and serious allergic reactions
2. Grades 2 to 5 injection site reaction, including erythema, pain, and induration (See APPENDIX 6)
3. Drug Induced Liver Injury (DILI) assessed following Hy's Law
4. Malignancy (not including basal cell carcinoma or squamous cell carcinoma of skin)
5. Opportunistic infections such as disseminated histoplasmosis, cryptococcosis, disseminated herpes simplex, disseminated tuberculosis, *Aspergillus* sp., *Candida albicans*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Cytomegalovirus*, *Histoplasma capsulatum*, *Isospora belli*, and *Polyomavirus JC polyomavirus*
6. Cryptosporidiasis

6.2.2.6.1 Anaphylaxis and Serious Allergic Reactions

Anaphylaxis will be defined according to the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria.[42] In the event of anaphylactic reaction or severe/serious hypersensitivity/allergic reaction, the patient must discontinue IP and emergency resuscitation measures implemented. In case of other mild to moderate hypersensitivity reaction, depending on the severity, the investigator may manage in accordance with the standard-of-care.

Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus, or flushing, swollen lips-tongue-uvula) and at least 1 of the following:
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
   a. Systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from the patient's baseline

6.2.2.6.2 Injection Site Reactions

Injection site reactions are to be captured and reported as AEs. These will include Grades 2 to 5 injection site erythema, pain, and induration (see APPENDIX 6), which are also captured as Adverse Events of Special Interest (See Section 6.2.2.6). The investigator should provide a clear description of the observed or reported AE including location and severity. All concomitant treatments used to treat injection site reactions should be recorded and captured in the eCRF, together with the AE of injection site reactions.

6.2.2.6.3 Potential Drug-Induced Liver Injury

Abnormal values in AST and/or ALT levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of DILI, and as potential Hy's Law cases, and should always be considered important medical events. If symptoms compatible with DILI precede knowledge of serum chemical test abnormalities, liver enzyme measurements should be made immediately, regardless of when the next visit or monitoring interval is scheduled. In some cases, symptoms may be an early sign of injury and although typically less sensitive than serum enzyme elevations, they may indicate a need for prompt serum testing. An increase in liver enzymes should be confirmed by a repeated test within 48 to 72 hours following the initial test, prior to reporting of a potential DILI event. Patients will continue to have weekly or biweekly liver enzyme measurements until resolution or levels return to baseline.

All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.2.2.7.2 for reporting details).

Potential DILI is defined as:

1. ALT or AST elevation > 3 × ULN

AND

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

AND

3. No other immediately apparent possible causes of ALT or AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

The patient should return to the investigational site and be evaluated as soon as possible, include laboratory tests, detailed history, and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, CK, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/International Normalized Ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

Study drug discontinuation is considered if there is marked serum AST or ALT elevation or evidence of functional impairment (as indicated by rising bilirubin or INR, which represent substantial liver injury) that is related to study drug. Discontinuation of treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5× ULN for more than 2 weeks

Discontinuation of treatment must occur if:

- ALT or AST >3 × ULN and (total bilirubin > 2 × ULN or INR > 1.5)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

6.2.2.6.4 Malignancy

The identification of a malignancy event will be made by the study site and communicated to the sponsor or designee. AEs should be reported as serious per the criteria in Section 6.2.2.5.

After the first dose of study drug, when there is a decision to biopsy a potentially malignant tumor, lymph node, or other tissue (with the exception of suspected basal cell/squamous cell), the investigator and/or consultant(s) should contact the sponsor clinicians or designee to discuss the issue and any decisions as soon as possible. Basal cell carcinoma or squamous cell carcinoma of skin is not considered an AE of special interest.

6.2.2.6.5 Specific Infections

Any diagnosis or suggested diagnosis of opportunistic infections such as disseminated histoplasmosis, cryptococcosis, disseminated herpes simplex, disseminated tuberculosis, *Aspergillus* sp., *Candida albicans*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Cytomegalovirus*, *Histoplasma capsulatum*, *Isospora belli*, or *Polyomavirus JC polyomavirus* will be recorded as AEs of special interest.

Cryptosporidiosis is also considered an AE of special interest. Patients will be evaluated for cryptosporidium in the stool at screening, and as clinically indicated (eg, watery diarrhea) during the study. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

6.2.2.7 Reporting of Adverse Events

AE reporting will be carried out in accordance with applicable local regulations, including regulatory agency and IRB reporting requirements.

Each AE is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate, and is further outlined in Section 6.2.2.7.2.

6.2.2.7.1 Reporting of Pregnancy

As information is available, a pregnancy diagnosed during the study will be reported within 24 hours to the sponsor via the Pregnancy Notification and Outcome Form, including pregnancy in female patients who received study drug and female partners of male study patients who received study drug. The pregnancy should be followed to term and/or outcome and this outcome should also be reported to the sponsor via the Pregnancy Notification and Outcome Form. Pregnancy itself is not regarded as an AE or SAE unless there is complication.

In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an AE or SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious

adverse events when the investigator assesses the neonatal death as related or possibly related to exposure to investigational product.

6.2.2.7.2 Reporting of Serious Adverse Events

The principal investigator is responsible for providing notification to the sponsor of any SAE via the Safety Adverse Event Form, whether deemed study drug related or not, that a patient experiences during their participation in this study within 24 hours of becoming aware of the event.

If an SAE is fatal or life threatening, notification to the sponsor must be made aware immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding cases. In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

The principal investigator will review each SAE and evaluate the intensity and the causal relationship of the event to the study drug. All SAEs will be recorded from the time of first dose of study drug through the safety follow-up period (up to Day 270). SAEs occurring after the final follow-up visit and coming to the attention of the principal investigator must be reported only if there is (in the opinion of the principal investigator) reasonable causal relationship with the study drug.

As a minimum requirement, the initial notification should provide the following information:

- Study number
- Patient number
- Details of the SAE (verbatim details are sufficient for immediate notification)
- Criterion for classification as ‘serious’
- Causality assessment (which may be updated in a follow-up report when sufficient information is available to make this classification)

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (eg, hospital reports, consultant reports, autopsy reports, etc), with the study patient’s personal identifiers removed. All relevant information obtained by the principal investigator through review of these documents will be recorded and submitted to the sponsor within 24 hours of receipt of the information. If a new Safety Adverse Event Form is submitted, then the principal investigator must sign and date the form. The sponsor may also request additional information on the SAE, or clarification of omitted or discrepant information from the initial notification, which the principal investigator or an authorized delegate should submit to the sponsor within 24 hours of the request as possible.

6.2.2.7.3 Reporting of Adverse Events of Special Interest

AEs of special interest will be reported to safety immediately or within 24 hours of the site becoming aware of the event and recorded as such on the Adverse Events eCRF and Safety Adverse Event Form.

Potential DILI will be reported based on specifications mentioned in Section 6.2.2.6.3.

Each AE of special interest is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate, and is further outlined in Section 6.2.2.7.2.

6.2.2.8 Follow Up of Adverse Events

All AEs will be followed up through the safety follow-up visits. All SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the event has resolved, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the principal investigator and medical monitor, until there is a satisfactory explanation for the changes observed, or until the patient is lost to follow-up.

See Section 6.2.2.7.1 for details related to follow-up of pregnancy. See Section 6.2.2.6.3 for details related to follow-up of potential DILI. See Section 6.2.2.6.4 for details related to follow-up of malignancy.

6.2.3 Vital Signs

Vital signs (blood pressure, heart rate, and body temperature) will be assessed as specified in the Schedule of Assessments (Table 1 and Table 4). Vital signs will be assessed on Day 0 at predose and at Day 0, 1 and 2 hours postdose, as well as on each of the scheduled visit days during the study (excluding PK-only site visits). Supine BP and heart rate recordings will be made after the patient has been recumbent and at rest ≥ 5 minutes. When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

6.2.4 12-Lead Electrocardiograms

ECG will be assessed as specified in the Schedule of Assessments (Table 1 and Table 4). ECG recording will initiate after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws, though timing will be such that PK draws are collected on their scheduled times where possible.

The ECG will include all 12 standard leads and a Lead II rhythm strip on the bottom of the tracing. The ECG will be recorded at a paper speed of 25 mm/second. The following ECG parameters will be collected: PR interval, QRS interval, RR interval, QT interval, and QT interval corrected for heart rate using Fridericia's formula (QTcF).

All ECGs must be evaluated by a qualified physician or qualified designee for the presence of abnormalities and will be captured electronically and retained for future evaluation if required, up to the time of the clinical study report (CSR) completion.

6.2.5 Physical Examinations

The full physical examination will be completed at screening and Day 0. It includes an assessment of general appearance and evaluation of head, eyes, ears, nose, mouth, throat, neck, thyroid, lymph nodes, and extremities, and dermatologic, respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurologic, and psychiatric systems.

The targeted (limited) physical examination will be completed at all other visits as indicated in the Schedule of Assessments (Table 1 and Table 4). It includes evaluation of patient complaints and SLE disease-related issues, and will exclude the genitourinary system.

6.2.6 C-SSRS

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed by Columbia University researchers for the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment. It is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening.[43]

The C-SSRS evaluation will be performed as specified in the Schedule of Assessments (Table 1 and Table 4). Patients with recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4, or 5 is exclusionary at screening will be excluded from the study. Patients with recent or active suicidal ideation or behavior at subsequent study visits will have responses to the C-SSRS reviewed in detail to assess patient risk, and appropriate consultative mental health services will be provided.

6.2.7 Injection Site Reactions

Patients will be monitored for local injection site reactions as specified in the Schedule of Assessments (Table 1 and Table 4). Local injection site reactions will be assessed at 2 hours postdose at baseline, and predose for each injection after baseline. Injection site reactions should be managed according to the standard of care. Injection site reactions, Grades 2 to 5, are to be reported as AEs of special interest (see Section 6.2.2.7.3).

6.2.8 Immunogenicity

The serum samples to measure the presence of ADA will be collected as specified in the Schedule of Assessments (Table 1 and Table 4). Blood samples (4 mL) to provide approximately 1.5 mL of plasma for anti BOS161721 antibody analysis will be collected into appropriately labeled tubes containing K_2EDTA. The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods. Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be

collected from all patients but only analyzed by a central lab if the patient had a positive ADA on Day 90.

After the first dose, if a patient tests positive in the validated confirmatory ADA assay, a sample from this patient will be further analyzed in the neutralizing antibody (nAb) assay by a central lab.

6.3 Efficacy Assessments

All efficacy assessments will be performed at times defined in the Schedule of Assessments (Table 1 and Table 4).

6.3.1 SLEDAI-2K

The SLEDAI-2K is a validated instrument that measures disease activity in SLE patients at the time of the visit and in the previous 30 days. It is a global index and includes 24 clinical and laboratory variables that are weighted by the type of manifestation, but not by severity. The total score falls between 0 and 105, with higher scores representing increased disease activity. The SLEDAI-2K has been shown to be a valid and reliable disease activity measure in multiple patient groups. A SLEDAI -2K of 6 or more generally represents moderately to severely active disease.[44]

6.3.2 BILAG 2004

The BILAG-2004 index is an organ-specific 97-question assessment based on the principle of the doctor's intent to treat. Only clinical features attributable to SLE disease activity are to be recorded and based on the patient's condition in the last 4 weeks compared with the previous 4 weeks. It will be scored as not present (0), improved (1), the same (2), worse (3), or new (4). Disease activity is graded separately for 9 body systems to 5 different grades (A to E) as follows: A ("Active") is very active disease, B ("Beware") is moderate activity, C ("Contentment") is mild stable disease, D ("Discount") is inactive now but previously active, and E ("Excluded") indicates the organ was never involved.[44] A shift from BILAG-2004 Grade A or B to a lower grade indicates a clinically relevant change in disease activity as the BILAG-2004 grades mirror the decision points for treatment interventions.

Only investigators that complete BILAG-2004 training will be allowed to perform the BILAG-2004 assessments. Preferably, the same investigator should evaluate the patient at each BILAG-2004 assessment from screening to study completion. The investigator must maintain documentation with descriptive details supporting the BILAG-2004 scoring (eg, chart, worksheet, clinic notes, and labs) at each visit.

See APPENDIX 5 for detailed specifications.

6.3.3 PGA of Disease Activity

The PGA is used to assess investigator's general impression on the patient's overall status of SLE disease activity via visual analogue scale (100 mm) with 0 being "very good, asymptomatic

and no limitation of normal activities" with 100 mm being "most severe possible disease ever seen in all SLE patients". PGA worsening is defined as an increase of ≥ 30 mm from baseline.

When scoring the PGA, the assessor should always look back at the score from the previous visit.

6.3.4 Composite Endpoints: SRI-4, SRI-5, SRI-6, and BICLA Response

6.3.4.1 SRI-4 Response

The SRI-4 is a composite index of SLE disease improvement that consists of scores derived from the SLEDAI-2K and the BILAG 2004 Index. Response based on the SRI-4 is defined by:

1) ≥ 4-point reduction in SLEDAI-2K global score, 2) no new severe disease activity (BILAG A organ score) or more than 1 new moderate organ score (BILAG B), and 3) no deterioration from baseline in the PGA by ≥ 30 mm. The SRI-4 response in patients with moderate to severe SLE is associated with broad improvements in clinical and patient-reported outcomes.[45]

6.3.4.2 SRI-5 and SRI-6 Response

Like the SRI-4, the SRI-5 and SRI-6 are composite indices of SLE disease improvement that consists of scores derived from the SLEDAI-2K and the BILAG 2004 Index. However, the SRI-5 and SRI-6 are computed with a minimal five-point or six-point improvement in SLEDAI-2K being required, respectively.[46]

6.3.4.3 BICLA Response

The BICLA is a responder index developed to measure response to therapy, and it includes scores from the BILAG, SLEDAI-2K, and PGA. BICLA response is defined as 1) at least 1 gradation of improvement in baseline BILAG 2004 scores in all body systems with moderate disease activity at entry (eg, all B [moderate disease] scores falling to C [mild], or D [no activity]); 2) no new BILAG A or more than 1 new BILAG B scores; 3) no worsening of total SLEDAI-2K score from baseline; 4) ≤ 10% deterioration in PGA score and 5) no treatment failure.[44] It is driven primarily by the BILAG, and has been used in Phase 2 and 3 mAb studies.[47]

For the endpoints of BICLA response at Days 210, 240, and 270, patient scores will be completed and response determined.

6.3.5 CLASI Response

The CLASI is a comprehensive tool for assessment of disease activity and damage in cutaneous lupus, shown to be valid, reliable, and sensitive to changes in disease activity.[48] Response is defined as 50% improvement from baseline in "A" or "B" scores. This assessment will be applied to all patients as all are required to have cutaneous disease activity.

For the secondary efficacy endpoint of CLASI response at Day 210, patient scores on MAD and POC studies will be compared with baseline for 50% improvement.

6.3.6 ACR-28 Joint Count

The ACR-28 joint count will evaluate the number of tender and swollen joints in the shoulder, elbow, wrist, hand, knee joints. Joints of the feet are excluded.

6.4 Other Variables

6.4.1 SLICC/ACR Damage Index

The SLICC/ACR damage index is a validated instrument to assess damage, defined as irreversible impairment, continuously persistent for 6 months (ascertained by clinical assessment), occurring since the onset of lupus, and it is based on a weighted scoring system. This index records damage occurring in patients with SLE regardless of cause, with demonstrated content, face, criterion, and discriminant validity.[49] It will be performed on Days 0 and 180.

6.4.2 PROs

Patients should be encouraged to complete the PROs at the clinic at the beginning of the study visit prior to any clinical assessments. A member of the staff should be available if a patient requires further instruction and to review the PRO questionnaires for completeness prior to leaving the clinic. The PROs include the CCI and the CCI and will be assessed as specified in the Schedule of Assessments (Table 1 and Table 4).

CCI [redacted][50]

CCI [redacted].

6.5 Pharmacokinetic Assessments

During the MAD Phase 1b (all sites) and POC Phase 2 (select sites only) parts of the study, blood samples for PK analysis of BOS161721 or placebo concentration will be collected according to Table 4 and Table 1.

Plasma concentrations of BOS161721 will be measured using a validated immunoassay. The PK parameters will be calculated from the plasma concentration actual time profiles.

6.6 Pharmacodynamic Assessments

Blood samples for PD parameters (plasma) will be collected at times indicated in the Schedule of Assessments (Table 1 and Table 4) for each of the following parameters:

- pSTAT3 (predose [trough] samples only Phase 1b)
- Antibodies: CCI [redacted]
- Plasma complement (CCI)

- Plasma CCI and CCI
- Whole blood for leukocyte immunophenotype (for MAD patients only)

6.7 Pharmacokinetic/Pharmacodynamic Relationship

Evidence of any PK/PD relationships will be evaluated between BOS161721 plasma concentrations and the available PD endpoints and biomarkers.

6.8 Protocol Deviations

Protocol deviations will be documented during the study.

7 STUDY DRUG MANAGEMENT

7.1 Description

7.1.1 Formulation

CCI

CCI

Additional information regarding dose preparation will be provided in a separate Pharmacy Manual.

7.1.2 Storage

All supplies of BOS161721 or placebo must be stored in accordance with the manufacturer's instructions. BOS161721 or placebo will be stored in a securely locked area, accessible to authorized persons only, until needed for dosing.

Information regarding storage and dose preparation will be provided in a separate Pharmacy Manual.

7.2 Packaging and Shipment

Investigational medicinal products will be supplied by Boston Pharmaceuticals, Inc. Investigational medicinal products will be packaged and labeled according to applicable local and regulatory requirements.

7.3 Dose and Administration

Details of dosing are provided in Section 3.1.

Each unit dose will be prepared by a qualified staff member. The vials of investigational product (IP) will appear identical and will have a "blinded" label on the vials that will state CCI mg or placebo. When the site goes into the IWRS to request the patient kit(s), the IWRS will assign the appropriate number of kits (regardless of assignment to placebo or active treatment) per the dose (ie, CCI [redacted]). If a patient is randomized to the placebo arm, they will receive the matching number of kits.

The designated staff member (or designee under the direction of the designated staff member) will dispense BOS161721 or placebo for each patient according to the protocol, randomization list, and Pharmacy Manual, if applicable.

After receiving sponsor approval in writing, the investigational site is responsible for returning all unused or partially used BOS161721 or placebo to the sponsor or designated third party or for preparing BOS161721 or placebo for destruction via incineration.

Further details are found in a separate Pharmacy Manual.

7.4 Accountability

The Principal Investigator or designee is responsible for maintaining accurate accountability records of BOS161721 or placebo throughout the clinical study. The drug accountability log includes information such as, randomization number, amount dispensed and amount returned to the pharmacy (if any). Used investigational product returned to the pharmacy may be maintained in an ambient condition. Unused product should follow the instructions in the Pharmacy Manual. The used product that is returned should be marked as ‘returned’ and kept separate from the products not yet dispensed.

All dispensing and accountability records will be available for sponsor review after database lock procedures are completed. During safety monitoring, the drug accountability log will be reconciled with the products stored in the pharmacy.

7.5 Prohibited Concomitant Therapy

Prohibited concomitant medications are discussed in Section 4.6 and APPENDIX 4 and will be listed as protocol violations if taken when not permitted.

7.6 Compliance

Dosing will be performed by trained, qualified personnel designated by the principal investigator. The date and time of dosing will be documented on each dosing day. Comments will be recorded if there are any deviations from the planned dosing procedures.

8 STATISTICS

The following analyses are planned:

- An IA will be performed during the last cohort of the MAD portion to determine dose selection for the POC part of the study.

- An additional analysis may be performed for the MAD portion of the study when all MAD patients have completed the safety follow-up or withdrawn from the study, and prior to final analysis. Data from the POC part of the study will be excluded from this additional analysis.
- The final analysis will be performed when all patients have completed the POC safety follow-up or withdrawn from the study.
- Safety analyses will be performed for DMC reviews throughout the study to evaluate dose escalation decisions and accumulating safety data. The frequency and details of the content and format of the safety review meetings will be described in the SAP and/or DMC charter.

All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9 or higher.

The following standards will be applied for the analysis unless otherwise specified. Data will be summarized descriptively by treatment and overall for each study portion. For the MAD part of the study, BOS161721 will be summarized overall and by each dose level, and placebo patients from each cohort will be combined. Select parameters may be summarized using patients from both study parts. Statistical testing will be performed on data from the Phase 2 portion only.

Continuous data will be summarized using number, mean, standard deviation (SD), 25th and 75th percentiles, minimum, median, and maximum. Categorical data will be summarized by treatment group using frequency tables (number and percentage). Time to event data will be summarized using counts, medians, 25th and 75th percentiles, and standard error. All data will be listed for all patients.

Statistical inference will be based on a 2-tailed test with an overall 0.10 level of significance, unless stated otherwise.

The effects of noncompliance, background therapy use, treatment discontinuations, premature withdrawal from study and covariates will be assessed to determine the impact on the general applicability of results from this study. Exploratory analyses of the data will be conducted as deemed appropriate. Any deviations from the planned analyses will be described and justified in the final integrated CSR.

Protocol deviations and prohibited medications that define medication failures will be fully assigned and documented before database lock and unblinding.

Further details of the analysis, including the handling of missing data, transformations and other data handling procedures will be provided in the SAP.

8.1 Sample Size

Sample size in the Phase 1b part of the study is based on operational consideration.

The sample size in the Phase 2 portion is based on the primary endpoint, SRI-4 Response at Day 210. Approximately 156 additional patients will be randomized in a 2:1 ratio to BOS161721 versus placebo to achieve 132 evaluable patients in the FAS. This assumes

24 patients will drop prior to having received treatment and an evaluable post-baseline efficacy measure. Enrollment and randomization will be monitored in a blinded fashion and increased if needed to ensure at least 132 patients are randomized into the FAS.

A total of 132 patients randomized provides more than 80% power to detect a treatment difference of 25% in SRI-4 response rates at Day 210, based on a targeted 2-sided significance level of 10% and using a 2-sided Pearson's chi-squared test. This assumes of a response rate of 65% for BOS161721 and 40% for placebo, where missing data at Day 210 is carried forward from most recent non-missing result and patients are treated as a non-responder if a prohibited medication defined as a medication failure occurs.

8.2 Statistical Methods

8.2.1 Analysis Populations

The primary efficacy analysis will be based on the FAS, defined as all patients who receive at least 1 dose of study treatment and have at least 1 evaluable post-baseline efficacy evaluation. FAS analyses will be conducted on the basis of the randomized treatment.

A per protocol (PP) analysis set may be defined to exclude major protocol violations from the efficacy analysis. The PP Population will include all patients from the FAS except those with major violations to the protocol deemed to impact the analysis of the primary endpoint. These violations will be identified based on blinded data prior to study unblinding. PP analyses will be conducted on the basis of the randomized treatment.

Safety analyses will be based on the safety analysis set (SS), defined as all patients who receive at least 1 dose of study treatment. Safety analyses will be conducted on the basis of actual treatment received.

Pharmacokinetic analysis will be conducted on the PK analysis set, defined as the FAS with sufficient concentration data for the calculation of PK parameters.

8.2.2 Demographics and Baseline Characteristics

Baseline and patient characteristics will be summarized using all randomized patients.

8.2.3 Primary Efficacy Endpoint(s)

The proportion of patients who achieve a SRI-4 response at Day 210 will be assessed via Pearson's chi-squared analysis. The primary efficacy endpoint will be analyzed using the FAS and if needed repeated in the PP analysis set. Missing values will be addressed by employing a last observation carried forward (LOCF) analysis. Other imputation methods may be employed as a sensitivity analysis and will be described in the SAP. Additional analyses exploring impact of baseline factors such as baseline disease severity, race, and other characteristics may be performed.

Patients that received prohibited medications or unallowable CS usage as described in Section 4.6 will be considered "medication failures" and will be treated as statistical

non-responders at time points on or following the first date of prohibited medication or unallowable CS usage for the primary efficacy analysis. The determination of medication failures will be reviewed using blinded data and finalized prior to unblinding.

The superiority of BOS161721 relative to placebo will be evaluated. If the proportion of SRI-4 responders for the selected POC dose in BOS161721 arm is higher than that of the placebo arm, then BOS161721 will be considered superior to placebo if the 2-sided p-value is less than 0.10. Secondary and exploratory endpoints for this POC portion will be evaluated based on the same statistical hypothesis.

8.2.4 Secondary Efficacy Endpoint(s)

Binary efficacy endpoints will be assessed via Pearson's chi-squared analysis. Continuous efficacy endpoints will be assessed via analysis of variance (ANOVA) or analysis of covariance (ANCOVA) and treatment will be compared using the F-test. Repeated measures mixed models may be performed to evaluate data collected at each visit and overall. Time-to-event endpoints will be assessed via Kaplan-Meier methodology and treatment will be compared using the log-rank test. The secondary efficacy endpoints will be analyzed on the FAS and if needed repeated in the PP analysis set. Details including handling of missing data and "medication failures" will be available in the SAP.

8.2.5 Analysis of Safety

8.2.5.1 Safety Analysis

Safety analyses will be performed on the SS. AE data will be coded to system organ class and preferred term using MedDRA. The number and percentage of patients experiencing any treatment-emergent AE, overall, and by system organ class and preferred term, will be tabulated. Treatment-emergent AEs will also be summarized by severity and relationship.

Concomitant medications will be coded using the WHO Drug dictionary. Observed values and changes from baseline in vital signs, ECG readings, and hematology and clinical chemistry parameters will be summarized at each individual visit.

8.2.6 Pharmacokinetic and Pharmacodynamic Data

8.2.6.1 Analysis of Pharmacokinetic Data

PK parameters will be calculated from concentration data collected during the MAD Phase 1b portion of the study using non-compartmental analysis and include the following:

- C_{max}, T_{max}, AUC, $t_{½}$, CL, V_d

The PK parameter data will be listed and summarized descriptively in tabular format.

If data permit, the following analyses will be performed for plasma BOS161721 concentration data:

- A listing of all plasma BOS161721 concentrations by patient at actual times post dose;

- A descriptive summary of plasma BOS161721 concentrations. Summary statistics of geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum will be tabulated by study days with PK assessments.

8.2.6.2 Analysis of Pharmacodynamic Data

The PD parameter data will be listed and summarized descriptively in tabular format.

Exploratory analyses examining the relationship between PD parameters and PK concentration and PK parameters will be performed.

8.2.6.3 Population Pharmacokinetic Analysis or PK/PD Modeling

Plots of individual patient values for each relevant PD parameter on Y-axis and each relevant PK parameter on X-axis will be examined for relationship. If relationships are revealed by these diagnostic plots, PK and PD data from this study may be analyzed using modeling approaches to describe the relationship and may also be pooled with data from other studies to investigate any association between BOS161721 exposure and biomarkers or significant safety endpoints.

8.3 Interim Analysis and Power

One IA is planned for this study and will be conducted at the time of the POC decision for dose selection.

Since there is no IA during the POC part of the study, there is no impact on the type 1 error.

9 ETHICS AND RESPONSIBILITIES

9.1 Good Clinical Practice

The procedures set out in this protocol are designed to ensure that the sponsor and the principal investigator abide by the principles of the International Council for Harmonisation (ICH) guidelines on GCP and the Declaration of Helsinki (Version 2013). The clinical study also will be carried out in the keeping with national and local legal requirements (in accordance with US IND regulations [21 CFR 56]).

9.2 DMC

This study will use an external DMC. The DMC is an independent committee established to provide oversight of safety considerations in study and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of enrolled patients and those yet to be recruited to the trial as well as for the continuing validity and scientific merit of the study results. The DMC is charged with assessing such actions in light of an acceptable benefit/risk profile for BOS161721. The recommendations made by the DMC (ie, dose escalation, etc.) will be forwarded to the sponsor for final decision. The sponsor will

forward such decisions, which may include summaries of safety data which are not endpoints, to regulatory authorities, as appropriate.

The sponsor will appoint a DMC for the periodic review of available study data. The DMC is an independent group of experts that advises the sponsor and the study investigators. The members of the DMC serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DMC are to (1) periodically review and evaluate the accumulated study data for participant safety, study conduct, and progress, (2) make recommendations to the sponsor concerning the continuation, modification, or termination of the study and (3) suggest dose for POC portion of the study as described in Section 3.1.1.3.

The DMC considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. The DMC is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking (unblinding), and voting procedures prior to initiating any data review. The DMC is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

The DMC will have access to unblinded treatment information during the clinical trial. Details regarding management and process of this committee are found in the DMC Charter.

The DMC may recommend termination of BOS161721 treatment arm or the entire BOS161721 MAD/POC trial for any safety concern that is felt to outweigh potential benefits. The recommendation must be supported by the sponsor as indicated in the DMC Charter.

9.3 Institutional Review Board/Independent Ethics Committee

Independent Ethics Committees/IRB must meet the guidelines set out by the U.S. Food and Drug Administration (FDA) and conform to local laws and customs where appropriate. Written IRB/IEC approval for the protocol and the signed ICF must be obtained and transmitted to Boston Pharmaceuticals or representative before the study can be initiated. The IRB/IEC must be informed of and approve all protocol amendments. The investigator will ensure that this study is conducted in full conformance with all applicable local and regional laws and regulations. The complete text of the World Medical Association Declaration of Helsinki is given in APPENDIX 2.

9.4 Informed Consent

Before each patient undergoes any protocol required assessments or procedure, the written informed consent will be obtained according to the regulatory and legal requirements of the participating country. As part of this procedure, the principal investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study patient should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. The principal investigator or designee will provide the sponsor with a copy of the IRB-approved ICF prior to the start of the study.

The informed consent document must be signed and dated; 1 copy will be handed to the patient and the principal investigator will retain a copy as part of the clinical study records. The principal investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

If the informed consent document is revised, it must be reviewed and approved by the responsible IRB/IEC. Patients currently enrolled may need to sign this revision (based on IRB/IEC requirements) and all future patients enrolled in the clinical study will be required to sign this revised ICF.

9.5 Records Management

The principal investigator will ensure the accuracy, completeness, and timeliness of the data reported to the sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The principal investigator or designee will cooperate with the sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The principal investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each patient receiving BOS161721 or placebo.

The principal investigator will allow sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB to have direct access to all documents pertaining to the study.

Electronic case report forms are required and should be completed for each randomized patient. It is the principal investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported on the patients' eCRF. Electronic case report forms should be completed in a timely fashion to support the study timelines. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status. The principal investigator or designated representative should complete and the principal investigator should verify the source documents as the information is collected. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The principal investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes.

9.6 Source Documentation

The documents that will form the source data for the clinical study (eg, patient charts, laboratory reports) must be defined and documented in the in-house study master file prior to the start of the study. Data on the eCRFs which will be checked against source data during monitoring visits must also be defined and documented in the in-house study master file including the percentage of each of the source data to be verified and the percentage of patients' eCRFs to be monitored.

9.7 Study Files and Record Retention

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of BOS161721. However, these documents should be retained for a longer period if required by the applicable legal requirements.

10 AUDITING AND MONITORING

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and on-site visits. The study will be routinely monitored to ensure compliance with the study protocol and the overall quality of data collected. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor may periodically request review of the investigator study file to assure the completeness of documentation in all respects of clinical study conduct. The study monitor will verify that each patient has proper consent documentation from the patient and/or patient's authorized representative for study procedures and for the release of medical records to the sponsor, FDA, other regulatory authorities, and the IRB. The study monitor will also verify that assent was obtained for patients not capable of providing informed consent or that documentation is provided by the investigator explaining why the patient was unable to provide assent. The investigator or appointed delegate will receive the study monitor during these on-site visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies. On completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

Throughout the course of the study, the medical monitor will determine eligibility of all screened patients, will address any medical issues that might arise, clarify medical questions, review patient safety data (eg, AE/SAE, laboratory, and ECG), and partner with the study team in the overall study management. The study medical monitoring plan will document additional details of the study medical oversight and monitoring.

11 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by Boston Pharmaceuticals. A protocol change intended to eliminate an apparent

immediate hazard to patients may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. Boston Pharmaceuticals will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, and/or Boston Pharmaceuticals, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the patient and/or has an impact on the patient's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for patients enrolled in the study before continued participation.

12 STUDY REPORT AND PUBLICATIONS

Boston Pharmaceuticals is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

By signing the protocol, the principal investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the competent authorities will be notified of the principal investigator’s name, address, qualifications, and extent of involvement.

The principal investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted and obtained approval from the sponsor in advance.

13 STUDY DISCONTINUATION

Both Boston Pharmaceuticals and the principal investigator reserve the right to terminate the study at the investigator’s site at any time. Should this be necessary, Boston Pharmaceuticals or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the principal investigator will inform the IRB/IEC of the same. In terminating the study Boston Pharmaceuticals and the principal investigator will assure that adequate consideration is given to the protection of the patients’ interests.

14 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Boston Pharmaceuticals, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial or to comply with regulatory requirements. However, authorized regulatory officials, IRB/IEC personnel, Boston Pharmaceuticals, and its authorized representatives are allowed full access to the records.

Identification of patients and eCRFs shall be by initials, birthdate, or patient number. Documents that identify the patient (eg, the signed informed consent document) must be

maintained in confidence by the principal investigator. If required, the patient's full name may be made known to an authorized regulatory agency or other authorized official.

15 REFERENCES

1 Urowitz MB, Gladman DD. How to improve morbidity and mortality in systemic lupus erythematosus. Rheumatology 2000;39:238-44.

2 Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Morbidity and Mortality in Systemic Lupus Erythematosus During a 10-Year Period. Medicine 2003;82(5):299-308.

3 Pons-Estel GJ, Alarcón GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. Semin Arthritis Rheum. 2010;39(4):257. Epub 2009 Jan 10.

4 Kanta H, Mohan C. Three Checkpoints in lupus development: central tolerance in adaptive immunity, peripheral amplification by innate immunity, and end-organ inflammation. Genes and Immunity 2009;10:390-6.

5 Dall'Aqua WF, Kiener PA, Wu H. Properties of Human IgG1s Engineered for Enhanced Binding to the Neonatal Fc Receptor (FcRn). J Biol Chem. 2006 Aug 18, 281(33):23514-24.

6 Spolski R, Leonard WJ. The Yin and Yang of interleukin-21 in allergy, autoimmunity and cancer. Curr Opin Immunol. 2008a;20:295-301.

7 Asao H, Okuyama C, Kumaki S, Ishii N, Tsuchiya S, Foster D, et al. Cutting edge: the common gamma-chain is an indispensable subunit of the IL-21 receptor complex. J Immunol. 2001;167:1-5.

8 Habib T, Senadheera S, Weinberg K, Kaushansky K. The common gamma chain (gamma c) is a required signaling component of the IL-21 receptor and supports IL-21-induced cell proliferation via JAK3. Biochemistry. 2002;41:8725-31.

9 Spolski R, Leonard WJ. Interleukin-21: basic biology and implications for cancer and autoimmunity. Annu Rev Immunol. 2008b;26:57-79.

10 Puga I, Cols M, Barra CM, He B, Cassis L, Gentile M, et al. B-cell-helper neutrophils stimulate the diversification and production of immunoglobulin in the marginal zone of the spleen. Nat Immunol. 2011;13(2):170-80.

11 Costanzo A, Chimenti MS, Botti E, Caruso R, Sarra M, Monteleone G. IL-21 in the pathogenesis and treatment of skin diseases. J Dermatol Sci. 2010;60(2):61-6.

12 Avery DT, Bryant VL, Ma CS, de Waal Malefy R, Tangye SG. IL-21-induced isotype switching to IgG and IgA by human naive B cells is differentially regulated by IL-4. J Immunol. 2008;181:1767-79.

13 Rasmussen TK, Andersen T, Bak, RO, Yiu G, Sorensen CM, Stengaard-Pedersen K, et al. Overexpression of microRNA-155 increases IL-21 mediated STAT3 signaling and IL-21 production in systemic lupus erythematosus. Arthritis Research & Therapy 2015;17(154)

14 Ettinger R, Kuchen S, Lipsky PE. The role of IL-21 in regulating B-cell function in health and disease. Immunol Rev. 2008;223:60-86.

15 Caprioli F, Sarra M, Caruso R, Stolfi C, Fina D, Sica G, et al. Autocrine regulation of IL-21 production in human T lymphocytes. J Immunol. 2008;180(3):1800-7.

16 Yang L, Anderson DE, Baecher-Allan C, Hastings WD, Bettelli E, Oukka M, et al. IL-21 and TGF-beta are required for differentiation of human T(H)17 cells. Nature. 2008;454(7202):350-2.

17 Tangye SG, Ma CS, Brink R, Deenick EK. The good, the bad and the ugly - TFH cells in human health and disease. Nat Rev Immunol. 2013;13(6):412-26.

18 Fantini MC, Rizzo A, Fina D, Caruso R, Becker C, Neurath MF, et al. IL-21 regulates experimental colitis by modulating the balance between Treg and Th17 cells. Eur J Immunol. 2007;37(11):3155-63.

19 Peluso I, Fantini MC, Fina D, Caruso R, Boirivant M, MacDonald TT, et al. IL-21 counteracts the regulatory T-cell-mediated suppression of human CD4+ T lymphocytes. J Immunol. 2007;178(2):732-9.

20 Hippen KL, Bucher C, Schirm DK, Bearl AM, Brender T, Mink KA, et al. Blocking IL-21 signaling ameliorates xenogeneic GVHD induced by human lymphocytes. Blood. 2012;119(2):619-28.

21 Davis ID, Skrumsager BK, Cebon J, Nicholaou T, Barlow JW, Moller NP, et al. An open-label, two-arm, phase I trial of recombinant human interleukin-21 in patients with metastatic melanoma. Clin Cancer Res. 2007;13:3630-6.

22 Frederiksen KS, Lundsgaard D, Freeman JA, Hughes SD, Holm TL, Skrumsager BK, et al. IL-21 induces in vivo immune activation of NK cells and CD8(+) T-cells in patients with metastatic melanoma and renal cell carcinoma. Cancer Immunol Immunother. 2008;57(10):1439-49.

23 Karrich JJ, Jachimowski LC, Nagasawa M, Kamp A, Balzarolo M, Wolkers MC, et al. IL-21- stimulated human plasmacytoid dendritic cells secrete granzyme B, which impairs their capacity to induce T-cell proliferation. Blood. 2013;121(16):3103-11.

24 Lindner S, Dahlke K, Sontheimer K, Hagn M, Kaltenmeier C, Barth TF, et al. Interleukin-21-induced granzyme B-expressing B-cells infiltrate tumors and regulate T-cells. Cancer Res. 2013;73(8):2468-79.

25 Monteleone G, Caruso R, Fina D, Peluso I, Gioia V, Stolfi C, et al. Control of matrix metalloproteinase production in human intestinal fibroblasts by interleukin 21. Gut. 2006;55(12):1774-80.

26 Nakou M, Papadimitraki ED, Fanouriakis A, Bertsias GK, Choulaki C, Goulidaki N, et al. Interleukin-21 is increased in active systemic lupus erythematosus patients and contributes to the generation of plasma B-cells. Clin Exp Rheumatol. 2013;31(2):172-9.

27 Li Q, Liu Z, Dang E, Jin L, He Z, Yang L, et al. Follicular helper T-cells (Tfh) and IL-21 involvement in the pathogenesis of bullous pemphigoid. PLoS One. 2013;8(7):e68145.

28 Liu R, Wu Q, Su D, Che N, Chen H, Geng L, et al. A regulatory effect of IL-21 on T follicular helper-like cell and B-cell in rheumatoid arthritis. Arthritis Res Ther. 2012;14(6):R255.

29 Kang KY, Kim HO, Kwok SK, Ju JH, Park KS, Sun DI, et al. Impact of interleukin-21 in the pathogenesis of primary Sjögren's syndrome: increased serum levels of interleukin-21 and its expression in the labial salivary glands. Arthritis Res Ther. 2011;13(5):R179.

30 Terrier B, Geri G, Chaara W, Allenbach Y, Rosenzwajg M, Costedoat-Chalumeau N, et al. Interleukin-21 modulates Th1 and Th17 responses in gianT-cell arteritis. Arthritis Rheum. 2012a;64(6):2001-11.

31 Terrier B, Costedoat-Chalumeau N, Garrido M, Geri G, Rosenzwajg M, Musset L, et al. Interleukin 21 correlates with T-cell and B-cell subset alterations in systemic lupus erythematosus. J Rheumatol. 2012b;39(9):1819-28.

32 International Conference on Harmonisation. Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6 (R1). 2011.

33 Wang W, Wang EQ, Balthasar JP. Monoclonal Antibody Pharmacokinetics and Pharmacodynamics. Clin Pharm & Ther 2008; 84(5):548-58.

34 Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. Journal of Allergy and Clinical Immunology 2006;117:391–7.

35 Elsaesser H, Sauer K, Brooks DG. IL-21 is required to control chronic viral infection. Science. 2009;324(5934):1569-72

36 Kotlarz D, Zietara N, Uzel G, Weidemann T, Braun CJ, Diestelhorst J, et al. Loss-of-function mutations in the IL-21 receptor gene cause a primary immunodeficiency syndrome. J Exp Med. 2013;210(3):433-43.

37 Hunter PR, Nichols G. Epidemiology and clinical features of Cryptosporidium infection in immunocompromised patients. Clinical microbiology reviews. 2002;15(1):145-54.

38 Desjardins M, Mazer BD. B-cell memory and primary immune deficiencies: interleukin-21 related defects. Curr Opin Allergy Clin Immunol. 2013;13(6):639-45.

39 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.

40 Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, US: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a4.htm.

41 NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, available at https://evs.nci.nih.gov/ftp1/CTCAE/About.html.

42 Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. Journal of Allergy and Clinical Immunology 2006;117:391–7.

43 Posner K, Melvin G a, Stanley B, Oquendo M a, Gould M. Factors in the assessment of suicidality in youth. *CNS Spectr*. 2007;12(2):156-162.

44 Castrejon I, Tani C, Jolly M, Huang A, Mosca M. Indices to assess patients with systemic lupus erythematosus in clinical trials, long-term observational studies, and clinical care. Clin Exp Rheumatol 2014; 32(85):S85-95.

45 Furie R, Wang L, Drappa J, Illei G. Systemic Lupus Erythematosus (SLE) Responder Index [SRI(4)] Response Is Associated with Global Benefit in Patients with Moderate to Severe SLE [abstract]. *Arthritis Rheumatol.* 2016; 68 (suppl 10).

46 Thanou A, Chakravarty E, James JA, Merrill JT. Which outcome measures in SLE clinical trials best reflect medical judgment? Lupus Science & Medicine 2014;1:e000005. doi:10.1136/lupus-2013-000005.

47 Wallace DJ, Kalunian K, Petri MA, Strand V, Houssiau FA, Pike M,*et al.* Efficacy and safety of epratuzumab in patients with moderate/severe active systemic lupus erythematosus: results from EMBLEM, a phase IIb, randomised, double-blind, placebo-controlled, multicentre study. *Ann Rheum Dis* 2014;73:183-90.

48 Albrecht J, Taylor L, Berlin JA, Dulay S, Ang G, Fakharzadeh S. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): An Outcome Instrument for Cutaneous Lupus Erythematosus. J Invest Derm. 2005;125(5):889-94.

49 Stoll T, Seifert B, Isenberg DA. SLICC/ACR Damage Index is Valid, and Renal and Pulmonary Organ Scores are Predictors of Sever Outcome in Patients with Systemic Lupus Erythematosus. Br J Rheumatol. 1996;35:248-54.

50 CCI [redacted].

16 APPENDICES

APPENDIX 1 NAMES OF STUDY PERSONNEL

Sponsor:	Boston Pharmaceuticals 55 Cambridge Parkway Suite 400 Cambridge, MA 02142, USA
Medical Monitor:	PPD PPD PPD
Clinical Research Organizations:	PPD PPD PPD
Bioanalytical Laboratory:	PPD
Central Laboratory:	PPD PPD

APPENDIX 2 DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles
For
Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subject."

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic, and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility, and quality.

In current medical practice and in medical research, most prophylactic, diagnostic, and therapeutic procedures involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Research investigators should be aware of the ethical, legal, and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal, or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any SAEs. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a subject of the research, even though the subject has given consent.

Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

The subjects must be volunteers and informed participants in the research project.

The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the subject's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the

review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic, or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the subjects who are research subjects.

The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists.

At the conclusion of the study, every subject entered into the study should be assured of access to the best-proven prophylactic, diagnostic, and therapeutic methods identified by the study.

The physician should fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study must never interfere with the subject-physician relationship.

In the treatment of a subject, where proven prophylactic, diagnostic, and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the subject, must be free to use unproven or new prophylactic, diagnostic, and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health, or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

APPENDIX 3 COMMONLY USED CORTICOSTEROID EQUIVALENTS

Medication	Prednisone Dose Equivalence
Prednisone	1 mg
Cortisone	5 mg
Hydrocortisone	4 mg
Prednisolone	1 mg
Methylprednisolone	0.8 mg
Triamcinolone	0.8 mg
Budesonide	0.25 mg
Dexamethasone	0.16 mg
Bethamethasone	0.16 mg

APPENDIX 4 MEDICATION WASHOUT PERIODS

WASHOUT TIMES OF MEDICATIONS BASED ON 5 HALF-LIVES

Medication	**Discontinuing Prior to Signing Consent**
Abatacept (CTLA4Ig)	24 weeks
Alefacept	12 weeks
AMG 623 (blisibimod)	24 weeks
Anifrolumab	12 weeks
Atacicept (TACI-Ig)	12 weeks
Belimumab	24 weeks
Cyclophosphamide	24 weeks
Cyclosporine (except for CSA eye drops)	4 weeks for oral and 8 weeks for topical
Danazol	4 weeks
Dapsone	4 weeks
Eculizumab	12 weeks
Efalizumab	12 weeks
Epratuzumab	24 weeks
Intravenous globulin	4 weeks
Leflunomide	8 weeks (4 weeks for washout with cholestyramine)
Lenalidomide with cholestiramine	8 weeks
Lupuzor	12 weeks
Memantine	4 weeks
Natalizumab	24 weeks
Ocrelizumab	48 weeks (or 24 weeks with recovery of B cell)
Pimecrolimus	4 weeks
Plasmapheresis	24 weeks
Retinoids (oral or topical)	4 weeks
Rituximab	48 weeks (or 24 weeks with recovery of B cell)
Sirolimus	4 weeks
Tacrolimus	4 weeks
Thalidomide	8 weeks
Tocilizumab	12 weeks

APPENDIX 5 BILAG-2004 (STUDY-SPECIFIC MODIFIED CRITERIA)

CCI

APPENDIX 6 INJECTION SITE REACTION GRADING SCALE

Adverse event Injection site reaction	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection	Tenderness with or without associated symptoms (eg, warmth, erythema, itching)	Pain; Lipodystrophy; Edema; phlebitis	Ulceration or necrosis; Severe tissue damage; Operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	-
Rash maculopapular/Erythema /Induration Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally, and associated with pruritus.	Macules/papules covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness) Erythema covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness)	Macules/papules covering 10% - 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL; Erythema 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering > 30% BSA with or without associated symptoms; limiting self-care ADL Erythema covering > 30% BSA with or without associated symptoms; limiting self-careADL	-	-

ADL = active daily living

APPENDIX 7 OPIOID ORAL MORPHINE MILLIGRAM EQUIVALENTS OF COMMONLY USED OPIOIDS

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

Note that this list is not comprehensive. If an opioid is being used which is not in this list, please see the appropriate conversion factor below.

Opioid Oral Morphine Equivalent Conversion Factors[a,b]

Type of Opioid (strength in units)	MME Conversion Factor
Buprenorphine film/table[c] (mg)	30
Buprenorphine patch[d] (mcg/hr)	12.6
Buprenorphine film (mcg)	0.03
Butorphanol (mg)	7
Codeine (mg)	0.15
Dihydrocodeine (mg)	0.25
Fentanyl buccal or SL tablets, or lozenge/troche[e] (mcg)	0.13
Fentanyl film or oral spray[f] (mcg)	0.18
Fentanyl nasal spray[g] (mcg)	0.16
Fentanyl patch[h] (mcg)	7.2
Hydrocodone (mg)	1
Hydromorphone (mg)	4
Levorphanol tartrate (mg)	11
Meperidine hydrochloride (mg)	0.1
Methadone[i] (mg)	3
> 0, ≤ 20	4
> 20, ≤ 40	8
> 40, ≤ 60	10
> 60	12
Morphine (mg)	1
Opium (mg)	1
Oxycodone (mg)	1.5
Oxymorphone (mg)	3
Pentazocine (mg)	0.37
Tapentadol[j] (mg)	0.4
Tramadol (mg)	0.1

CDC = Centers for Disease Control; CMS = Centers for Medicare and Medicaid Services; FDA = Food and Drug Administration; MAT = Medication Assisted Treatment; MME = morphine milligram equivalent; OMS = Overutilization Monitoring System.

a. The MME conversion factor is intended only for analytic purposes where prescription data is used to calculate daily MME. It is to be used in the formula: Strength per Unit × (Number of Units/Days Supply) × MME conversion factor = MME/Day. This value does not constitute clinical guidance or recommendations for converting patients from one form of opioid analgesic to another. Please consult the manufacturer's full prescribing information for such guidance. Use of this file for the purposes of any clinical decision-making warrants caution.

b. National Center for Injury Prevention and Control. CDC compilation of benzodiazepines, muscle relaxants, stimulants, zolpidem, and opioid analgesics with oral morphine milligram equivalent conversion factors, 2016 version. Atlanta, GA: Centers for Disease Control and Prevention; 2016. Available at https://www.cdc.gov/drugoverdose/media/. For more information, send an email to Mbohm@cdc.gov.

c. Buprenorphine formulations with a FDA approved indication for MAT are excluded from Medicare's Overutilization Monitoring System's opioid overutilization reporting.

d. The MME conversion factor for buprenorphine patches is based on the assumption that 1 milligram of parenteral buprenorphine is equivalent to 75 milligrams of oral morphine and that one patch delivers the dispensed micrograms per hour over a 24 hour day. Example: 5 µg/hr buprenorphine patch × 24 hrs = 120 ug/day buprenorphine = 0.12 mg/day = 9 mg/day oral MME. In other words, the conversion factor not accounting for days of use would be 9/5 or 1.8.
   However, since the buprenorphine patch remains in place for 7 days, we have multiplied the conversion factor by 7 (1.8 × 7 = 12.6). In this example, MME/day for 4 5 µg/hr buprenorphine patches dispensed for use over 28 days would work out as follows: Example: 5 µg/hr buprenorphine patch × (4 patches/28 days) × 12.6 = 9 MME/day. Please note that because this allowance has been made based on the typical dosage of 1 buprenorphine patch per 7 days, you should first change all Days Supply in your prescription data to follow this standard, i.e., Days Supply for buprenorphine patches = number of patches x 7.
e. The MME conversion factor for fentanyl buccal tablets, sublingual tablets, and lozenges/troche is 0.13. This conversion factor should be multiplied by the number of micrograms in a given tablet or lozenge/troche.
f. The MME conversion factor for fentanyl film and oral spray is 0.18. This reflects a 40% greater bioavailability for films compared to lozenges/tablets and 38% greater bioavailability for oral sprays compared to lozenges/tablets.
g. The MME conversion factor for fentanyl nasal spray is 0.16, which reflects a 20% greater bioavailability for sprays compared to lozenges/tablets.
h. The MME conversion factor for fentanyl patches is based on the assumption that 1 milligram of parenteral fentanyl is equivalent to 100 milligrams of oral morphine and that 1 patch delivers the dispensed micrograms per hour over a 24 hour day. Example: 25 µg/hr fentanyl patch × 24 hrs = 600 ug/day fentanyl = 60 mg/day oral morphine milligram equivalent.
   In other words, the conversion factor not accounting for days of use would be 60/25 or 2.4.
   However, since the fentanyl patch remains in place for 3 days, we have multiplied the conversion factor by 3 (2.4 × 3 = 7.2). In this example, MME/day for 10 25 µg/hr fentanyl patches dispensed for use over 30 days would work out as follows:
   Example: 25 µg/hr fentanyl patch × (10 patches/30 days) × 7.2 = 60 MME/day. Please note that because this allowance has been made based on the typical dosage of 1 fentanyl patch per 3 days, you should first change all Days Supply in your prescription data to follow this standard, i.e., Days Supply for fentanyl patches = number of patches × 3.
i. The CDC MME conversion factor to calculate morphine milligram equivalents is 3. CMS uses this conversion factor when analyzing Medicare population opioid use. CMS uses the graduated methadone MME conversion factors to calculate MME within the OMS for identifying and reporting potential opioid overutilizers. https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf.
j. Tapentadol is a mu receptor agonist and norepinephrine reuptake inhibitor. Oral MMEs are based on degree of mu-receptor agonist activity, but it is unknown if this drug is associated with overdose in the same dose-dependent manner as observed with medications that are solely mu receptor agonists.

APPENDIX 8 SCHEDULE OF ASSESSMENTS - PHASE 1B MULTIPLE ASCENDING DOSE

Table 4 Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
GENERAL ASSESSMENTS																
Informed consent	X															
Inclusion/Exclusion criteria	X															
Medical history	X															
Demographics	X															
SLICC Criteria for SLE	X															
Concomitant medication[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[c]		X														
BOS161721 or placebo dosing		X			X		X	X	X	X	X					
SAFETY ASSESSMENTS																
Full physical exam	X	X														
Chest x-ray[d]	X															
C-SSRS	X	X						X			X					
AEs and SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	X	X			X			X								X
Injection site reaction assessment		X[f]	X		X		X	X	X	X	X	X	X	X	X	X
Targeted physical examination				X	X	X	X	X	X	X	X			X	X	X
Vital signs (BP, HR, and temperature)[g]	X	X		X	X	X	X	X	X	X	X			X	X	X

Table 4 Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
EFFICACY ASSESSMENTS																
BILAG-2004 Index	X	X			X		X	X	X	X	X			X	X	X
SLEDAI-2K[h]	X	X			X		X	X	X	X	X			X	X	X
PGA of disease activity	X	X			X		X	X	X	X	X			X	X	X
ACR-28 joint count	X	X			X		X	X	X	X	X			X	X	X
CLASI	X	X			X		X	X	X	X	X			X	X	X
CCI		X			X		X	X	X	X	X			X	X	X
SLICC/ACR Damage Index		X									X					
CCI		X			X		X	X	X	X	X			X	X	X
LABORATORY ASSESSMENTS																
CD4+ count	X	X		X	X	X		X			X					
Clinical laboratory assessments (hematology and clinical chemistry)[i]	X	X			X	X	X	X	X	X	X			X	X	X
Coomb's test direct[j]	X	X			X		X	X	X	X	X			X	X	X
Total IgG and IgM	X	X		X	X	X		X			X					
Plasma CCI	X	X			X		X	X	X	X	X			X	X	X
Plasma CCI & CCI		X		X	X		X	X			X					
Whole blood for leukocyte immunophenotype		X		X	X		X	X			X					
ADA[k]		X		X	X		X	X			X					X
nAb[l]								X			X					
pSTAT3[m]		X			X	X	X	X								
CCI		X		X				X			X					X

Table 4 Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
CCI [redacted]		X														
CCI [redacted]	X	X			X		X	X	X	X	X			X[n]	X[n]	X[n]
CRP	X							X								X
Serum pregnancy test (women)	X															
FSH (postmenopausal women)	X															
Urine pregnancy test (women)[o]		X			X		X	X	X	X	X					X
TB test (QuantiFERON-TB Gold In-Tube)[d]	X															
Serology (hepatitis B and C, HIV-1/2 combination)	X															
Stool sample[p]	X															
Spot urine for protein/creatinine ratio	X	X			X		X	X	X	X	X			X	X	X
Urinalysis	X	X			X		X	X	X	X	X			X	X	X

Table 4 Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
PK Labs																
Predose		X			X		X	X	X	X	X					
Predose PK Window		60 m			± 3 d		± 3 d	± 3 d	± 3 d	± 3 d	± 3 d					
Postdose		X[q]	X	X	X[q]						X[q]	X	X	X	X	X
Postdose PK Window		4 h ± 30 m 8 h ± 45 m 24 h ± 60 m	± 1d	± 3 d	4 h ± 30 m 8 h ± 45 m 24 h ± 60 m						4 h ± 30 m 8 h ± 45 m 24h ± 60 m	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d

Abbreviations: ACR = American College of Rheumatology; ADA= anti-drug antibody; AE = adverse event; APL = antiphospholipid; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; C = complement; CD4+ = cluster of differentiation 4; CLASI = Cutaneous Lupus Area and Severity Index; CRP = C-reactive protein; C-SSRS = Columbia Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; CCI [redacted]; FSH = follicle stimulating hormone; h = hour; HR = heart rate; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IL-21 = interleukin 21; IV = intravenous; m = minute; nAb = neutralizing antibody; PGA = Physician's Global Assessment; PK = pharmacokinetic; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; SAE = serious adverse event; SC = subcutaneous; CCI [redacted]; SLEDAI-2K = SLE Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; CCI [redacted]; TB = tuberculosis; TDAR = T-cell dependent antigen response.

[a] Screening assessments will be performed over more than 1 visit.

[b] Concomitant use of oral corticosteroids: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). See Section 4.6.1 for further details.

[c] Randomization should occur after patient eligibility has been confirmed by central eligibility review.

[d] If patients have had a TB test and chest x ray within 3 months prior to screening, then these assessments do not need to be repeated during screening. The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

[e] ECGs will be performed after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws.

[f] Injection site reaction assessments to be performed at 2 hours postdose.

[g] Vital signs will be assessed after the patient has been supine and at rest ≥ 5 minutes. Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours postdose, as well as on each of the scheduled outpatient days in the table above (excluding PK-only site visits at Days 7, 187, and 195). When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

Table 4 Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**

[h] SLEDAI-2K should be done before randomization and dosing on Day 0 as SLEDAI-2K < 6 is exclusionary.

[i] Clinical laboratory assessments will include a fasting glucose and lipid panel, with exception of screening (Visit 1) which will be non-fasting.

[j] When clinically indicated for hemolytic anemia.

[k] Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients, but only assayed (analyzed) if the patient had a positive ADA on Day 90.

[l] nAb is collected for all patients, though will only be analyzed by central lab if patient is positive for ADA at Day 90.

[m] Predose (trough) samples only.

[n] Antibodies and autoantibodies (CCI [redacted]) will not be analyzed during safety follow-up visits.

[o] Urine pregnancy test will be collected on WOCBP prior to study drug administration on dosing visits.

[p] Cryptosporidium test is required at screening. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

[q] Postdose samples will be collected at 4, 8, and 24 hours after study drug administration on Days 0, 30, and 180.

APPENDIX 9 PROTOCOL SUMMARY OF CHANGES

The protocol summary of changes was moved to the end of the protocol for easier readability.

Significant changes are described in the table below. Changed text is displayed for the first major occurrence only. Deleted text is presented in strikethrough format, and added text is presented in bold format.

Section	Description of Changes	Rationale
Global	Replace: Protocol Date and Version: 23 January 2019; V5.0 With: Protocol Date and Version: **23 July** 201**9**; V**6**.0	Administrative
Global	Change: Changed Version number from V5.0 (Amendment 4) to V**6**.0 (Amendment **5**) and Version date from 23 January 2019 to **23 July 2019**.	Administrative
Global	Made administrative and editorial (formatting, typographical, and grammatical) updates.	Administrative
CLINICAL PROTOCOL APPROVAL FORM	Replace: Name and Title PPD , MD, FACR Vice President, Clinical Development Boston Pharmaceuticals With: Name and Title PPD **, PhD** **Senior Vice President** **Clinical Development and Head of Clinical Operations** **Boston Pharmaceuticals**	Administrative
CLINICAL PROTOCOL APPROVAL FORM	Delete: Name and Title	Administrative

Section	Description of Changes	Rationale
	PPD ~~, MD, PhD~~ ~~Vice President, Clinical Development and Safety Officer~~ ~~Boston Pharmaceuticals~~	
PROTOCOL SUMMARY, Objectives and Endpoints, MAD Phase 1b, Exploratory Endpoints, Bullet 1 (sub-bullet 3) Section 2.1, Study Objectives and Endpoints, Phase 1b Multiple Ascending Dose, Exploratory Endpoints, Bullet 1 (sub-bullet 3)	Replace: • CCI With: • CCI	Protocol clarification; CCI
PROTOCOL SUMMARY, Objectives and Endpoints, MAD Phase 1b, Exploratory Endpoints, Bullet 1 (sub-bullet 4) Section 2.1, Study Objectives and Endpoints, Phase 1b Multiple Ascending Dose, Exploratory Endpoints, Bullet 1 (sub-bullet 4)	Replace: • CCI With: • CCI	CCI
PROTOCOL SUMMARY, Objectives and Endpoints, MAD Phase 1b, Exploratory Endpoints, Bullet 2 (sub-bullet 2) Section 2.1, Study Objectives and Endpoints, Phase 1b Multiple Ascending Dose, Exploratory Endpoints, Bullet 2	Replace: • CCI With: • CCI	Clarified to describe CCI.

Section	Description of Changes	Rationale
(sub-bullet 2) PROTOCOL SUMMARY, Objectives and Endpoints, MAD Phase 1b, Exploratory Endpoints, Bullet 6 Section 2.1, Study Objectives and Endpoints, Phase 1b Multiple Ascending Dose, Exploratory Endpoints, Bullet 6	Replace: • CCI With: • CCI	CCI
PROTOCOL SUMMARY, Objectives and Endpoints, POC Phase 2, Secondary Endpoints, Bullet 1 (sub-bullet 3) Section 2.2, Study Objectives and Endpoints, Phase 2 Proof of Concept, Secondary Endpoints, Bullet 1 (sub-bullet 3)	Replace: • The proportion of patients with: ○ a sustained reduction of oral corticosteroid (CS) (≤ 10 mg/day and ≤ Day 0 dose) between Day 120 and Day 210 With: • The proportion of patients with: ○ a sustained reduction **from baseline** of oral corticosteroid (CS) (≤ **7.5** mg/day and **<** Day 0 dose) between Day **150** and Day 210	Protocol clarification
PROTOCOL SUMMARY, Objectives and Endpoints, POC Phase 2, Secondary Endpoints, Bullet 1 (sub-bullet 4) Section 2.2, Study Objectives and Endpoints, Phase 2 Proof of Concept, Secondary Endpoints, Bullet 1 (sub-bullet 4)	Replace: • The proportion of patients with: ○ new BILAG A flare or > 1 BILAG B flares relative to baseline through Day 210 With: • The proportion of patients with: ○ new **or recurrent** BILAG flare**s (≥ 1 qualifying BILAG A** or > 1 **qualifying** BILAG B**)** through Day 210	Clarified to be performed against previous visits, not only baseline.
PROTOCOL SUMMARY, Objectives and Endpoints, POC Phase 2, Secondary Endpoints, Bullet 2	Replace: • Results and changes from baseline in: ○ Swollen and tender joints ACR-28 With:	Clarified to describe swollen joint changes from baseline.

Section	Description of Changes	Rationale
(sub-bullet 2) Section 2.2, Study Objectives and Endpoints Phase 2 Proof of Concept, Secondary Endpoints, Bullet 2 (sub-bullet 2)	• Results and changes from baseline in: ○ **Total number of** swollen **joints,** tender joints**, and active joints (swelling and tenderness in the same joint) in the** ACR-28 **joint count**	
PROTOCOL SUMMARY, Objectives and Endpoints, POC Phase 2, Secondary Endpoints, Bullet 4 Section 2.2, Study Objectives and Endpoints, Phase 2 Proof of Concept, Secondary Endpoints, Bullet 4	Add: • **Group mean percent reduction in CS administration from baseline Day 0 dose through Day 210 in patients receiving ≥ 7.5 mg/day prednisone equivalent at Day 0**	Add endpoint to measure overall CS reduction in patients receiving CS at baseline.
PROTOCOL SUMMARY, Objectives and Endpoints, POC Phase 2, Secondary Endpoints, Bullet 7 Section 2.2, Study Objectives and Endpoints, Phase 2 Proof of Concept, Secondary Endpoints, Bullet 7	Replace: • Time to BILAG A flare or > 1 BILAG B flare compared to baseline through Day 210 With: • Time to **first** BILAG flare **(≥ 1 new or recurrent BILAG A** or > 1 **new or recurrent** BILAG B**) relative** to baseline through Day 210	Clarified this is for the time to first flare and allowed for new or recurrent BILAG flare to allow for improvement and subsequent worsening.
PROTOCOL SUMMARY, Objectives and Endpoints, POC Phase 2, Exploratory Endpoints (Pharmacodynamic) Section 2.2, Study Objectives and Endpoints, Phase 2 Proof of Concept, Exploratory Endpoints (Pharmacodynamic)	Delete: • CCI [redacted]	CCI [redacted]

Section	Description of Changes	Rationale
PROTOCOL SUMMARY, Study Design, Paragraph 5	Replace: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). One oral CS "burst" for increased SLE disease activity may occur during the study between Day 0 and Day 60. Tapering of steroids during the course of the study will be highly encouraged and should be evaluated at the protocol permitted visits (Day 0 through Day 60 and Day 120 through Day 150). Between Day 60 and Day 120, and between Day 150 and Day 210, oral CS doses must be held constant due to the endpoint evaluations occurring at Day 120 and Day 210. With: A maximum **stable (for at least 6 weeks prior to Day 0)** daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study. One oral CS "burst" for increased SLE disease activity may occur during the study between Day 0 and Day **120**. Tapering of steroids during the course of the study will be highly encouraged and should be evaluated **during the protocol-allowed tapering windows (Day 0 through Day 150) with the target of achieving a CS daily dose of ≤ 7.5 mg and < Day 0 dose between Day 150 and Day 210**. Between Day 150 and Day 210, oral CS doses must be held constant due to the **Day 210** endpoint evaluations.	Protocol clarification.
PROTOCOL SUMMARY, Main Criteria for Inclusion and Exclusion, Inclusion Criteria, criteria 4, c Section 4.4, Inclusion Criteria, criteria 4, c	Delete: ~~c. CCI levels below normal as determined by the central lab~~	Allowing patients to enroll on low compliment alone is not specific enough for SLE.
PROTOCOL SUMMARY, Main Criteria for Inclusion and Exclusion, Inclusion Criteria, criteria 5	Replace: 5. At screening, the SLEDAI-2K must be ≥ 6, including points from at least 1 of the following clinical components: a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis i. Excluding parameters which require central laboratory results: (hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia) ii. Points from lupus headache and organic brain syndrome will also be excluded With: 5. At screening, the **total** SLEDAI-2K **score** must be ≥ **8**, including	To ensure patients with Moderate to Severe active disease are enrolled.

Section	Description of Changes	Rationale
	points from at least 1 of the following clinical components: a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis **Note: Points from lupus headache and organic brain syndrome will also be excluded from qualifying total and clinical SLEDAI-2K scores at screening and Day 0.**	
PROTOCOL SUMMARY, Main Criteria for Inclusion and Exclusion, Inclusion Criteria, criteria 6 Section 4.4, Inclusion Criteria, criteria 6	Replace: 6. On Day 0, the SLEDAI-2K must be ≥ 6, including points from at least 1 of the following clinical components: a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis i. Excluding parameters which require central laboratory results: (hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia) ii. Points from lupus headache and organic brain syndrome will also be excluded With: 6. **A clinical SLEDAI-2K score of ≥ 6 at screening at Day 0. Clinical SLEDAI-2K score is defined as follows:** a. **Contains points from a**rthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, **or** vasculitis **b. Excludes parameters which require central laboratory results: hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia** **Note: Points from lupus headache and organic brain syndrome will also be excluded from qualifying total and clinical SLEDAI-2K scores at screening and Day 0.**	To ensure patients with Moderate to Severe active disease are enrolled.
PROTOCOL SUMMARY, Main Criteria for Inclusion and Exclusion, Inclusion Criteria, criteria 7	Replace: 7. Patients must have at least 1A or 2Bs from the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer: a. BILAG A or B score in the mucocutaneous body system b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis defined in the protocol Section 4.4 If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in the other body systems for a total of 2 "B" BILAG body system scores With: 7. Patients must have at least 1 **qualifying** A or 2Bs from the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the	To ensure patients with Moderate to Severe active disease are enrolled. Clarification of active joint term.

Section	Description of Changes	Rationale
	central data reviewer: a. BILAG A or B score in the mucocutaneous body system. **If a BILAG B score is due to BILAG number 6, mild skin eruption, the CLASI activity score including erythema and scale/hypertrophy must be ≥ 3 excluding points from mucosal ulcers and alopecia.** b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis defined in the protocol Section 4.4 **Note: Hips, shoulders, back, neck, and temporomandibular joints do not count towards the total number of joints with active synovitis.** If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in **at least 1** other body system for a total of **2** "B" BILAG body system scores**.**	
PROTOCOL SUMMARY, Main Criteria for Inclusion and Exclusion, Inclusion Criteria, criteria 8 Section 4.4, Inclusion Criteria, criteria 8	Replace: 8. Patients must be currently receiving at least 1 of the following: a. Administration for a minimum of 12 weeks, and a stable dose for at least 56 days (8 weeks prior to signing consent) of the following permitted steroid-sparing agents: i. Azathioprine (AZA), mycophenolate mofetil or mycophenolic acid, chloroquine, hydroxychloroquine, or methotrexate (MTX) b. Prednisone (or prednisone-equivalent) cannot exceed 30 mg/day at screening for a patient to be eligible and must be stable at a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization) With: 8. Patients must be currently receiving at least 1 of the following: a. Administration for a minimum of 12 weeks, and a stable dose for at least 56 days (8 weeks prior to **Day 0**) of the following permitted steroid-sparing agents: i. Azathioprine (AZA), mycophenolate mofetil or mycophenolic acid, chloroquine, hydroxychloroquine, or methotrexate (MTX) b. **If AZA, myocophenolate mofetil, mycophenolic acid, hydroxychloroquine, or MTX were discontinued prior to screening, the washout period must be ≥ 12 weeks.** c. **Corticosteroids (p**rednisone or prednisone-equivalent) **at a stable dose of up to** 30 mg/day **for at least 6 weeks** prior to Day 0 (see APPENDIX 3) **i. For patients whose only SLE treatment is CSs, the stable CS dose must be ≥ 10 mg/day for at least 6 weeks prior to Day 0 and no more than 30 mg/day at the time of randomization.** **ii. Topical steroids may be used, but the dose must be stable for at least 6 weeks prior to Day 0. PRN topical**	A stable dose is needed 8 weeks prior to Day 0; it is not necessary to be longer. Removed the tapering requirement prior to randomization, determined not to be required. To ensure patients with Moderate to Severe active disease are enrolled.

Section	Description of Changes	Rationale
	steroids are not permitted.	
PROTOCOL SUMMARY, Main Criteria for Inclusion and Exclusion, Exclusion Criteria criterion 7, 23, and 27 Section 4.5, Exclusion Criteria, criterion 7, 23, and 27	Add: 7. Concomitant illness that, in the opinion of the investigator **or the sponsor or their designee**, is likely to require additional systemic glucocorticosteroid therapy during the study, (eg, asthma), is exclusionary 23. Any other laboratory test results that, in the opinion of the Investigator **or the sponsor or sponsor's designee**, might place a patient at unacceptable risk for participating in this study 27. Any other severe acute or chronic medical or psychiatric condition, including recent (within the past year) medical conditions (eg, cardiovascular conditions, respiratory illnesses) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator**, sponsor or sponsor's designee**, would make the patient inappropriate for entry into this study	To clarify that sponsor or designee can determine a patient is not eligible.
PROTOCOL SUMMARY, Main Criteria for Inclusion and Exclusion, Exclusion Criteria criterion 15 Section 4.5, Exclusion Criteria, criterion 15	Replace: 15. CD4+ count < 350/µL at screening With: 15. CD4+ count < **150**/µL at screening	Reduced based on safety data from MAD portion of the study.
PROTOCOL SUMMARY, Main Criteria for Inclusion and Exclusion, Exclusion Criteria criterion 22 Section 4.5, Exclusion Criteria, criterion 22	Replace: 22. Direct bilirubin > 1.5 × ULN at screening (unless related to Gilbert's syndrome) With: 22. **Total** bilirubin > 1.5 × ULN at screening (unless related to Gilbert's syndrome)	Total bilirubin is tested at screening, but direct bilirubin is only tested when there is potential liver injury.
PROTOCOL SUMMARY, Main Criteria for Inclusion and Exclusion, Exclusion Criteria criterion 33 Section 4.5, Exclusion Criteria, criterion 33	Add: 33. **Currently taking a total daily dose of > 30 mg morphine or morphine equivalent (see Appendix 7)**	Opioid will mask SLE symptoms.
PROTOCOL SUMMARY, Main Criteria for Inclusion and Exclusion,	Add: 34. **Body mass index (BMI) ≥ 40.0**	Added restriction due to increased co-morbidities

Section	Description of Changes	Rationale
Exclusion Criteria criterion 34 Section 4.5, Exclusion Criteria, criterion 34		in patients with high BMI that will hinder SLE Assessments.
LIST OF ABBREVIATIONS	Add: **ADL activities of daily living** **BMI body mass index** **NSAID nonsteroidal anti-inflammatory drug**	Terms added to protocol amendment.
Section 3.1.2.1, BOS161721 POC Dose Selection and Justification, Paragraph 5	Replace: The 120 mg dose will be communicated to site investigators participating in the POC Phase 2 portion, and to Institutional Review Boards (IRBs) and the Independent Ethics Committee (IEC). With: The 120 mg dose **was** communicated to site investigators participating in the POC Phase 2 portion, and to Institutional Review Boards (IRBs) and the Independent Ethics Committee (IEC).	Protocol clarification.
Section 3.1.2.2, POC Study Design, Paragraph 2	Replace: As in the MAD part of the study, each patient in the POC portion may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180. Assessments will be completed according to the Schedule of Assessments (Section 3.4). With: As in the MAD part of the study, each patient in the POC portion may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180. Assessments will be completed according to the Schedule of Assessments (**Table 1 and Table 4**).	Protocol clarification.
Section 3.4, Schedule of Assessments, Table 1	Delete:	Since Phase 1b MAD has completed, the Schedule of Assessments for Phase 1b MAD was moved to the Appendix.

Section	Description of Changes	Rationale

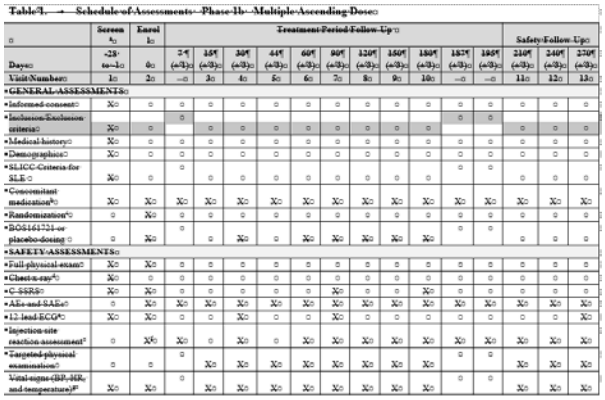


Table 1. Schedule of Assessments: Phase 1b: Multiple Ascending Dose																
	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	-28 to -1	0	7 (±1)	15 (±3)	30 (±3)	44 (±3)	60 (±3)	90 (±3)	120 (±3)	150 (±3)	180 (±3)	187 (±3)	195 (±3)	210 (±3)	240 (±3)	270 (±3)
Visit Number	1	2	–	3	4	5	6	7	8	9	10	–	–	11	12	13
GENERAL ASSESSMENTS																
Informed consent	X															
Inclusion/Exclusion criteria	X															
Medical history	X															
Demographics	X															
SLICC Criteria for SLE	X															
Concomitant medication[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[c]		X														
BOS161721 or placebo dosing		X			X		X	X	X	X	X					
SAFETY ASSESSMENTS																
Full physical exam[d]	X	X														
Chest x-ray[e]	X															
C-SSRS	X	X						X			X					
AEs and SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[f]	X	X			X			X								X
Injection site reaction assessment[g]		X	X		X		X	X	X	X	X	X	X	X	X	X
Targeted physical examination[h]				X	X	X	X	X	X	X	X			X	X	X
Vital signs (BP, HR, and temperature)[i]	X	X		X	X	X	X	X	X	X	X			X	X	X

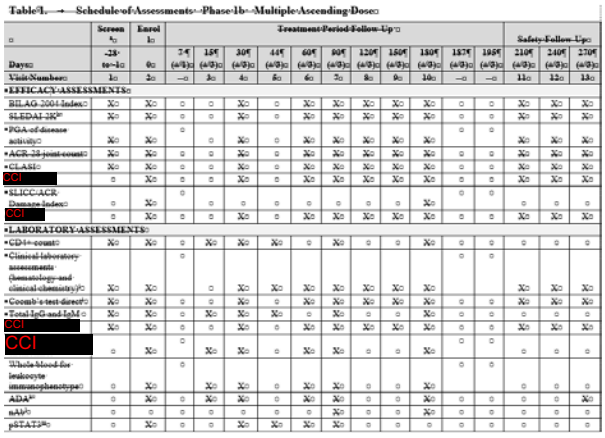


Table 1. Schedule of Assessments: Phase 1b: Multiple Ascending Dose																
	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	-28 to -1	0	7 (±1)	15 (±3)	30 (±3)	44 (±3)	60 (±3)	90 (±3)	120 (±3)	150 (±3)	180 (±3)	187 (±3)	195 (±3)	210 (±3)	240 (±3)	270 (±3)
Visit Number	1	2	–	3	4	5	6	7	8	9	10	–	–	11	12	13
EFFICACY ASSESSMENTS																
BILAG 2004 Index	X	X			X		X	X	X	X	X			X	X	X
SLEDAI-2K[j]	X	X			X		X	X	X	X	X			X	X	X
PGA of disease activity	X	X			X		X	X	X	X	X			X	X	X
ACR 28 joint count	X	X			X		X	X	X	X	X			X	X	X
CLASI	X	X			X		X	X	X	X	X			X	X	X
CCI		X			X		X	X	X	X	X			X	X	X
SLICC/ACR Damage Index		X			X		X	X	X	X	X			X	X	X
CCI		X			X		X	X	X	X	X			X	X	X
LABORATORY ASSESSMENTS																
CD4+ count	X	X		X	X	X		X			X					
Clinical laboratory assessments (hematology and clinical chemistry)[c]	X	X			X	X	X	X	X	X	X			X	X	X
Coomb's test direct[c]	X	X			X		X	X	X	X	X			X	X	X
Total IgG and IgM	X	X		X	X	X		X			X					
CCI	X	X			X		X	X	X	X	X			X	X	X
CCI		X		X	X		X	X			X					
Whole blood for leukocyte immunophenotype		X		X	X		X	X			X					
ADA[k]		X		X	X		X	X			X					X
nAb[l]								X			X					
pSTAT3[m]		X			X	X	X	X								

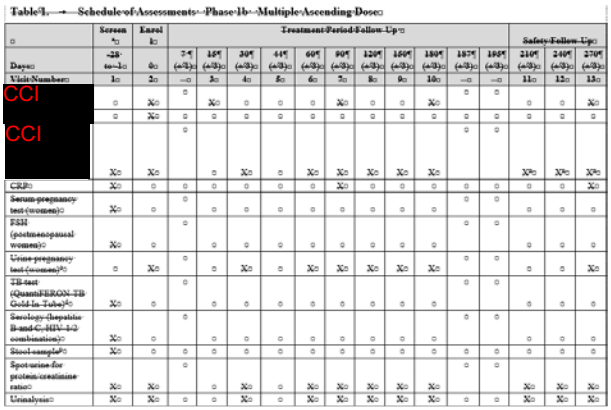


Table 1. Schedule of Assessments: Phase 1b: Multiple Ascending Dose																
	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	-28 to -1	0	7 (±1)	15 (±3)	30 (±3)	44 (±3)	60 (±3)	90 (±3)	120 (±3)	150 (±3)	180 (±3)	187 (±3)	195 (±3)	210 (±3)	240 (±3)	270 (±3)
Visit Number	1	2	–	3	4	5	6	7	8	9	10	–	–	11	12	13
CCI		X		X				X			X					X
CCI		X			X		X	X	X	X	X			X[n]	X[n]	X[n]
CRP	X							X								X
Serum pregnancy test (women)	X															
FSH (postmenopausal women)	X															
Urine pregnancy test (women)[o]		X			X		X	X	X	X	X					X
TB test (QuantiFERON-TB Gold In-Tube)[p]	X															
Serology (hepatitis B and C, HIV 1/2 combination)	X															
Stool sample[q]	X															
Spot urine for protein/creatinine ratio	X	X			X		X	X	X	X	X			X	X	X
Urinalysis	X	X			X		X	X	X	X	X			X	X	X

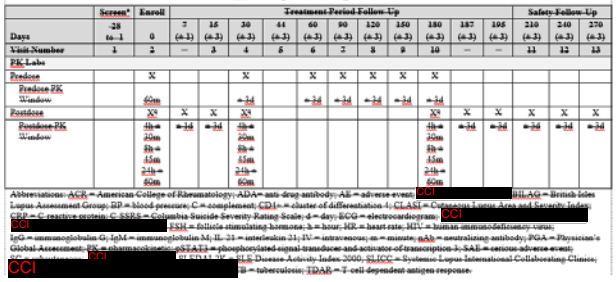


Table 1. Schedule of Assessments: Phase 1b: Multiple Ascending Dose																
	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	-28 to -1	0	7 (±1)	15 (±3)	30 (±3)	44 (±3)	60 (±3)	90 (±3)	120 (±3)	150 (±3)	180 (±3)	187 (±3)	195 (±3)	210 (±3)	240 (±3)	270 (±3)
Visit Number	1	2	–	3	4	5	6	7	8	9	10	–	–	11	12	13
PK Labs																
Predose		X			X		X	X	X	X	X					
Predose PK Window		60m			± 3d		± 3d	± 3d	± 3d	± 3d	± 3d					
Postdose		X[s]	X	X	X[t]						X[s]	X	X	X	X	X
Postdose PK Window		4h ± 20m 8h ± 15m 24h ± 60m	± 3d	± 3d	4h ± 20m 8h ± 15m 24h ± 60m						4h ± 20m 8h ± 15m 24h ± 60m	± 3d	± 3d	± 3d	± 3d	± 3d

Abbreviations: ACR = American College of Rheumatology; ADA = anti-drug antibody; AE = adverse event; CCI BILAG = British Isles Lupus Assessment Group; BP = blood pressure; C = complement; CD4+ = cluster of differentiation 4; CLASI = Cutaneous Lupus Area and Severity Index; CRP = C-reactive protein; C-SSRS = Columbia Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; CCI CCI FSH = follicle stimulating hormone; h = hour; HR = heart rate; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IL 21 = interleukin 21; IV = intravenous; m = minute; nAb = neutralizing antibody; PGA = Physician's Global Assessment; PK = pharmacokinetic; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; SAE = serious adverse event; SC = subcutaneous; CCI SLE = systemic lupus erythematosus; SLEDAI-2K = SLE Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; CCI TB = tuberculosis; TDAR = T cell dependent antigen response.

Section	Description of Changes	Rationale

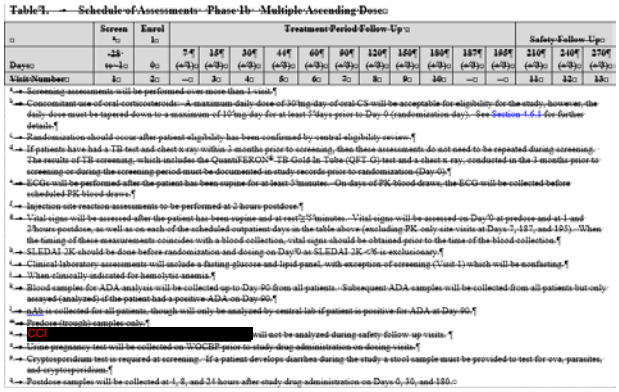


Table 1 Schedule of Assessments – Phase 1b – Multiple Ascending Dose

	Screen	Enrol	Treatment Period Follow-Up											Safety Follow-Up		
Days	-28 to -1	0	7 (±3)	15 (±3)	30 (±3)	44 (±3)	60 (±3)	90 (±3)	120 (±3)	150 (±3)	180 (±3)	187 (±3)	195 (±3)	210 (±3)	240 (±3)	270 (±3)
Visit Number	1	2	--	3	4	5	6	7	8	9	10	--	--	11	12	13

a Screening assessments will be performed over more than 1 visit.

b Concomitant use of oral corticosteroids: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). See Section 4.6.1 for further details.

c Randomization should occur after patient eligibility has been confirmed by central eligibility review.

d If patients have had a TB test and chest x-ray within 3 months prior to screening, then these assessments do not need to be repeated during screening. The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

e ECGs will be performed after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws.

f Injection site reaction assessments to be performed at 2 hours postdose.

g Vital signs will be assessed after the patient has been supine and at rest ≥5 minutes. Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours postdose, as well as on each of the scheduled outpatient days in the table above (excluding PK only site visits at Days 7, 187, and 195). When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

h SLEDAI-2K should be done before randomization and dosing on Day 0 as SLEDAI-2K-C is exploratory.

i Clinical laboratory assessments will include a fasting glucose and lipid panel, with exception of screening (Visit 1) which will be nonfasting.

j When clinically indicated for hemolytic anemia.

k Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only assayed (analyzed) if the patient had a positive ADA on Day 90.

l nAb is collected for all patients, though will only be analyzed by central lab if patient is positive for ADA at Day 90.

m Predose (trough) samples only.

n CCI will not be analyzed during safety follow-up visits.

o Urine pregnancy test will be collected on WOCBP prior to study drug administration on dosing visits.

p Cryptosporidium test is required at screening. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

q Postdose samples will be collected at 1, 8, and 24 hours after study drug administration on Days 0, 30, and 180.

Section 3.4, Schedule of Assessments, Table 1 footnote "c"

Replace:

c Concomitant use of oral corticosteroids: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0.

With:

c Concomitant use of oral corticosteroids: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, **the dose must be stable for at least 6 weeks prior to Day 0**.

Protocol clarification.

Section 3.4, Schedule of Assessments, Table 1 footnote "n"

Replace:

n Only CCI collected during safety follow-up visits.

With:

n **Antibodies and autoantibodies (CCI) will not be analyzed** during safety follow-up visits.

Correcting error in protocol.

Section 3.4, Schedule of Assessments, Table 1, Whole blood leukocyte immunophenotype row

Delete:

	Screen[m]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	-28 to -1	0	15 (±3)	30 (±3)	60 (±3)	90 (±3)	120 (±3)	150 (±3)	180 (±3)	187 (±3)	195 (±3)	210 (±3)	240 (±3)	270 (±3)
Visit Number	1	2	3	4	5	6	7	8	9	--	--	10	11	12
LABORATORY ASSESSMENTS														
~~Whole blood for leukocyte immunophenotype~~		X	X	X		X			X					

This data is no longer necessary; the MAD data collected has been sufficient.

Section 4.3, Patient Screening

Replace:

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular individual. Patient eligibility will be reviewed and confirmed by the medical monitor or designee prior to randomization. Screening assessments (see the Schedule of Assessments [Section 3.4]) for this

Protocol clarification.

Section	Description of Changes	Rationale
	study must be performed between Day -28 and Day -1. With: This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular individual. Patient eligibility will be reviewed and confirmed by the medical monitor or designee prior to randomization. Screening assessments (see the Schedule of Assessments [Table 1 and Table 4]) for this study must be performed between Day -28 and Day -1	
Section 4.4, Inclusion Criteria, criteria 5	Replace: 5. At screening, the SLE Disease Activity Index 2000 (SLEDAI-2K) must be ≥ 6, including points from at least 1 of the following clinical components: a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis i. Excluding parameters which require central laboratory results: (hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia) ii. Points from lupus headache and organic brain syndrome will also be excluded With: 5. At screening, the **total** SLEDAI-2K **score** must be ≥ **8**, including points from at least 1 of the following clinical components: a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis **Note: Points from lupus headache and organic brain syndrome will also be excluded from qualifying total and clinical SLEDAI-2K scores at screening and Day 0.**	To ensure patients with Moderate to Severe active disease are enrolled.
Section 4.4, Inclusion Criteria, criteria 7	Replace: 7. Patients must have at least 1A or 2Bs from the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer: a. BILAG A or B score in the mucocutaneous body system b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis defined as follows: i. "BILAG A:" Severe Arthritis, (BILAG item number 41), manifested by observed active synovitis in ≥ 2 joints with marked loss of functional range of movements and significant impairment of basic activities of daily living that has been present on several days cumulatively over the past 30 days, including at the time of the screening visit. See	To ensure patients with Moderate to Severe active disease are enrolled. Clarification of active joint term.

Section	Description of Changes	Rationale

APPENDIX 5 for additional detailed specifications.

- Basic ADLs are defined as the following activities which require assistance or assistive devices, (at least 1 must be present and documented in source):
  - Ambulation, toileting, grooming- including bathing and dressing; feeding oneself

ii. "BILAG B:" Moderate Arthritis, Tendonitis or Tenosynovitis, (BILAG item number 42), defined as tendonitis/tenosynovitis, or active synovitis in ≥ 1 joint, (observed or throughout history), with some loss of functional range of movements manifested by effects on instrumental ADLs such as:

- Cooking, driving, using the telephone or computer, shopping, cleaning, etc., and has been present on several days over the last 30 days, and is present at the time of the screening visit

If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in the other body systems for a total of 2 "B" BILAG body system scores

With:

7. Patients must have at least 1 **qualifying** A or 2Bs from the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer:
   a. BILAG A or B score in the mucocutaneous body system. **If a BILAG B score is due to BILAG number 6, mild skin eruption, the CLASI activity score must be ≥ 3 excluding points from mucosal ulcers and alopecia.**
   b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis defined as follows:
      i. "BILAG A:" Severe Arthritis, (BILAG item number 41), manifested by observed active synovitis **defined by BOTH swelling and tenderness** in ≥ **6** joints with marked loss of functional range of movements and significant impairment of basic activities of daily living **(ADLs)** that has been present on several days **(> 4 days).**cumulatively over the past 30 days, including at the time of the screening visit. See APPENDIX 5 for additional detailed specifications.

- Basic ADLs are defined as the following activities which require assistance or assistive devices, (at least 1 must be present and documented in source):
  - Ambulation, toileting, grooming- including bathing and dressing; feeding oneself

      ii. "BILAG B:" Moderate Arthritis, Tendonitis or Tenosynovitis, (BILAG item number 42), defined as tendonitis/tenosynovitis, or active synovitis **defined by BOTH swelling and tenderness** in ≥ **3** joint**s**, (observed or through **patient** history), with some loss of functional range

Section	Description of Changes	Rationale
	of movements manifested by effects on instrumental ADLs such as: • Cooking, driving, using the telephone or computer, shopping, cleaning, etc., and has been present on several days over the last 30 days, and is present at the time of the screening visit **Note: Hips, shoulders, back, neck, and temporomandibular joints do not count towards the total number of joints with active synovitis.** If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in **at least 1** other body system for a total of 2 "B" BILAG body system scores**.**	
Section 4.6, Concomitant Medications	Add: Any medicinal product, prescribed or OTC, including herbal and other nontraditional remedies, is considered a concomitant medication. Patients should stay on stable regimen **(not PRN)** of other concomitant medications for the treatment of SLE (eg, analgesics, **nonsteroidal anti-inflammatory drugs [**NSAIDs**]**, statins, ACE inhibitors/ARBs and other antihypertensive drugs), unless changes in these treatments are clinically indicated. **Patients should refrain from Tylenol, NSAIDs, and any pain medications including tramadol and other opiates for at least 12 hours before each visit, with the exception of the Screening Visit.** Use of any other drugs for non-SLE conditions, including over-the-counter medications and herbal preparations, should remain stable unless change or addition is clinically necessary. Discussion with the medical monitor prior to initiation of new medication is strongly recommended. Any concomitant therapies must be recorded on the eCRF. Prior and concomitant medication use will be recorded for the 30 days prior to screening until the last follow-up visit. In addition, historical treatment for SLE (including immunosuppressant, anti-malarial, corticosteroid, and/or biologic agent **including investigational agents**) will be recorded for the 48 weeks prior to screening in the eCRF.	Protocol clarification. Protocol text further clarified to include investigational agents.
Section 4.6.1, Corticosteroid	Replace: 4.6.1 Oral Corticosteroid Dose Prior to randomization, oral CSs (prednisone or prednisone equivalent), may be used in accordance with the investigator's clinical judgment and best standard of care. See APPENDIX 3 for examples of equivalents. A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day).	Added further clarity to section regarding tapering and allowed burst Removed the restrictions of max burst dose and extended protocol allowed burst window to assist sites in managing their patients SLE. Text modified to

Section	Description of Changes	Rationale
	Tapering of steroids during the course of the study will be highly encouraged and should be evaluated at the protocol permitted visits (Day 0 through Day 60 and Day 120 through Day 150). Between Day 60 and Day 120, and between Day 150 and Day 210, oral CS doses must be held constant due to the endpoint evaluations occurring at Day 120 and Day 210. • Once a patient has received the first dose of study drug (after Day 0), prednisone (or prednisone equivalent) dose is highly encouraged to continue tapering down as appropriate. The investigator should evaluate the prednisone dose at each visit and make the decision, within the protocol allowed windows. o Exception: Between Day 60 and Day 120, and between Day 150 and Day 210 (ie, within 60 days of primary and secondary endpoint assessments), oral CS doses must be held constant. After Day 0 (first dose of study drug), a maximum of 1 oral CS "burst" for increased SLE disease activity will be allowed between Day 0 and Day 60, according to the following: • The oral CS dose is allowed to increase to ≤ 40 mg/day of prednisone or equivalent, which must be tapered down to ≤ 10 mg/day within 2 weeks of initiation of the "burst" o Alternatively, a single intramuscular (IM) dose of methylprednisolone (40 mg or equivalent) is permitted o No increase of oral CS above baseline is permitted beyond Day 60 Treatment with inhalational CS therapy (eg, for asthma), or by any other route, but systemic administration, is allowed. Treatment with intra-articular or intravenous CS is prohibited during the course of the study. With: 4.6.1 Corticosteroid Prior to randomization, oral CSs (prednisone or prednisone equivalent), may be used in accordance with the investigator's clinical judgment and best standard of care. See APPENDIX 3 for examples of equivalents. A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study. **For patients whose only SLE treatment is steroids, their stable steroid dose must be at least 10 mg/day and no more than 30 mg/day for a minimum of 6 weeks at time of randomization on Day 0.** **Topical steroids may be used, but the dose must be stable for at**	ensure patients with Moderate to Severe active disease are enrolled. Further clarification of protocol intention.

Section	Description of Changes	Rationale
	least 6 weeks prior to Day 0, and be maintained at a constant dose throughout the study duration until the rashes resolve. PRN topical steroids are not permitted. **Once the patient has received the first dose of study drug (Day 0),** tapering of **oral** steroids will be highly encouraged and should be **continually evaluated during the protocol-allowed tapering windows (Day 0 through Day 150) with the target of achieving a CS daily dose of < 7.5 mg and < Day 0 dose between Day 150 and Day 210**. Between Day 150 and Day 210 **(ie, within 60 days of primary endpoint assessments)**, oral CS doses must be held constant. ***CS Burst for SLE-related Indications*** After Day 0 (first dose of study drug), a maximum of 1 oral CS "burst" **equivalent to ≤ 40 mg/day prednisone** for increased SLE disease activity will be allowed between Day 0 and Day **120, which must be tapered down to the baseline (Day 0) CS dose or lower within 14 days of initiation of the "burst." Any "burst" continuing after Day 120 or occurring after Day 120 is considered a protocol deviation.** o Alternatively, a single intramuscular (IM) dose of methylprednisolone (<40 mg) is permitted **during this period**. ***CS Burst for Non-SLE-related Indications*** **A single treatment of oral prednisone equivalent of ≤ 40 mg/day for 14 days is permitted for a non-SLE indication, though it must be completed prior to Day 120. No long acting steroid injections are permitted.** **Note: Treatment with inhaled CS are allowed for the treatment of non-SLE-related indications only (eg, for asthma).** **Any other increase from baseline of CS dose or systemic use of CS of any kind (including intra-articular and intravenous administration) are not permitted from Day 0 through Day 210 and will result in the patient being considered a treatment failure. There is no restriction of CS usage after Day 210.**	
Section 4.6.2, Other Prohibited and/or Restricted Treatments, Paragraph 1	Replace: Prohibited and/or restricted medications taken prior to study drug administration and during the study are described below, and washout requirements are provided in APPENDIX 4. Medications taken within 30 days prior to screening must be recorded on the eCRF.	Protocol clarification.

Section	Description of Changes	Rationale
	With: Prohibited and/or restricted medications taken prior to study drug administration and during the study are described below, and washout requirements are provided in APPENDIX 4. **All m**edications taken within 30 days prior to screening must be recorded on the eCRF.	
Section 4.6.2, Other Prohibited and/or Restricted Treatments, Item 2	Delete: 2. Patients who have received treatment with anti-CD20 monoclonal antibodies within 24 weeks of screening~~; recovery of B cells (CD19+) must be documented (record absolute number of CD19+ B cells)~~	Protocol text removed as it was no longer necessary.
Section 4.7.2, Contraception, Paragraph 4	Replace: At a minimum, patients must agree to the use of 1 method of highly effective contraception from the following: With: **P**atients must agree to **either complete abstinence, defined as a complete avoidance of heterosexual activity, or** the use of **2** method**s** of highly effective contraception from the following:	To ensure patients have appropriate contraception during the study.
Section 4.7.2, Contraception, Paragraph 4, Bullet 4 and 5	Replace: • Vasectomy • Complete abstinence, defined as complete avoidance of heterosexual intercourse, is an acceptable form of contraception. Women who are abstinent while participating in the study must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the patient chooses to forego complete abstinence. With: • Vasectomy **Note:** Women who are abstinent while participating in the study must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the patient chooses to forego complete abstinence.	Protocol clarification.
Section 5.1, Screening, Paragraph 5	Replace: Screening procedures are listed in the Schedule of Assessments (Section 3.4), and details are provided in Section 6. With: Screening procedures are listed in the Schedule of Assessments	Protocol clarification.

Section	Description of Changes	Rationale
	(Table 1 and Table 4), and details are provided in Section 6.	
Section 5.2, Enrollment/ Randomization and Day 0 Treatment, Paragraph 1	Add: Randomization should occur after patient eligibility for enrollment has been confirmed by the central eligibility review. **The central eligibility review team has the final decision on patient eligibility and can decide the patient is not eligible for the study based on their review of the eligibility packet.**	To provide further clarification that the central eligibility review team can deem a patient in-eligible for randomization even if all entrance criteria are met.
Section 5.2, Enrollment/ Randomization and Day 0 Treatment, bullet 3, sub-bullet 3	Add: • Laboratory evaluations (fasting): o CD4+ count, total IgG and IgM levels, plasma CCI, plasma CCI and CCI, whole blood for leukocyte immunophenotype **(leukocyte immunophenotype for MAD patients only)**	No longer necessary in POC portion of the study. MAD data collected has been sufficient.
Section 5.2, Enrollment/ Randomization and Day 0 Treatment, bullet 3, sub-bullet 9	Replace: • Laboratory evaluations (non-fasting): o See Table 1 and Table 2 for details of PK sampling in the MAD and POC portions With: • Laboratory evaluations (non-fasting) : o See **Table 4** and **Table 1** for details of PK sampling in the MAD and POC portions	Protocol clarification.
Section 5.2, Enrollment/ Randomization and Day 0 Treatment, Paragraph 4	Replace: Procedures on Day 0 are listed in the Schedule of Assessments (Section 3.4), and details are provided in Section 6. With: Procedures on Day 0 are listed in the Schedule of Assessments (**Table 1** and **Table 4**), and details are provided in Section 6.	Protocol clarification.
Section 5.3, Treatment Period/Follow-Up Visits, Pararaph 1 and bullet 17	Replace: The following procedures will be performed as indicated in the Schedule of Assessments (Table 1 and Table 2). See Schedule of Assessment tables for allowable windows for each visit. • See Table 1 and Table 2 for details of PK sampling in the MAD	Protocol clarification.

Section	Description of Changes	Rationale
	and POC studies, respectively With: The following procedures will be performed as indicated in the Schedule of Assessments (**Table 1** and **Table 4**). See Schedule of Assessment tables for allowable windows for each visit. • See **Table 4** and **Table 1** for details of PK sampling in the MAD and POC studies, respectively	
Section 5.3, Treatment Period/Follow-Up Visits, bullet 20	Replace: • Plasma CCI & CCI, ADA, and whole blood for leukocyte immunophenotype With: • Plasma CCI **and** CCI, ADA, and whole blood for leukocyte immunophenotype **(leukocyte immunophenotype for MAD patients only)**	No longer necessary for POC portion of study. MAD data collected has been sufficient.
Section 5.4, Safety Follow-Up Visits, Paragraph 1 and bullet 18	Replace: Safety follow-up visits will take place at Days 210, 240, and 270. These visits will include the following assessments as indicated in the Schedule of Assessments (Table 1 and Table 2): • See Table 1 and Table 2 for details of PK sampling in the MAD and POC portions, respectively Replace: Safety follow-up visits will take place at Days 210, 240, and 270. These visits will include the following assessments as indicated in the Schedule of Assessments (**Table 1** and **Table 4**): • See **Table 4** and **Table 1** for details of PK sampling in the MAD and POC portions, respectively	Protocol clarification.
Section 6.2.1, Laboratory Assessments, Paragraph 1	Replace: Laboratory tests will be performed at times defined in the Schedule of Assessments (Section 3.4). Patient eligibility will be determined based on these tests at screening. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns. With: Laboratory tests will be performed at times defined in the Schedule of Assessments (**Table 1 and Table 4**). Patient eligibility will be determined based on these tests at screening. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived	Protocol clarification.

Section	Description of Changes	Rationale
	safety concerns.	
Section 6.2.1, Laboratory Assessments, Table 2, Immunogenicity, PD and other Biomarker Tests column	Add: Immunogenicity, PD, and other Biomarker Tests ADA nAb[g] pSTAT3 (predose [trough] samples only in Phase 1b) Total IgG & IgM Plasma CCI Plasma CCI & CCI Whole blood for leukocyte immunophenotype **(for MAD patients only)** CCI CCI CCI CRP Direct Coomb's test[h]	No longer necessary for POC patients. MAD data collected has been sufficient.
Section 6.2.1.1, Pregnancy testing	Replace: For WOCBP, a serum pregnancy test will be performed at screening. Following a negative serum pregnancy result at screening, appropriate contraception must be commenced or continued and a further negative urine pregnancy test results will then be required at the baseline visit before the patient may receive the investigational product. Urine pregnancy tests will also be routinely repeated at study drug administration visits prior to study drug administration, at the last follow up visit day (Day 270) and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive pregnancy test or confirmed pregnancy, the patient will be discontinued from study drug, an EOT visit should be performed (Day 180), and a last follow-up visit 90 days after last dose should be scheduled (Day 270). Safety follow-up visit procedures (see Section 5.4) are specified in the Schedule of Assessments (see Section 3.4). With: For WOCBP, a serum pregnancy test will be performed at screening. Following a negative serum pregnancy result at screening, appropriate contraception must be commenced or continued and a further negative urine pregnancy test results will then be required at the baseline visit before the patient may receive the investigational product. Urine pregnancy tests will also be routinely repeated at study drug administration visits prior to study drug administration, at the last follow up visit day (Day 270) and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive pregnancy test or confirmed pregnancy, the patient will be discontinued from study drug, an EOT visit should be performed (Day 180), and a last follow-up visit 90 days after last dose should be scheduled (Day 270). Safety follow-up visit procedures (see	Protocol clarification.

Section	Description of Changes	Rationale
	Section 5.4) are specified in the Schedule of Assessments (see **Table 1 and Table 4**).	
Section 6.2.2.4, Causality of Adverse Events, Paragraph 1	Replace: The principal investigator will assess the causal relationship between BOS161721 or placebo and the AE. One of the following categories (**Table 4**) should be selected based on medical judgment, considering the definitions below and all contributing factors. With: The principal investigator will assess the causal relationship between BOS161721 or placebo and the AE. One of the following categories (**Table 3**) should be selected based on medical judgment, considering the definitions below and all contributing factors.	Protocol clarification.
Section 6.2.3, Vital Signs	Replace: Vital signs (blood pressure, heart rate, and body temperature) will be assessed as specified in the Schedule of Assessments (Section 3.4). Vital signs will be assessed on Day 0 at predose and at Day 0, 1 and 2 hours postdose, as well as on each of the scheduled visit days during the study (excluding PK-only site visits). Supine BP and heart rate recordings will be made after the patient has been recumbent and at rest ≥ 5 minutes. When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection. With: Vital signs (blood pressure, heart rate, and body temperature) will be assessed as specified in the Schedule of Assessments (**Table 1 and Table 4**). Vital signs will be assessed on Day 0 at predose and at Day 0, 1 and 2 hours postdose, as well as on each of the scheduled visit days during the study (excluding PK-only site visits). Supine BP and heart rate recordings will be made after the patient has been recumbent and at rest ≥ 5 minutes. When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.	Protocol clarification
Section 6.2.4, 12-Lead Electrocardiogram, Paragraph 1	Replace: ECG will be assessed as specified in the Schedule of Assessments (Section 3.4). ECG recording will initiate after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws, though timing will be such that PK draws are collected on their scheduled times where possible. With: ECG will be assessed as specified in the Schedule of Assessments	Protocol clarification.

Section	Description of Changes	Rationale
	(**Table 1 and Table 4**). ECG recording will initiate after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws, though timing will be such that PK draws are collected on their scheduled times where possible.	
Section 6.2.5, Physical Examination, Paragraph 2	Replace: The targeted (limited) physical examination will be completed at all other visits as indicated in the Schedule of Assessments (Section 3.4). It includes evaluation of patient complaints and SLE disease-related issues, and will exclude the genitourinary system. With: The targeted (limited) physical examination will be completed at all other visits as indicated in the Schedule of Assessments (**Table 1 and Table 4**). It includes evaluation of patient complaints and SLE disease-related issues, and will exclude the genitourinary system.	Protocol clarification.
Section 6.2.6, C-SSRS, Paragraph 2	Replace: The C-SSRS evaluation will be performed as specified in the Schedule of Assessments (Section 3.4). Patients with recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4, or 5 is exclusionary at screening will be excluded from the study. Patients with recent or active suicidal ideation or behavior at subsequent study visits will have responses to the C-SSRS reviewed in detail to assess patient risk, and appropriate consultative mental health services will be provided. With: The C-SSRS evaluation will be performed as specified in the Schedule of Assessments (**Table 1 and Table 4**). Patients with recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4, or 5 is exclusionary at screening will be excluded from the study. Patients with recent or active suicidal ideation or behavior at subsequent study visits will have responses to the C-SSRS reviewed in detail to assess patient risk, and appropriate consultative mental health services will be provided.	Protocol clarification.
Section 6.2.7, Injection Site Reactions	Replace: Patients will be monitored for local injection site reactions as specified in the Schedule of Assessments (Section 3.4). Local injection site reactions will be assessed at 2 hours postdose at baseline, and predose for each injection after baseline. Injection site reactions should be managed according to the standard of care. Injection site reactions, Grades 2 to 5, are to be reported as AEs of special interest (see Section 6.2.2.7.3).	Protocol clarification.

Section	Description of Changes	Rationale
	With: Patients will be monitored for local injection site reactions as specified in the Schedule of Assessments (**Table 1 and Table 4**). Local injection site reactions will be assessed at 2 hours postdose at baseline, and predose for each injection after baseline. Injection site reactions should be managed according to the standard of care. Injection site reactions, Grades 2 to 5, are to be reported as AEs of special interest (see Section 6.2.2.7.3).	
Section 6.2.8, Immunogenicity, Paragraph 1	Replace: The serum samples to measure the presence of ADA will be collected as specified in the Schedule of Assessments (Section 3.4). Blood samples (4 mL) to provide approximately 1.5 mL of plasma for anti BOS161721 antibody analysis will be collected into appropriately labeled tubes containing K2EDTA. The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods. Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only analyzed by a central lab if the patient had a positive ADA on Day 90. With: The serum samples to measure the presence of ADA will be collected as specified in the Schedule of Assessments (**Table 1 and Table 4**). Blood samples (4 mL) to provide approximately 1.5 mL of plasma for anti BOS161721 antibody analysis will be collected into appropriately labeled tubes containing K2EDTA. The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods. Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only analyzed by a central lab if the patient had a positive ADA on Day 90.	Protocol clarification.
Section 6.3, Efficacy Assessments	Replace: All efficacy assessments will be performed at times defined in the Schedule of Assessments (Section 3.4). With: All efficacy assessments will be performed at times defined in the Schedule of Assessments (**Table 1 and Table 4**).	Protocol clarification.
Section 6.4.2, PROs, Paragraph 1	Replace: Patients should be encouraged to complete the PROs at the clinic at the beginning of the study visit prior to any clinical assessments. A member of the staff should be available if a patient requires further instruction and to review the PRO questionnaires for completeness prior to leaving the clinic. The PROs include the CCI and the CCI	Protocol clarification.

Section	Description of Changes	Rationale
	CCI and will be assessed as specified in the Schedule of Assessments (Section 3.4). With: Patients should be encouraged to complete the PROs at the clinic at the beginning of the study visit prior to any clinical assessments. A member of the staff should be available if a patient requires further instruction and to review the PRO questionnaires for completeness prior to leaving the clinic. The PROs include the CCI and the CCI and will be assessed as specified in the Schedule of Assessments (**Table 1 and Table 4**).	
Section 6.5, Pharmacokinetic Assessments, Paragraph 1	Replace: During the MAD Phase 1b (all sites) and POC Phase 2 (select sites only) parts of the study, blood samples for PK analysis of BOS161721 or placebo concentration will be collected according to Table 1 and Table 2. With: During the MAD Phase 1b (all sites) and POC Phase 2 (select sites only) parts of the study, blood samples for PK analysis of BOS161721 or placebo concentration will be collected according to **Table 4** and **Table 1**.	Protocol clarification.
Section 6.6, Pharmacodynamic Assessments, Paragraph 1	Replace: Blood samples for PD parameters (plasma) will be collected at times indicated in the Schedule of Assessments (Section 3.4) for each of the following parameters: With: Blood samples for PD parameters (plasma) will be collected at times indicated in the Schedule of Assessments (**Table 1 and Table 4**) for each of the following parameters:	Protocol clarification.
Section 6.6, Pharmacodynamic Assessments, Bullet 5	Add: • Whole blood for leukocyte immunophenotype **(for MAD patients only)**	No longer necessary for POC patients. MAD data collected has been sufficient.
Section 7.4, Accountability, Paragraph 1	Replace: The Principal Investigator or designee is responsible for maintaining accurate accountability records of BOS161721 or placebo throughout the clinical study. The drug accountability log includes information such as, randomization number, amount dispensed and amount returned to the pharmacy (if any). Products returned to the pharmacy will be stored under the same conditions as products not yet dispensed.	Clarification regarding handling of returned product.

Section	Description of Changes	Rationale
	The returned products should be marked as 'returned' and kept separate from the products not yet dispensed. With: The Principal Investigator or designee is responsible for maintaining accurate accountability records of BOS161721 or placebo throughout the clinical study. The drug accountability log includes information such as, randomization number, amount dispensed and amount returned to the pharmacy (if any). **Used investigational p**roduct returned to the pharmacy **may be maintained in an ambient condition. Unused product should follow the instructions in the Pharmacy Manual**. The **used product that is** returned should be marked as 'returned' and kept separate from the products not yet dispensed.	
Section 8.2.1, Analysis Populations, Paragraph 1	Replace: The primary efficacy analysis will be based on the FAS, defined as all patients who receive at least 1 dose of study treatment and at have least 1 evaluable post-baseline efficacy evaluation. FAS analyses will be conducted on the basis of the randomized treatment. With: The primary efficacy analysis will be based on the FAS, defined as all patients who receive at least 1 dose of study treatment and have **at** least 1 evaluable post-baseline efficacy evaluation. FAS analyses will be conducted on the basis of the randomized treatment.	Correction of typo.
Section 8.2.3, Primary Efficacy Endpoint(s), Paragraph 2	Add: Patients that received prohibited medications or unallowable CS usage as described in Section 4.6 will be considered "medication failures" and will be treated as **statistical** non-responders **at the time points on or following the first date of prohibited medication or unallowable CS usage** for the primary efficacy analysis. The determination of medication failures will be reviewed using blinded data and finalized prior to unblinding.	Text added to address usage relative to analysis time points (ie patients are deemed non-responders after usage but may still be responders prior to usage of prohibitive meds or CS).
Appendix 5	Replace: CCI [redacted]	Clarification of active joint term.

Section	Description of Changes	Rationale
	i. CCI [redacted]	

Section	Description of Changes	Rationale
	CCI [redacted]	
Appendix 7	Add:	Added for opioid dosing in SLE patients.

APPENDIX 7 OPIOID ORAL MORPHINE MILLIGRAM EQUIVALENTS OF COMMONLY USED OPIOIDS

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

Note that this list is not comprehensive. If an opioid is being used which is not in this list, please see the appropriate conversion factor below.

Section	Description of Changes	Rationale

Opioid Oral Morphine Equivalent Conversion Factors[a,b]

Type of Opioid (strength in units)	MME Conversion Factor
Buprenorphine film/table[c] (mg)	30
Buprenorphine patch[d] (mcg/hr)	12.6
Buprenorphine film (mcg)	0.03
Butorphanol (mg)	7
Codeine (mg)	0.15
Dihydrocodeine (mg)	0.25
Fentanyl buccal or SL tablets, or lozenge/troche[e] (mcg)	0.13
Fentanyl film or oral spray[f] (mcg)	0.18
Fentanyl nasal spray[g] (mcg)	0.16
Fentanyl patch[h] (mcg)	7.2
Hydrocodone (mg)	1
Hydromorphone (mg)	4
Levorphanol tartrate (mg)	11
Meperidine hydrochloride (mg)	0.1
Methadone[i] (mg)	3
> 0, ≤ 20	4
> 20, ≤ 40	8
> 40, ≤ 60	10
> 60	12
Morphine (mg)	1
Opium (mg)	1
Oxycodone (mg)	1.5
Oxymorphone (mg)	3
Pentazocine (mg)	0.37
Tapentadol[j] (mg)	0.4
Tramadol (mg)	0.1

CDC = Centers for Disease Control; CMS = Centers for Medicare and Medicaid Services; FDA = Food and Drug Administration; MAT = Medication Assisted Treatment; MME = morphine milligram equivalent; OMS = Overutilization Monitoring System.

Section	Description of Changes	Rationale

a. The MME conversion factor is intended only for analytic purposes where prescription data is used to calculate daily MME. It is to be used in the formula: Strength per Unit × (Number of Units/Days Supply) × MME conversion factor = MME/Day. This value does not constitute clinical guidance or recommendations for converting patients from one form of opioid analgesic to another. Please consult the manufacturer's full prescribing information for such guidance. Use of this file for the purposes of any clinical decision-making warrants caution.
b. National Center for Injury Prevention and Control. CDC compilation of benzodiazepines, muscle relaxants, stimulants, zolpidem, and opioid analgesics with oral morphine milligram equivalent conversion factors, 2016 version. Atlanta, GA: Centers for Disease Control and Prevention; 2016. Available at https://www.cdc.gov/drugoverdose/media/. For more information, send an email to Mbohm@cdc.gov.
c. Buprenorphine formulations with a FDA approved indication for MAT are excluded from Medicare's Overutilization Monitoring System's opioid overutilization reporting.
d. The MME conversion factor for buprenorphine patches is based on the assumption that 1 milligram of parenteral buprenorphine is equivalent to 75 milligrams of oral morphine and that one patch delivers the dispensed micrograms per hour over a 24 hour day. Example: 5 µg/hr buprenorphine patch × 24 hrs = 120 ug/day buprenorphine = 0.12 mg/day = 9 mg/day oral MME. In other words, the conversion factor not accounting for days of use would be 9/5 or 1.8.
However, since the buprenorphine patch remains in place for 7 days, we have multiplied the conversion factor by 7 (1.8 × 7 = 12.6). In this example, MME/day for 4 5 µg/hr buprenorphine patches dispensed for use over 28 days would work out as follows: Example: 5 µg/hr buprenorphine patch × (4 patches/28 days) × 12.6 = 9 MME/day. Please note that because this allowance has been made based on the typical dosage of 1 buprenorphine patch per 7 days, you should first change all Days Supply in your prescription data to follow this standard, i.e., Days Supply for buprenorphine patches = number of patches x 7.
e. The MME conversion factor for fentanyl buccal tablets, sublingual tablets, and lozenges/troche is 0.13. This conversion factor should be multiplied by the number of micrograms in a given tablet or lozenge/troche.
f. The MME conversion factor for fentanyl film and oral spray is 0.18. This reflects a 40% greater bioavailability for films compared to lozenges/tablets and 38% greater bioavailability for oral sprays compared to lozenges/tablets.
g. The MME conversion factor for fentanyl nasal spray is 0.16, which reflects a 20% greater bioavailability for sprays compared to lozenges/tablets.
h. The MME conversion factor for fentanyl patches is based on the assumption that 1 milligram of parenteral fentanyl is equivalent to 100 milligrams of oral morphine and that 1 patch delivers the dispensed micrograms per hour over a 24 hour day. Example: 25 µg/hr fentanyl patch × 24 hrs = 600 ug/day fentanyl = 60 mg/day oral morphine milligram equivalent.
In other words, the conversion factor not accounting for days of use would be 60/25 or 2.4.
However, since the fentanyl patch remains in place for 3 days, we have multiplied the conversion factor by 3 (2.4 × 3 = 7.2). In this example, MME/day for 10 25 µg/hr fentanyl patches dispensed for use over 30 days would work out as follows:
Example: 25 µg/hr fentanyl patch × (10 patches/30 days) × 7.2 = 60 MME/day. Please note that because this allowance has been made based on the typical dosage of 1 fentanyl patch per 3 days, you should first change all Days Supply in your prescription data to follow this standard, i.e., Days Supply for fentanyl patches = number of patches × 3.
i. The CDC MME conversion factor to calculate morphine milligram equivalents is 3. CMS uses this conversion factor when analyzing Medicare population opioid use. CMS uses the graduated methadone MME conversion factors to calculate MME within the OMS for identifying and reporting potential opioid overutilizers. https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf.
j. Tapentadol is a mu receptor agonist and norepinephrine reuptake inhibitor. Oral MMEs are based on degree of mu-receptor agonist activity, but it is unknown if this drug is associated with overdose in the same dose-dependent manner as observed with medications that are solely mu receptor agonists.

Appendix 8, Table 4 — Add:

Since Phase 1b MAD has completed, the Schedule of Assessments for Phase 1b MAD was moved to the Appendix.

Table 4 → Schedule of Assessments – Phase 1b – Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period/Follow-Up												Safety Follow-Up		
Days	-28- to -1	0	7 (±3)	15 (±3)	30 (±3)	44 (±3)	60 (±3)	90 (±3)	120 (±3)	150 (±3)	180 (±3)	187 (±3)	195 (±3)	210 (±3)	240 (±3)	270 (±3)
Visit Number	1	2	–0	3	4	5	6	7	8	9	10	–0	–0	11	12	13
GENERAL ASSESSMENTS																
Informed consent	X															
Inclusion/Exclusion criteria	X															
Medical history	X															
Demographics	X															
SLICC Criteria for SLE[b]	X															
Concomitant medication[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[b]		X														
BOS161721 or placebo dosing[d]		X			X		X	X	X	X	X					
SAFETY ASSESSMENTS																
Full physical exam	X	X														
Chest x-ray[e]	X															
C-SSRS	X	X					X			X						
AEs and SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[b]	X	X			X			X								X
Injection site reaction assessment[c]		X[b]	X		X		X	X	X	X	X	X	X	X	X	X
Targeted physical examination				X	X	X	X	X	X	X	X			X	X	X
Vital signs (BP, HR, and temperature)[f]	X	X		X	X	X	X	X	X	X	X			X	X	X
EFFICACY ASSESSMENTS																
BILAG-2004 Index	X	X			X		X	X	X	X	X			X	X	X
SLEDAI-2K[b]	X	X			X		X	X	X	X	X			X	X	X

Section	Description of Changes	Rationale

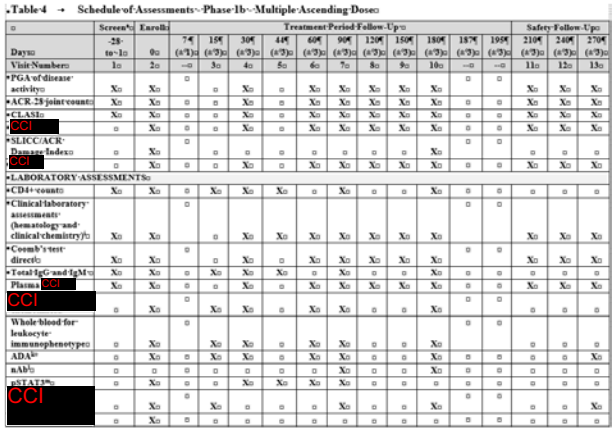


Table 4 → Schedule of Assessments – Phase 1b – Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Day	-28 to -1	0	7 (±1)	15 (±3)	30 (±3)	44 (±3)	60 (±3)	90 (±3)	120 (±3)	150 (±3)	180 (±3)	187 (±3)	195 (±3)	210 (±3)	240 (±3)	270 (±3)
Visit Number	1	2	–3	3	4	5	6	7	8	9	10	–3	–3	11	12	13
PGA of disease activity	X	X			X		X	X	X	X	X			X	X	X
ACR 28 joint count	X	X			X		X	X	X	X	X			X	X	X
CLASI	X	X			X		X	X	X	X	X			X	X	X
CCI		X			X		X	X	X	X	X			X	X	X
SLICC/ACR Damage Index		X									X					
CCI		X			X		X	X	X	X	X			X	X	X
LABORATORY ASSESSMENTS																
CD4+ count	X	X		X	X	X		X			X					
Clinical laboratory assessments (hematology and clinical chemistry)[f]	X	X			X	X	X	X	X	X	X			X	X	X
Coomb's test: direct	X	X			X		X	X	X	X	X			X	X	X
Total IgG and IgM	X	X		X	X	X		X			X					
Plasma CCI	X	X			X		X	X	X	X	X			X	X	X
CCI		X		X	X		X	X			X					
Whole blood for leukocyte immunophenotype		X		X	X		X	X			X					
ADA[k]		X		X	X		X	X			X					X
nAb[l]								X			X					
pSTAT3[m]		X			X	X	X	X								
CCI		X		X				X			X					X
		X														

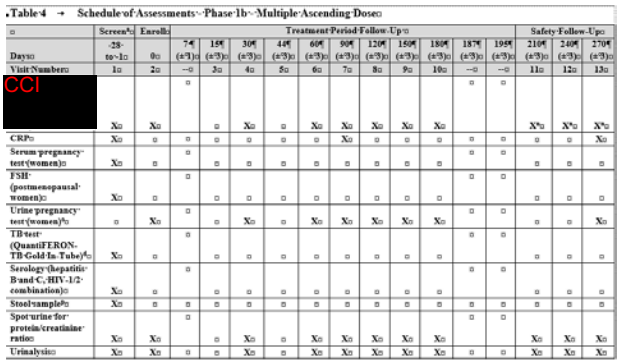


Table 4 → Schedule of Assessments – Phase 1b – Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Day	-28 to -1	0	7 (±1)	15 (±3)	30 (±3)	44 (±3)	60 (±3)	90 (±3)	120 (±3)	150 (±3)	180 (±3)	187 (±3)	195 (±3)	210 (±3)	240 (±3)	270 (±3)
Visit Number	1	2	–3	3	4	5	6	7	8	9	10	–3	–3	11	12	13
CCI	X	X			X		X	X	X	X	X			X[n]	X[n]	X[n]
CRP	X				X		X	X	X	X	X					X
Serum pregnancy test (women)	X															
FSH (postmenopausal women)	X															
Urine pregnancy test (women)[o]		X			X		X	X	X	X	X					X
TB test (QuantiFERON-TB Gold In-Tube)[d]	X															
Serology (hepatitis B and C, HIV-1/2 combination)	X															
Stool sample[p]	X															
Spot urine for protein/creatinine ratio	X	X			X		X	X	X	X	X			X	X	X
Urinalysis	X	X			X		X	X	X	X	X			X	X	X

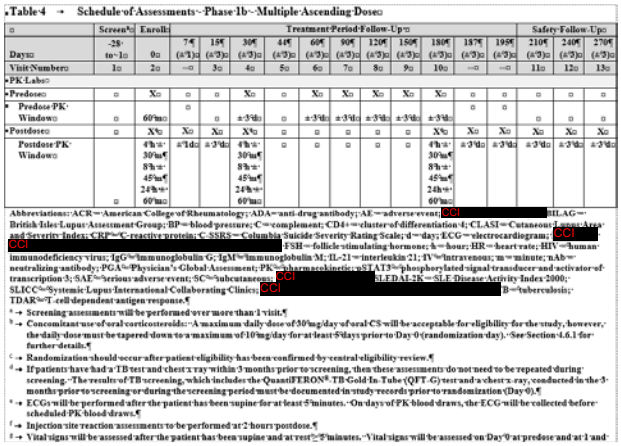


Table 4 → Schedule of Assessments – Phase 1b – Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Day	-28 to -1	0	7 (±1)	15 (±3)	30 (±3)	44 (±3)	60 (±3)	90 (±3)	120 (±3)	150 (±3)	180 (±3)	187 (±3)	195 (±3)	210 (±3)	240 (±3)	270 (±3)
Visit Number	1	2	–3	3	4	5	6	7	8	9	10	–3	–3	11	12	13
PK Labs																
Predose		X			X		X	X	X	X	X					
Predose PK Window		60 min			±3 h		±3 h	±3 h	±3 h	±3 h	±3 h					
Postdose		X[q]	X	X	X[q]						X[q]	X	X	X	X	X
Postdose PK Window		4 h ± 30 min; 8 h ± 45 min; 24 h ± 60 min	±1 d	±3 d	4 h ± 30 min; 8 h ± 45 min; 24 h ± 60 min						4 h ± 30 min; 8 h ± 45 min; 24 h ± 60 min	±3 d	±3 d	±3 d	±3 d	±3 d

Abbreviations: ACR = American College of Rheumatology; ADA = anti-drug antibody; AE = adverse event; CCI; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; C = complement; CD4+ = cluster of differentiation 4; CLASI = Cutaneous Lupus Area and Severity Index; CRP = C-reactive protein; C-SSRS = Columbia Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; CCI; FSH = follicle stimulating hormone; h = hour; HR = heart rate; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IL-21 = interleukin 21; IV = intravenous; m = minute; nAb = neutralizing antibody; PGA = Physician's Global Assessment; PK = pharmacokinetic; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; SAE = serious adverse event; SC = subcutaneous; CCI; SLEDAI-2K = SLE Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; CCI; TB = tuberculosis; TDAR = T cell-dependent antigen response.

[a] → Screening assessments will be performed over more than 1 visit.

[b] → Concomitant use of oral corticosteroids: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). See Section 4.6.1 for further details.

[c] → Randomization should occur after patient eligibility has been confirmed by central eligibility review.

[d] → If patients have had a TB test and chest x-ray within 3 months prior to screening, then these assessments do not need to be repeated during screening. The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

[e] → ECGs will be performed after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws.

[f] → Injection site reaction assessments to be performed at 2 hours postdose.

[g] → Vital signs will be assessed after the patient has been supine and at rest ≥ 5 minutes. Vital signs will be assessed on Day 0 at predose and at 1 and

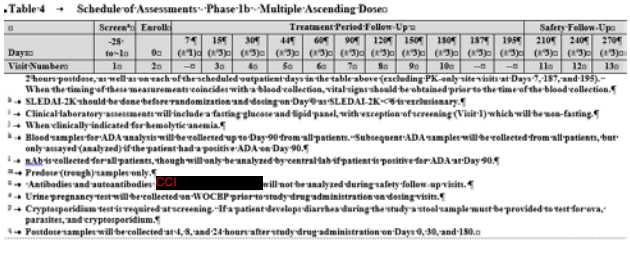


Table 4 → Schedule of Assessments – Phase 1b – Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Day	-28 to -1	0	7 (±1)	15 (±3)	30 (±3)	44 (±3)	60 (±3)	90 (±3)	120 (±3)	150 (±3)	180 (±3)	187 (±3)	195 (±3)	210 (±3)	240 (±3)	270 (±3)
Visit Number	1	2	–3	3	4	5	6	7	8	9	10	–3	–3	11	12	13

2 hours postdose, as well as on each of the scheduled outpatient days in the table above (excluding PK-only site visits at Days -7, 187, and 195).

When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

[h] → SLEDAI-2K should be done before randomization and dosing on Day 0 as SLEDAI-2K < 6 is exclusionary.

[i] → Clinical laboratory assessments will include a fasting glucose and lipid panel, with exception of screening (Visit 1) which will be non-fasting.

[j] → When clinically indicated for hemolytic anemia.

[k] → Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients, but only assayed (analyzed) if the patient had a positive ADA on Day 90.

[l] → nAb is collected for all patients, though will only be analyzed by central lab if patient is positive for ADA at Day 90.

[m] → Predose (trough) samples only.

[n] → Antibodies and autoantibodies CCI will not be analyzed during safety follow-up visits.

[o] → Urine pregnancy test will be collected on WOCBP prior to study drug administration on dosing visits.

[p] → Cryptosporidium test is required at screening. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

[q] → Postdose samples will be collected at 4, 8, and 24 hours after study drug administration on Days 0, 30, and 180.

A RANDOMIZED DOUBLE-BLIND PHASE 1b/2 COMBINED STAGGERED MULTIPLE DOSE ESCALATION STUDY OF BOS161721 IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS ON A BACKGROUND OF LIMITED STANDARD OF CARE

SPONSOR	Boston Pharmaceuticals, Inc. 55 Cambridge Parkway, Suite 400 Cambridge, MA 02142 United States of America (USA)
INVESTIGATIONAL COMPOUND:	BOS161721
PROTOCOL NUMBER:	BOS161721-02
PHASE	Phase 1b/2
INVESTIGATIONAL NEW DRUG (IND) NUMBER:	131796
ORIGINAL PROTOCOL DATE:	06 October 2017
VERSION NUMBER:	V5.0 (Amendment 4)
VERSION DATE:	23 January 2019

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care **Study Number: BOS161721-02**	
Version	**Date**
Original Protocol	06 October 2017
Protocol Version 2.0 (Amendment 1)	14 November 2017
Protocol Version 3.0 (Amendment 2)	21 March 2018
Protocol Version 4.0 (Amendment 3)	27 July 2018
Protocol Version 5.0 (Amendment 4)	23 January 2019

This study protocol was subject to critical review and has been approved by sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (APPENDIX 2), and principles of Good Clinical Practices (GCP) as described in 21 Code of Federal Regulations (CFR) parts 50, 54, 56 and 312 and according to applicable local requirements.

The investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

I agree with these statements and indicate my approval by signature for this protocol:

Name and Title	**Signature and Date**
PPD , MD, PhD Chief Medical Officer Boston Pharmaceuticals	PPD
PPD MD, FACR Vice President, Clinical Development Boston Pharmaceuticals	PPD
PPD Clinical Operations Lead Boston Pharmaceuticals	PPD
PPD MD, PhD Vice President, Clinical Development and Safety Officer Boston Pharmaceuticals	PPD

BOS161721-02

A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to BOS161721 are the confidential and proprietary information of Boston Pharmaceuticals, Inc., and except as may be required by federal, state, or local laws or regulation, may not be disclosed to others without prior written permission of Boston Pharmaceuticals, Inc.

I have read the protocol (Version 5.0, dated 23 January 2019), including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Council for Harmonisation (ICH) guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Boston Pharmaceuticals, Inc., or specified designees. I will discuss the material with them to ensure that they are fully informed about BOS161721 and the study.

_____ _____

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

PROTOCOL SUMMARY

Title:	A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care
Indication	Adults with moderately to severely active SLE
Background and Rationale	SLE is a chronic systemic autoimmune disease with considerable heterogeneity in clinical manifestations and disease course. There is evidence that B- and T-cells are critical to the development of the disease, and that T-cell-derived cytokines such as interleukin-21 (IL-21) are involved in the SLE-associated inflammatory pathological response. BOS161721 is a humanized immunoglobulin G1 (IgG1) triple mutation monoclonal antibody (mAb) intended to have an extended terminal elimination half-life ($t_{½}$) that selectively binds to and neutralizes IL-21, which acts on multiple cell types that drive inflammation and autoimmunity. *In vivo*, BOS161721 inhibits T-cell dependent antigen responses of B-cells and is being developed as a potential treatment for adults with moderately to severely active SLE. Nonclinical studies have evaluated the toxicity, pharmacodynamics (PD), toxicokinetics (TK), pharmacokinetics (PK), and immunogenicity of BOS161721 administered intravenously (IV) and subcutaneously (SC). The no observed adverse effect level (NOAEL) in Cynomolgus monkeys was determined to be 100 mg/kg (SC and IV), the highest dose tested. There were no injection site reactions in animals dosed subcutaneously. In a Phase 1 single ascending dose (SAD) study, BOS161721 was administered IV and SC to healthy male and female adult subjects. This double-blind, placebo-controlled study evaluated 8 ascending dose levels (1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg) for safety, tolerability, PK, PD and immunogenicity. Overall, there were no clinically significant safety or tolerability findings from this study. Results from the Phase 1 SAD study informed the dose regimens used for the multiple ascending doses (MAD) Phase 1b portion of this trial. The MAD portion will involve 3 cohorts. The Phase 2 portion will be a proof of concept (POC) part, where dose selection will be based on the data monitoring committee (DMC) and sponsor's assessment of safety, tolerability, immunogenicity, and PK and PD data from the MAD portion of 30 patients treated with BOS161721/placebo. The purpose of the study is to establish a safe and effective dosage for adult patients with moderately to severely active SLE.

Objectives and Endpoints:

MAD Phase 1b

OBJECTIVES	ENDPOINTS
Primary	
• To assess safety, tolerability, and immunogenicity of repeat doses of BOS161721 (20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment, in order to estimate the optimal dose.	Safety Endpoints • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • Columbia Suicide Severity Rating Scale (C-SSRS) • 12-lead electrocardiograms (ECGs) parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from baseline • Physical examinations changes from baseline • Anti-drug antibodies (ADAs) • Study drug exposure/compliance
Secondary	
• To characterize the PK of BOS161721 and select the optimal dose of BOS161721 based on safety, PK, and PD effects in patients with moderately to severely active SLE.	Pharmacokinetic Endpoints • BOS161721 concentration by visit and time point • Maximum observed concentration (C_{max}), first time to maximum concentration (T_{max}), area under the concentration-time curve (AUC), $t_{½}$, systematic clearance (C_L), volume of distribution (V_d) Pharmacodynamic Endpoints • Results and changes (or shifts) from baseline to each visit in phosphorylated signal transducer and activator of transcription 3 (pSTAT3), C3 and C4 levels, and leukocyte immunophenotype • Results and changes (or shifts) from baseline in anti-double-stranded DNA (dsDNA), antinuclear antibodies (ANA), anti-Sjögren syndrome A and B (SSA, SSB), Smith (Sm), and antiphospholipid (APL) autoantibodies at each visit • Results and changes (or shifts) from baseline in abrogation of IL-21 gene signature at each indicated visit

Exploratory	
• CCI	CCI - CCI • CCI
• CCI	• CCI
• CCI	• CCI

POC Phase 2

OBJECTIVES	ENDPOINTS
Primary	
• To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on the SLE Responder Index 4 (SRI-4)	Primary Efficacy Endpoint • The proportion of patients with a SRI-4 response at Day 210 (see Section 6.3.4.1)
Secondary	
• To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on clinical indicators of SLE activity, in adult patients with moderately to severely active SLE on limited background standard of care treatment	Secondary Efficacy Endpoints • The proportion of patients with: - SRI-4 response at each visit - SRI-5 and SRI-6 response at each visit (Section 6.3.4.2) - a sustained reduction of oral corticosteroid (CS) (≤ 10 mg/day and ≤ Day 0 dose) between Day 120 and Day 210 - new BILAG A flare or > 1 BILAG B flares relative to baseline through Day 210 - PGA worsening - a BICLA response - a CLASI response - medication failures • Results and changes from baseline in: - CLASI - swollen and tender joints ACR-28 - SLEDAI-2K - SLICC/ACR damage index • Time to medication failure • Duration of longest SRI-4 response • Time to first SRI-4 response • Time to BILAG A flare or > 1 BILAG B flare compared to baseline through Day 210
Safety	
• To assess safety and tolerability of repeat doses of BOS161721 at the chosen dose administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment	Safety Endpoints • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • C-SSRS • 12-lead ECGs parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from

	baseline • Physical examinations changes from baseline • ADAs • Study drug exposure/compliance
Exploratory	
• CCI	CCI
• CCI	• CCI
• CCI	• CCI

Study Design: This is a Phase 1b/2 combined, randomized, multicenter, double-blind, placebo-controlled trial to study the clinical efficacy, safety, and PK of multiple SC doses of BOS161721 in adult patients with moderately to severely active SLE. After successfully completing a screening phase, eligible patients will be randomized to a specified dose of BOS161721 or placebo. The dosing schedule will be monthly. The trial will consist of 2 double-blinded portions: MAD Phase 1b and POC Phase 2. Patients may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180, followed by safety follow-up visits at Days 210, 240, and 270.

The MAD Phase 1b portion of the study design will consist of 3 cohorts, with Cohort 1 containing 6 patients, where 5 of these patients will receive BOS161721 (active), and 1 will receive placebo. Cohorts 2 and 3 will each contain 12 patients, including 9 active and 3 placebo patients. Dose selection for each cohort is based on 90-day safety, tolerability, PK, and PD data review from the Phase 1 SAD study (BOS161721-01) in healthy subjects. Each of the 3 doses (20, 60, and 120 mg) selected for the MAD portion are projected not to exceed the mean exposure of that achieved in the SAD study following the single 240 mg SC dose. Each patient may receive a total of

7 SC monthly doses on Days 0, 30, 60, 90, 120, 150, and 180.

The MAD portion design is staggered, where after the 6 patients in Cohort 1 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 2 begins dosing (after the DMC evaluates the safety and tolerability data from Cohort 1). Similarly, after 8 of the 12 patients in Cohort 2 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 3 begins dosing after the DMC evaluation of the safety and tolerability data from Cohort 2 and Cohort 1. Thirty days after the last patient in Cohort 3 receives the third dose, the DMC and Boston Pharmaceuticals will conduct a data review to determine which dose will be carried forward into the POC part of the study. This dose will not exceed doses tested during the MAD portion.

For the POC portion, approximately 156 additional patients will be randomized to active or placebo groups in a 2:1 ratio. As in the MAD portion, each patient in the POC portion may receive a total of 7 SC monthly doses on Days 0, 30, 60, 90, 120, 150, and 180.

A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). One oral CS "burst" for increased SLE disease activity may occur during the study between Day 0 and Day 60. Tapering of steroids during the course of the study will be highly encouraged and should be evaluated at the protocol permitted visits (Day 0 through Day 60 and Day 120 through Day 150). Between Day 60 and Day 120, and between Day 150 and Day 210, oral CS doses must be held constant due to the endpoint evaluations occurring at Day 120 and Day 210.

DMC safety reviews will be conducted periodically throughout the study as described in the DMC charter.

Main Criteria for Inclusion and Exclusion

Inclusion Criteria:

1. Men and women, ages 18 to 70 years, inclusive

2. Patients must be mentally capable of giving consent and there must be evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study

3. Patients must have SLE as defined by meeting 4 of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE (with at least 1 clinical and 1 immunologic criterion OR Lupus nephritis as the sole clinical criterion in the presence of antinuclear antibodies [ANA] or anti- double-stranded deoxyribonucleic acid [dsDNA] antibodies), either sequentially or simultaneously

4. At screening, patients must have at least 1 of the following:

    a. Elevated ANA ≥ 1:80 via immunofluorescent assay at the central laboratory

    b. Positive anti-dsDNA or anti-Smith (Sm) above the normal level as determined by the central laboratory

    c. C3 or C4 levels below normal as determined by the central lab

5. At screening, the SLEDAI-2K must be ≥ 6, including points from at least 1 of the following clinical components:

    a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis

        i. Excluding parameters which require central laboratory results: (hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia)

        ii. Points from lupus headache and organic brain syndrome will also be excluded

6. On Day 0, the SLEDAI-2K must be ≥ 6, including points from at least 1 of the following clinical components:

    a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis

        i. Excluding parameters which require central laboratory results: hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA,

decreased complement, thrombocytopenia, and leukopenia

ii. Points from lupus headache and organic brain syndrome will also be excluded

7. Patients must have at least 1A or 2Bs from the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer:

   a. BILAG A or B score in the mucocutaneous body system

   b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis as defined in the protocol Section 4.4

   If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in the other body systems for a total of 2 "B" BILAG body system scores

8. Patients must be currently receiving at least 1 of the following:

   a. Administration for a minimum of 12 weeks, and a stable dose for at least 56 days (8 weeks prior to signing consent) of the following permitted steroid-sparing agents:

      i. Azathioprine (AZA), mycophenolate mofetil or mycophenolic acid, chloroquine, hydroxychloroquine, or methotrexate (MTX)

   b. Prednisone (or prednisone-equivalent) cannot exceed 30 mg/day at screening for a patient to be eligible and must be stable at a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization)

9. Women of childbearing potential (WOCBP; see Section 4.7 for full information regarding WOCBP, definition of menopause, and contraception):

   a. Must have a negative serum pregnancy test at screening. Urine pregnancy test must be negative prior to first dose

   b. Must not be breastfeeding

   c. Must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 52 weeks

10. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment

with study drug plus 52 weeks

11. Patients must demonstrate willingness and ability to comply with the scheduled study visits, treatment plans, laboratory tests, and other procedures

Exclusion Criteria

Patients presenting with any of the following will not be included in this study:

1. Drug-induced SLE, rather than "idiopathic" SLE
2. Other systemic autoimmune disease (eg, erosive arthritis, rheumatoid arthritis [RA], multiple sclerosis [MS], systemic sclerosis, or vasculitis not related to SLE)
    a. RA-Lupus overlap (Rupus), and secondary Sjögren syndrome are allowed
3. Any major surgery within 6 weeks of study drug administration, (Day 0), or any elective surgery planned during the course of the study
4. Any history or risk for tuberculosis (TB), specifically those with:
    a. Current clinical, radiographic, or laboratory evidence of active TB
    b. History of active TB
    c. Latent TB defined as positive QuantiFERON-TB Gold In-Tube (QFT-G) or other diagnostic test in the absence of clinical manifestations. Latent TB is not excluded if the patient has documented completion of adequate course of prophylactic treatment with regimen recommended by local health authority guideline, or the patient has started treatment with isoniazid, or other regimen recommended by local health authority guidelines for at least 1 month before Day 0 and continues to receive the prophylactic treatment during study until the treatment course is completed
5. Active or unstable lupus neuropsychiatric manifestations, including but not limited to any condition defined by BILAG A criteria, with the exception of mononeuritis multiplex and polyneuropathy, which are allowed
6. Severe proliferative lupus nephritis, (WHO Class III, IV), which requires or may require induction treatment with cytotoxic agents or high dose CS
7. Concomitant illness that, in the opinion of the investigator, is likely to require additional systemic glucocorticosteroid therapy during the study, (eg, asthma), is exclusionary
    a. However, treatment for asthma with inhalational CS therapy is allowed

8. Use or planned use of concomitant medication outside of standard of baseline treatment for SLE from Day -1 or for any time during the study
9. Active and clinically significant infection (bacterial, fungal, viral, or other) within 60 days prior to first dose of study drug. Clinically significant is defined as requiring systemic parenteral antibiotics or hospitalization
10. A history of opportunistic infection, or a history of recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years
11. Chronic viral hepatitis including hepatitis B (HBV) and hepatitis C (HCV) unless patient received curative treatment for HCV and has a documented negative viral load, known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness
12. Cryptosporidium in the stool sample at screening
13. White blood cells (WBC) < 1,200/mm^3 (1.2×10^9/L) at screening
14. Absolute neutrophil count (ANC) < 500/mm^3 at screening
15. CD4+ count < 350/μL at screening
16. Platelets < 50,000/mm^3 (50×10^9/L) or < 35,000/ mm^3 (35×10^9/L) if related to SLE, at screening
17. Hemoglobin < 8 g/dL or < 7 g/dL at screening if related to SLE
18. Proteinuria > 3.0 g/day (3000 mg/day) at screening or equivalent level of proteinuria as assessed by protein/creatinine ratio (3 mg/mg or 339 mg/mmol)
19. Serum creatinine > 2.0 mg/dL at screening or creatinine clearance (CrCL) < 40 ml/minute based on Cockcroft-Gault calculation
20. Serum alanine aminotransferase (ALT) and/or serum aspartate aminotransferase (AST) > 2 × the upper limit of normal (ULN) at screening, unless explicitly related to lupus based on the investigator's judgment
21. Creatinine kinase (CK) > 3.0 × ULN at screening unless related to lupus myositis
22. Direct bilirubin > 1.5 × ULN at screening (unless related to Gilbert's syndrome)
23. Any other laboratory test results that, in the opinion of the Investigator, might place a patient at unacceptable risk for participating in this study
24. History of allergic or anaphylactic reaction to any therapeutic or diagnostic mAb (eg, IgG protein) or molecules made of components of mAbs
25. History substance and/or alcohol abuse, or dependence within the past 1

year, at the investigator's judgment

26. History of cancer within the last 5 years (except for cutaneous basal cell or squamous cell cancer, or cervical cancer in situ resolved by excision)
27. Any other severe acute or chronic medical or psychiatric condition, including recent (within the past year) medical conditions (eg, cardiovascular conditions, respiratory illnesses) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study
28. Investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or patients who are employees of the sponsor or directly involved in the conduct of the trial
29. Currently participating in, or who have participated in other interventional (drug or device) clinical study within 30 days or 5 half-lives of baseline, whichever is longer
30. Recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4, or 5 on the C-SSRS
31. Current or pending incarceration
32. Current or pending compulsory detainment for treatment of either a psychiatric or physical (eg, infectious disease) illness

Statistical Considerations

Below is a summary of the statistical methods. Further details can be found in Section 8.

Two analyses are planned: 1) an interim analysis to select the POC dose based on the MAD data, and 2) a final analysis at study completion. Additionally, DMC safety analyses will be performed for each MAD cohort and throughout the POC to monitor patient safety as described in the DMC charter. An additional analysis may be performed for the MAD portion of the study when all MAD patients have completed the safety follow-up, or withdrawn from the study, and prior to the final analysis. Data from the POC part of the study will be excluded from this additional analysis.

Unless stated otherwise, statistical testing will only be performed on the POC data and will be done using 2-sided overall alpha of 0.10. Data will be summarized descriptively by treatment and overall for each study phase. For the MAD portion, BOS161721 will be summarized overall and by each dose level and placebo patients from each cohort will be combined.

The descriptive summaries for the categorical data will include number and percentage. The descriptive summaries for the continuous data will include number, mean, median, standard deviations (SD), 25^{th} and 75^{th} percentiles,

minimum, median, and maximum. Counts, medians, 25th and 75th percentiles, and standard error will be presented for time-to-event data.

All safety analyses will be performed using the safety analysis set (SS), defined as all patients who receive at least 1 dose of study treatment. All efficacy analyses will be performed using the full analysis set (FAS), defined as all patients who receive at least 1 dose of study treatment and have at least 1 evaluable post-baseline efficacy evaluation. Select efficacy analyses may also be performed on the per protocol (PP) set.

Binary efficacy endpoints, including the primary efficacy endpoint, will be assessed via Pearson's chi-squared analysis.

Continuous efficacy endpoints will be assessed via analysis of variance (ANOVA) or analysis of covariance (ANCOVA) when applicable, adjusting for the baseline value. Repeated measures mixed models may be performed to evaluate data collected at each visit and overall. Time-to-event endpoints will be assessed via Kaplan-Meier methodology and treatment will be compared using the log-rank test.

Adverse event data will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients experiencing any treatment-emergent AE, overall, and by system organ class and preferred term will be tabulated. Treatment-emergent AEs will also be summarized by severity and relationship.

Concomitant medications will be summarized, based on coded terms, using frequency and percentage of patients. Observed values and changes from baseline in vital signs, ECG readings, and hematology and clinical chemistry parameters, will be summarized at each individual visit.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADA	anti-drug antibody
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANC	absolute neutrophil count
ANOVA	analysis of variance
ANCOVA	analysis of covariance
APL	antiphospholipid
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AZA	azathioprine
BICLA	BILAG-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BP	blood pressure
BUN	blood urea nitrogen
BW	body weight
C	complement
C-SSRS	Columbia Suicide Severity Rating Scale
CD	cluster of differentiation
CK	creatine kinase
C_L	systematic clearance
CLASI	Cutaneous Lupus Erythematosus Area and Severity Index
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CS	corticosteroids
CSR	clinical study report
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
dsDNA	double-stranded deoxyribonucleic acid
ECG	electrocardiogram
EOT	end of treatment
eCRF	electronic case report form
F	female
CCI	[redacted]
FAS	full analysis set
Fc	fragment crystallizable

FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
eGFR	estimated glomerular filtration rate
GLP	Good Laboratory Practice
GWAS	genome-wide association studies
γc	gamma chain
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCl	hydrochloride
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IL	interleukin
IL-21R	interleukin 21 receptor
IM	intramuscular
IFNγ	interferon gamma
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
IVRS	interactive voice response system
JAK	Janus kinase
kg	kilogram
KLH	keyhole limpet hemocyanin
LOCF	last observation carried forward
M	male
mAb	monoclonal antibody
MAD	multiple ascending dose
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary of Regulatory Activities
MS	multiple sclerosis
MTX	methotrexate
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

NIAID/FAAN	National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network
NK	natural killer
NOAEL	no observed adverse event level
NO	nitric oxide
OTC	over-the-counter
PD	pharmacodynamics
PEF	peak expiratory flow
PGA	Physician's Global Assessment
PK	pharmacokinetics
POC	proof of concept
PP	per protocol
PR	(interval) from onset of the p-wave to the end of the r-wave
pSS	primary Sjögren's syndrome
pSTAT3	phosphorylated signal transducer and activator of transcription 3
PT	preferred term
QRS	(interval) from the onset of the q-wave to the end of the s-wave
QT	(interval) from onset of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
QFT-G	QuantiFERON-TB Gold In-Tube
RA	rheumatoid arthritis
RR	(interval) from the onset of the r-wave to the onset of the next consecutive r-wave
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SDMT	safety data monitoring board
CCI	[redacted]
SLE	systemic lupus erythematosus
SLEDAI-2K	SLE Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
Sm	Smith
SOC	system organ class
SRI-4	SLE Responder Index 4
SRI-5	SLE Responder Index 5
SRI-6	SLE Responder Index 6
SS	safety analysis set
SSA	Sjögren syndrome-A (Ro)
SSB	Sjögren syndrome-B (La)
STAT3	signal transducer and activator of transcription 3

SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
TB	tuberculosis
TDAR	T-cell dependent antibody response
Tfh	T-follicular helper
Th	T-helper
TK	toxicokinetics
T_{max}	first time to maximum concentration
Treg	regulatory T-cell
ULN	upper limit of normal
US	United States
Vd	volume of distribution
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
YTE	triple mutation

1. INTRODUCTION AND RATIONALE

1.1 Indication

BOS161721 is a humanized monoclonal antibody (mAb), which binds to and inhibits interleukin-21 (IL-21) bioactivity, and is being developed for the treatment of moderately to severely active systemic lupus erythematosus (SLE) in adults.

1.2 Background and Rationale

1.2.1 Overview of the Disease State

SLE is a chronic inflammatory autoimmune disease that has variable manifestations in multiple organ systems and follows a relapsing and remitting course. The disease process includes abnormal immune responses mediated by tissue-binding autoantibodies and immune complex deposition, giving rise to tissue damage often resulting in end organ disease and even mortality. Survival of SLE has improved due to earlier detection, improved overall medical care, and standardized SLE treatment with corticosteroids (CS), immunosuppressants, and cytotoxic agents.[1] However, some of the morbidity in patients with SLE is related to its treatment. Comparison of early and late outcomes in patients with SLE demonstrate that death in early disease is most commonly due to infections and active SLE causing multi-system organ damage, while thromboses were the most common cause of death during later disease.[2]

The reported prevalence of SLE in the United States (US) is 20 to 70 cases per 100,000 people.[3] More than 90% of cases of SLE occur in women, frequently starting at childbearing age. Women of color are disproportionately affected by SLE. This suggests multiple genetic and environmental factors are at play. Accordingly, a multifactorial view of the immunopathogenesis of SLE suggests more than 1 area of interest, including breach in central tolerance in the adaptive arm of the immune system, peripheral amplification of the autoimmune response by the innate immune system, and local processes in the target organ that facilitate end-organ disease.[4]

1.2.2 BOS161721 Development

Boston Pharmaceuticals is developing BOS161721 for the treatment of SLE. BOS161721 is a humanized immunoglobulin G1 (IgG1) mAb with extended half-life directed against human IL-21.

Murine mAb 19E3, the progenitor of BOS161721, was generated using mouse hybridoma technology. 19E3 has subpicomolar (pM) affinity to human IL-21 and was selected for its potent neutralization of IL-21 bioactivity. BOS161721 was generated by the humanization of mAb 19E3 where its complementarity-determining regions were grafted onto a human IgG1 kappa backbone. The fragment crystallizable (Fc) portion of BOS161721 contains a YTE (M252Y/S254T/T256E triple mutation) in the constant domain of the IgG1 heavy chain that was introduced into the parental molecule, 19E3, intended to prolong the *in vivo* terminal elimination half-life ($t_{½}$) of the mAb.[5] Thus, BOS161721 retains sub-pM binding to IL-21 and prevents IL-21 from binding to the IL-21 receptor (IL-21R), inhibiting IL-21 bioactivity.

BOS161721 binds to human IL-21 and Cynomolgus monkey IL-21, which are highly homologous, and neutralizes the bioactivity of both. BOS161721 is specific for IL-21 as it does not bind to or inhibit the other gamma-chain (γc) family of cytokines, and acts to specifically neutralize the IL-21 pathway. In *in vitro* studies, BOS161721 inhibited downstream IL-21-induced signaling, IL-21-induced plasma cell differentiation, and IL-21-induced natural killer (NK) cell activation. In *in vivo* studies, BOS161721 significantly inhibited the T-cell dependent antibody response (TDAR) to immunization with a protein antigen as well as B-cell expansion following a second protein antigen immunization in Cynomolgus monkeys.

1.2.2.1 Interleukin-21

IL-21 is an inflammatory cytokine, which belongs to a family of cytokines that also includes IL-2, IL-4, IL-7, IL-9, and IL-15, all of which bind to private receptors in complex with the common cytokine receptor γc.[6] Most cytokines in this family are critically important for both the maintenance and function of T-cell and B-cell responses. IL-21 signals through a receptor complex consisting of its own private receptor, the IL-21R and γc.[6,7] Engagement of the IL-21R/γc complex leads to the activation of several signaling pathways, including the Janus kinase/signal transducer and activator of transcription, mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase pathways.[8] IL-21 is produced mainly by T-cells and NK T-cells, but neutrophils have also been reported to produce IL-21.[9,10] The IL-21R is expressed on a broad array of cell types, including B-cells, T-cells, NK-cells, macrophages and dendritic cells, as well as other hematopoietic and nonhematopoietic cells such as fibroblasts, keratinocytes, and intestinal epithelial cells.[9,11] Activation of signal transducer and activator of transcription 3 (STAT3) via phosphorylation is critical in regulating human B-cell responses to IL-21[12]; phosphorylated STAT3 (pSTAT3) forms a homodimer, which translocates to the nucleus where it initiates transcription of the IL-21 gene, forming an autocrine loop for IL-21 production via STAT3 phosphorylation.[13] In addition, IL-21 has been shown to upregulate expression of its own receptor[14] and induces an autocrine feedback loop.[15]

IL-21 modulates various aspects of immune function. It promotes cluster of differentiation 4 (CD4+) T-cell differentiation and promotes the generation of T-helper (Th)17[16] and T-follicular helper (Tfh) cells.[15,17] In mice, IL-21 has been shown to regulate the balance between Th17 and regulatory T-cell (Treg), in that it increases Th17, while inhibiting Treg differentiation.[18] Less is understood with regards to human Tregs, although IL-21 has been reported to counteract Treg suppression of human effector T-cells[19] and blockade of IL-21 promotes Treg generation in a murine model of graft versus host disease induced by human T-cells.[20] IL-21 upregulates CD8+ T-cell and NK-cell expansion and cytolytic activity by increasing granzyme B and perforin.[21,22] IL-21 also has been reported to increase granzyme B in plasmacytoid dendritic cells and B-cells resulting in inhibition of T-cell responses.[23,24] IL-21 also has a variety of effects on nonhematopoietic cells, such as stromal cells and induces inflammation through matrix metalloproteinase release by gut intestinal fibroblasts.[25]

One principal non-redundant role of IL-21 is the promotion of B-cell activation, differentiation, or death during humoral immune responses.[14] Furthermore, increased IL-21 production is characteristic of several autoimmune diseases and is likely to contribute to autoantibody production as well as pathologic features of autoimmune disease.[26] The critical role of IL-21 in promoting humoral and other immune responses makes it an important focus of potential

therapeutic interventions in conditions characterized by overproduction of pathogenic autoantibodies. IL-21 production by Tfh cells in humans is believed to play a major role in driving the autoantibody production through its role in plasma cell differentiation. Importantly, Tfh cell populations are expanded in patients with autoimmune diseases such as lupus, bullous pemphigoid, rheumatoid arthritis (RA) and primary Sjögren's syndrome (pSS) and have been reported to correlate with IL-21 levels, autoantibodies, and disease severity.[26,27,28,29] Furthermore, loss of number and functionality of Tregs has been associated with autoimmune diseases such as SLE and giant cell arteritis, which IL-21 is expected to modulate.[30,31] Thus, neutralization of IL-21 in settings of autoimmunity is expected to impact several cell populations believed to be involved in the pathogenesis of autoimmune disorders including SLE.

BOS161721 selectively binds IL-21 with high affinity to neutralize IL-21, and due to its pleiotropic nature, neutralization of IL-21 is expected to impact several cell populations believed to be involved in the pathogenesis of SLE. Importantly, patients with SLE have elevated IL-21 plasma levels that correlate with the severity of the disease. Recently, genome-wide association studies (GWAS) have provided convincing evidence that the chromosomal 4q 27 region harbors the IL-21 genes and is associated with chronic inflammatory disorders, including SLE.[29]

1.2.2.2 Preclinical Studies

The pharmacokinetics (PK) of BOS161721 were characterized following single-dose intravenous (IV) administration of BOS161721 (0.01 to 30 mg/kg) in male Cynomolgus monkeys or repeat, every 2 weeks IV administration (15 to 100 mg/kg) and subcutaneous (SC) administration (50 mg/kg) in male and female Cynomolgus monkeys. Systemic exposure was approximately dose-proportional within the tested dose range. SC bioavailability was determined to be 64.3%. CCI [redacted]

Two single-dose (IV) non-good laboratory practice (GLP) studies conducted in Cynomolgus monkeys evaluated the toxicity, pharmacodynamics (PD), toxicokinetics (TK), and immunogenicity of BOS161721. Following a single IV administration (slow bolus), there were no BOS161721-related adverse changes, resulting in a no-observed-adverse-effect-level (NOAEL) value of 30 mg/kg, the highest dose tested among 2 studies. CCI [redacted]

In a repeat-dose GLP toxicology study in Cynomolgus monkeys, BOS161721 was administered every 2 weeks by IV or SC (50 mg/kg) administration for 3 months (a total of 7 doses). CCI [redacted]

CCI [redacted] The NOAEL was determined to be 100 mg/kg (SC and IV), the highest dose tested.

An additional GLP, repeat-dose toxicity study was conducted in Cynomolgus monkeys (4 males and 4 females per dose group) following every 2 weeks (Q2W) administration by SC (10, 30, and 100 mg/kg) injection for a total of 14 doses. CCI [redacted] There were no BOS161721-related effects on survival, clinical signs, male body weights, ophthalmologic parameters, electrocardiogram (ECG) findings, clinical pathology, macroscopic observations, organ weights, or microscopic observations. CCI [redacted] The 100 mg/kg/dose was the NOAEL CCI [redacted]

1.2.2.3 Clinical Studies

BOS161721-01 was a double-blind, Phase 1, single ascending dose (SAD) study to assess the safety, PK, and PD of BOS161721 in healthy subjects. The primary objective of the study was to characterize the safety and tolerability of IV and SC SADs of BOS161721 in an otherwise healthy subject population without concomitant illnesses, immune abnormalities, or concomitant medications. Secondary objectives included characterization of the PK and immunogenicity of BOS161721, and exploratory objectives included the evaluation of the effect of BOS161721 on TDAR to keyhole limpet hemocyanin (KLH) (primary and secondary immunizations) in healthy subjects, the effects of BOS161721 on plasma levels of IL-21 (free and bound), and the evaluation of the effect of BOS161721 on IL-21 gene expression (via gene signature) in blood. This study consisted of 8 cohorts. Subjects were randomized in a 3:1 ratio (BOS161721: placebo) and received either a single dose of BOS161721 (1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg) or placebo, with safety follow-up. For the first cohort, after the first 2 subjects were dosed (1 active and 1 placebo), there was a minimum gap of 48 hours before the remaining subjects from that cohort were dosed, to allow for an initial review of any emerging safety and tolerability data. For all cohorts, escalation to the next dose was not

sooner than 8 days after all the subjects in the prior cohort had been dosed and were based on a review of at least 7 days of safety and tolerability data by the Safety Data Monitoring Team (SDMT).

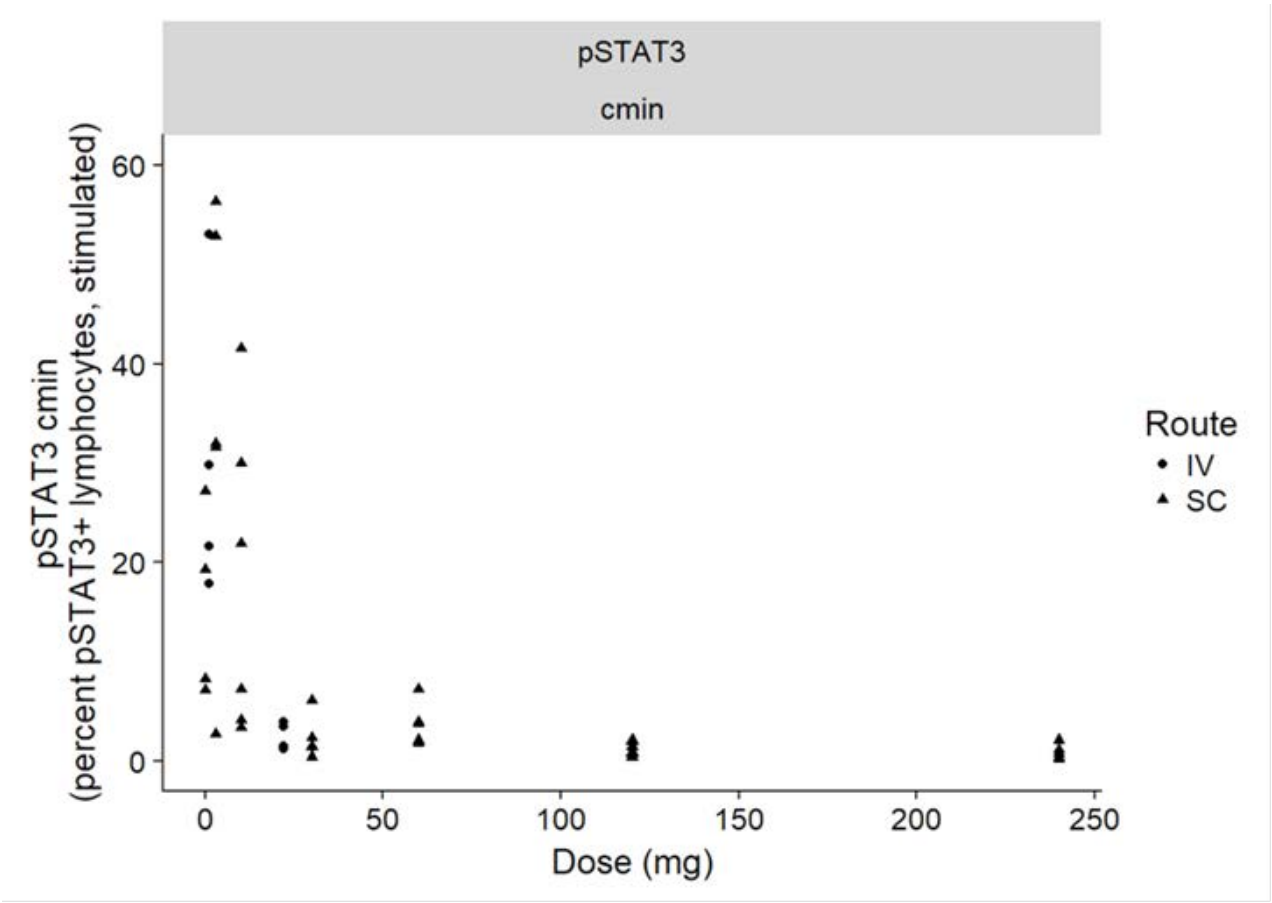
Blood samples were collected at every in-house study visit for BOS161721 concentration determinations. Blood samples were also collected for determination of IL-21 plasma levels (free and total). Safety was assessed based on the occurrence of treatment-emergent AEs, hepatic function abnormality, and acute and delayed hypersensitivity reactions. Other safety variables included ECGs, vital signs (blood pressure [BP], heart rate, and temperature), safety laboratory assessments, blood sampling for ADAs, total IgG and immunoglobulin M (IgM) levels, CD4+ count, and full and targeted physical examinations. Overall, there were no clinically significant findings from this study. Adverse events reported as related to the study drug, particularly infections, were expected for the compound, and there were no clinically relevant changes in laboratory and ECG results or vital signs. There was 1 serious adverse event (SAE; death due to pulmonary embolism) that occurred 127 days after a single administration of 240 mg SC dose of BOS161721. The causality of this single SAE was not attributed to study drug and further information can be found in the Investigator's Brochure. Final PK data from the SAD study demonstrates BOS161721 has a mean $t_{½}$ ranging from 80 to 87 days for doses of ≥ 30 mg in healthy subjects.

1.2.3 Study Dose Selection

Doses have been selected for the multiple ascending dose (MAD) Phase 1b portion based on a 90-day safety, tolerability, PK, and PD data review from the Phase 1 SAD study (BOS161721-01); the SDMT reviewed the blinded safety data from subjects for each dose cohort (8 cohorts, evaluating 1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg), along with the accumulated safety and available PK/PD data from all subjects in the previous dose cohorts, to make a decision on whether to proceed to the next higher dose level, repeat a dose level, or stop dose escalation. Overall, there were no clinically significant safety or tolerability findings from this study.

Based on the Day-90 interim cut of the PK and biomarker data in the BOS161721-01 study, the recommended doses for evaluation in the MAD portion of this study are 20, 60, and 120 mg SC monthly. This dose recommendation is supported by evidence of linear PK with BOS161721 resulting in a median first time to maximum concentration (T_{max}) of 6 days and an apparent terminal half-life of 44 days. Furthermore, pSTAT3 suppression, a marker of IL-21 target engagement, follows a similar time course of the mAb levels, with maximal and sustained suppression apparent with doses greater than 30 mg SC (Figure 1).

Figure 1. Individual pSTAT3 C_{min} Levels Versus Dose



IV = intravenous, pSTAT3 = phosphorylated signal transducer and activator of transcription 3; SC = subcutaneous

All doses selected for the MAD portion are projected not to exceed the mean exposure of that achieved following the highest single dose of 240 mg SC administered in the Phase 1 SAD study. Cohort 1 will include randomized treatment to the 20 mg dose. Based on the staggered study design, the data monitoring committee (DMC) will perform a scheduled review of safety data and sequentially consider dose escalation for Cohorts 2 and 3. In addition, the DMC and Boston Pharmaceuticals will conduct a data review to determine which dose will be carried forward into the proof of concept (POC) Phase 2 portion. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2 and 3 from the MAD portion (see Section 3.1.2.1 for the chosen POC dose and justification).

1.2.4 Risk-Benefit Assessment

The available preclinical data on BOS161721, the findings in clinical study BOS161721-01, and existing clinical information on IL-21 inhibitors suggest that the present clinical study has an acceptable risk-benefit ratio. In this study, the risk-benefit assessment of BOS161721 in adult patients with moderately to severely active SLE will be ongoing, with step-wise evaluations during the staggered MAD portion. The DMC used in this study is charged with assessing such actions in light of an acceptable benefit-risk profile for BOS161721 as an anti-IL-21 mAb.

Formal DMC monitoring meetings will occur as described in the DMC Charter. Two weeks after Cohort 1 has received a second dose of study drug, the DMC will evaluate the safety and tolerability data from Cohort 1 to determine the recommended dose for Cohort 2. Two weeks after 8 patients in Cohort 2 receive a second dose, the DMC will determine if dose escalation to Cohort 3 can proceed. Thirty days after the last patient in Cohort 3 receives the third dose, the DMC and Boston Pharmaceuticals will conduct a data review to determine which dose will be carried forward into the POC part of the study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2 and 3 during the MAD part of study. Thereafter, DMC safety reviews will be conducted periodically throughout the study as described in the DMC charter. With the agreement of the DMC and sponsor, this schedule may be modified depending on the rate of patient accrual. Additional details can be found in the DMC Charter.

The benefit of participation for all patients in this study is close monitoring of their medical condition and safety of their treatment. Those randomized to the active treatment arm may potentially experience improvement in their SLE disease. Those randomized to the placebo (in combination with standard of care) arm are not expected to obtain any additional benefit, beyond those of their background treatment, though close monitoring of their medical condition and safety may itself be associated with improving their SLE.

1.2.5 Potential Risks

Potential risks based on the mechanism of action of BOS161721 include infections, risks associated with the administration of any foreign protein or biologic agent, including injection site reaction, anaphylaxis, serious allergic reaction, and development of ADAs. ADAs could result in immune complex disease (with manifestations such as arthralgias, serum-sickness, and vasculitis), or altered BOS161721 levels or activity. Further details can be found in the current Investigator's Brochure (IB) for BOS161721, which contains comprehensive toxicology, preclinical and clinical information on BOS161721.

Two investigational drug products are considered to be in the same pharmacological class as BOS161721 based on interruption of signaling through the IL-21 signaling pathway. No potential risk generalizable across the class has been observed with these investigational products. Based on the clinical Phase 1 SAD study (BOS161721-01), AEs reported as related to the study drug, particularly infections (flu-like symptoms, etc.), were expected for the compound, and there were no clinically relevant changes in laboratory and ECG results or vital signs.

The majority of IgG elimination occurs via intracellular catabolism, following fluid-phase or receptor-mediated endocytosis. This type of endocytosis and elimination is a form of target-mediated disposition where the interaction of the drug and its pharmacological target (eg, a target receptor) serves as a significant contributor to the kinetics of antibody distribution and elimination. Renal elimination, which is a primary pathway of clearance of small-molecule drugs, is relatively unimportant for IgG, as its large size prevents efficient filtration through the glomerulus. Secretion into the bile is an important pathway of elimination of IgA antibodies, but

this route is not a significant contributor to the elimination of IgG antibodies. Thus, risk to renal and hepatic systems due to metabolism of BOS161721 is low.[33]

1.2.5.1 Anaphylaxis and Serious Allergic Reactions

As with the administration of any foreign protein and/or other biological agents, acute hypersensitivity reactions, including acute anaphylactic/hypersensitivity, severe allergic, and anaphylactoid reactions may follow infusion of mAbs and can be caused by various mechanisms. These acute hypersensitivity reactions may be severe and result in death.

Anaphylaxis will be defined according to the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria,[34] and are discussed in Section 6.2.2.6.1.

Based on the Phase 1 SAD study (BOS161721-01), anaphylaxis and serious allergic reactions in subjects who received BOS161721 was not observed.

Patients with a known history of allergy or severe hypersensitivity reaction to any component of BOS161721 formulation or patients with a history of anaphylaxis to any other biological therapy such as mAbs will be excluded from studies with BOS161721. In addition, appropriate drugs and medical equipment to treat acute hypotensive, bronchoconstrictive, or anaphylactic reactions will be immediately available at the unit and study personnel will be trained to recognize and treat these reactions.

1.2.5.2 Injection Site Reactions

In a repeat-dose GLP toxicology study in Cynomolgus monkeys, BOS161721 was administered every 2 weeks by IV or SC for 3 months (a total of 7 doses). There were no injection site reactions in animals dosed subcutaneously. Further, there were no reports of injection site reactions in the 26-week GLP toxicology study in Cynomolgus monkeys.

Based on the Phase 1 SAD study (BOS161721-01), incidence of injection site reactions in subjects who received BOS161721 was similar to placebo.

Patients will be monitored for local injection site reactions in this study. See Section 6.2.7.

1.2.5.3 Immune Complex Disease

The potential risk of immune complex disease for BOS161721 is theoretical, based on the known risks associated with mAbs. The administration of a mAb can result in the formation of ADAs. Administration of the mAb in the presence of ADA may result in the formation of circulating antibody-antigen complexes potentially resulting in altered BOS161721 levels or activity or deposition of the complexes in microvasculature. Complement is frequently involved in the latter setting, and the breakdown products of complement attract polymorphonuclear leukocytes to the site of deposition where they can provoke local tissue damage through specific or nonspecific release of enzymes. Two of the more common end-organ targets are the blood vessels (vasculitis) and kidney (nephritis). These clinical manifestations represent immune complex disease or Type III hypersensitivity. Although BOS161721 is a humanized mAb,

ADAs may develop; however, the likelihood of occurrence of immune complex disease with BOS161721 is low. The findings of immune complex disease are typically reversible when mAb administration stops and the antibody-antigen complexes are cleared from the body.

Based on the Phase 1 SAD study (BOS161721-01), immune complex disease in subjects who received BOS161721 was not observed.

1.2.5.4 Infections

BOS161721 is expected to diminish the activity of T-cell, B-cell and NK-cell lines. Like other medications modulating immune response, BOS161721 may increase the potential risk for infection, including serious infections. IL-21 produced by CD4+ Th cells is required to sustain the anti-viral function of CD8+ T-cells against chronic viral infections. Nonclinical evidence suggests that the risk of chronic viral infection recurrence or increased severity may occur with IL-21 inhibition.[35]

These conditions will be fully characterized with clinical descriptions and routine laboratory and/or specialty testing and treated where indicated with appropriate local standard of care.

Patients with a history of opportunistic infection, including recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years, or any other underlying pathology predisposing to serious infection, are excluded from studies with BOS161721 (for further details please refer to the current IB for BOS161721).

Patients will be assessed for hepatitis B, and C, and HIV-1/2 combination, at screening.

Cryptosporidium Infection

Cryptosporidium infection was noted in patients with an IL-21 receptor loss-of-function gene mutation and similar findings of cryptosporidium infection have been observed in immunosuppressed liver transplant and human immunodeficiency virus patients.[36,37] Since BOS161721 is expected to diminish the immunosurveillance activity of T-cell, B-cell, and NK-cell lines, a similar risk is biologically plausible with prolonged exposure to BOS161721.

Since the risk of opportunistic cryptosporidium infection increases with low levels of CD4+ T-cells,[37] patients with a CD4+ count < 500 cell/mm^3 were excluded from the Phase 1 SAD study (BOS161721-01), and CD4 + < 350 cells/mm^3 will be excluded from the MAD/POC parts of the study. Patients exposed to investigational product who develop diarrhea during the course of the study should immediately undergo an assessment for opportunistic infection including stool for ova and parasites and stool examination for cryptosporidium. Positive cryptosporidium in stool sample at screening is an exclusion. Treatment by the investigator where indicated should be guided by findings and be consistent with local standard of care.

Based on the Phase 1 SAD study (BOS161721-01), infections in subjects who received BOS161721 was not observed.

1.2.5.5 Malignancy

The stimulatory effect of IL-21 on NK cells and CD8+ T-cells suggests the cytokine may have anti-tumor activity. Nonclinical studies have demonstrated significant anti-tumor effects of IL-21 in a number of tumor models. IL-21 therapy of human metastatic melanoma and renal cell carcinoma has demonstrated POC with significant increases in levels of perforin, granzyme B, and interferon gamma (IFNγ) expression in CD8+ T-cells and NK T-cells. Clinical response has been limited in these generally unmanageable diseases.

The impact of treatment with anti-IL-21 therapy on the development or growth of malignancies is not known; however, as with other immunomodulatory biologic agents, treatment with BOS161721 may result in an increase in the risk of malignancies. NK cell suppression by IL-21 neutralization may represent a biological mechanism for a potential risk for malignancy. Patients with a history or current diagnosis of cancer within the past 5 years, with the exception of non-melanoma skin cancer or cervical cancer in situ treated with apparent success with curative therapy, are excluded from the study.

Based on the Phase 1 SAD study (BOS161721-01), malignancy in subjects who received BOS161721 was not observed.

1.2.5.6 Hepatic Function Abnormality

There is no substantial evidence suggesting BOS161721 is associated with liver function abnormality. However, as a precaution, patients with a history of abnormal alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), or bilirubin at screening (ALT/AST > 2 × upper limit of normal [ULN]; total bilirubin > 1.5 × [ULN] and judged by the investigator to be clinically significant) were excluded from the Phase 1 SAD study (BOS161721-01), and will be excluded from this trial. Patients with a positive hepatitis B or C test or a history of alcohol dependence will also be excluded.

Based on the Phase 1 SAD study (BOS161721-01), hepatic function abnormality in subjects who received BOS161721 was not observed.

1.2.5.7 Failure of Vaccination

IL-21 is a key cytokine in development of B-cells into immunoglobulin-secreting plasma cells. Abnormal signaling through the IL-21R/Janus Kinase (JAK)3/signal transducer and activator of transcription (STAT3) pathway leads to defective humoral immune responses to both T-dependent and T-independent antigens and impairs the establishment of long-lasting B-cell memory. Abnormal signaling through the pathway has been related to decreased specific antibody responses following vaccination, and to increased susceptibility to encapsulated bacterial infections.[38]

The effect of BOS161721 was evaluated in *in vivo* single dose studies in Cynomolgus monkey in which the animals received vaccination to T-cell dependent KLH antigen to stimulate a TDAR. These *in vivo* studies demonstrated that BOS161721 significantly inhibited B-cell proliferation and IgG antibody responses to the KLH protein antigen in a dose-dependent fashion; however,

BOS161721 administration did not affect anti-tetanus toxoid antibody data for IgM, IgG, IgG1, or immunoglobulin E (IgE) during the dosing phase in the same study.

1.2.5.8 Potential for Drug-Drug Interactions

Drug-drug interactions were not evaluated in the Phase 1 SAD study (BOS161721-01), which included only healthy adult subjects. Use of prescription medications (with the exceptions of oral contraceptives), and over-the-counter (OTC) treatments including herbal supplements such as St John's Wort (except multivitamins), in the 2 weeks prior to screening was prohibited in the SAD study.

See Section 4.5 for other specific exclusion criteria which support lowered risk of interactions, and Section 4.6.1 for corticosteroid (CS) dosing. In addition, Section 1.2.5.6 describes considerations for hepatic function for this study.

1.2.5.9 Potential Risk to Fetal Development

No data on preclinical reproductive toxicity are available at the time of this study.

2 STUDY OBJECTIVES AND ENDPOINTS

This trial has separate objectives and endpoints for the MAD Phase 1b and POC Phase 2 portions of the study. The primary, secondary, and exploratory objectives for each phase, as applicable, are described below with their corresponding endpoints.

2.1 Phase 1b Multiple Ascending Dose

OBJECTIVES	ENDPOINTS
Primary	
• To assess safety, tolerability, and immunogenicity of repeat doses of BOS161721 (20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment, in order to estimate the optimal dose.	Safety Endpoints • Incidence and severity of AEs and SAEs, related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • Columbia Suicide Severity Rating Scale (C-SSRS) • 12-lead ECGs parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from baseline • Physical examinations changes from baseline • ADAs • Study drug exposure/compliance
Secondary	
• To characterize the PK of BOS161721 and select the optimal dose of BOS161721 based on safety, PK, and PD effects in patients with moderately to	Pharmacokinetic Endpoints • BOS161721 concentration by visit and time point • Maximum observed concentration (C_{max}), T_{max}, area under the concentration-time curve (AUC), terminal elimination

severely active SLE.	half-life ($t_{½}$), systematic clearance (C_L), volume of distribution (V_d) Pharmacodynamic Endpoints • Results and changes (or shifts) from baseline to each visit in phosphorylated signal transducer and activator of transcription 3 (pSTAT3), C3 and C4 levels, and leukocyte immunophenotype • Results and changes (or shifts) from baseline in anti-double-stranded DNA (dsDNA), antinuclear antibodies (ANA), anti-Sjögren syndrome A and B (SSA, SSB), Smith (Sm), and antiphospholipid (APL) autoantibodies at each visit • Results and changes (or shifts) from baseline in abrogation of IL-21 gene signature at each indicated visit
Exploratory	
• CCI	CCI • CCI
• CCI	• CCI
• CCI	• CCI

2.2 Phase 2 Proof of Concept

OBJECTIVES	ENDPOINTS
Primary	
• To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on the SRI-4	Primary Efficacy Endpoint • The proportion of patients with a SRI-4 response at Day 210 (see Section 6.3.4.1)
Secondary	
To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on clinical indicators of SLE activity, in adult patients with moderately to severely active SLE on limited background standard of care treatment	Secondary Efficacy Endpoints • The proportion of patients with: - SRI-4 response at each visit - SRI-5 and SRI-6 response at each visit (Section 6.3.4.2) - a sustained reduction of oral corticosteroid (CS) (≤ 10 mg/day and ≤ Day 0 dose) between Day 120 and Day 210 - new BILAG A flare or > 1 BILAG B flares relative to baseline through Day 210 - PGA worsening - a BICLA response - a CLASI response - medication failures • Results and changes from baseline in**:** - CLASI - swollen and tender joints ACR-28 - SLEDAI-2K - SLICC/ACR damage index • Time to medication failure • Duration of longest SRI-4 response • Time to first SRI-4 response • Time to BILAG A flare or > 1 BILAG B flare compared to baseline through Day 210
Safety	
• To assess safety and tolerability of repeat doses of BOS161721 at the chosen dose administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment	Safety Endpoints • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • C-SSRS • 12-lead ECGs parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from baseline • Physical examinations changes from baseline • ADAs • Study drug exposure/compliance
Exploratory	

• CCI [redacted]	CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

3 STUDY PLAN

3.1 Study Design

This is a Phase 1b/2 combined, randomized, multicenter, double-blind, placebo-controlled trial to study the clinical efficacy, safety, and PK of SC doses of BOS161721 in adult patients with moderately to severely active SLE. After successfully completing a screening phase, eligible patients will be randomized to a specified dose of BOS161721 or placebo. The dosing schedule will be monthly.

The trial will consist of 2 double-blinded portions: MAD Phase 1b and POC Phase 2. Patients may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180, followed by safety follow-up visits at Days 210, 240, and 270.

SLE disease activity assessment data will be centrally reviewed by medical monitor and sponsor to ensure the scores are clinically meaningful and compliant with specific definition. The scope of responsibility includes, but is not limited to, review and confirmation of "A" and "B" BILAG system organ disease, confirmation of clinical components of the SLEDAI-2K score at screening and during the study, and cross-validation of the instruments used in this study to assess the disease activity. Further details on the content and methods of data reports by the medical monitor and sponsor will be outlined in the Medical Data Review Plan along with the processes and procedures that will be followed.

3.1.1 Multiple Ascending Dose Phase 1b

The MAD portion will consist of 3 cohorts:

- Cohort 1 (20 mg SC) will include 6 patients

- 5 patients will receive BOS161721 (active group) and 1 patient will receive placebo (placebo group)

- Cohorts 2 (60 mg SC) and 3 (120 mg SC) will include 12 patients each
  - 9 patients in the active group and 3 in the placebo group

Doses selected for each of the 3 cohorts is based on a 90-day safety, tolerability, PK and PD data review from the Phase 1 SAD study (BOS161721-01) in healthy subjects. All doses selected for the MAD part of the study are projected not to exceed the mean exposure of that achieved in the SAD study.

3.1.1.1 Dose Escalation for the MAD Portion

The MAD portion of the study design is staggered, where after the 6 patients in Cohort 1 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 2 begins dosing (after the DMC evaluation of the safety and tolerability data from Cohort 1). Similarly, after 8 of the 12 patients in Cohort 2 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 3 begins dosing after the DMC evaluation of the safety and tolerability data from Cohorts 1 and 2. Each cohort will continue at their assigned dose level through their respective 6-month treatment periods (See Study Schematic, Section 3.1). If patients discontinue the study in a cohort prior to adequate safety follow-up, he/she may be replaced.

Criteria for dose escalation are further described in the DMC Charter. See Section 3.1.1.2 for additional details about DLTs.

3.1.1.2 Dose Limiting Toxicity (DLT)

Severity of adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. For the purpose of dose escalation, any of the following AEs occurring after study drug administration, which are attributable to the study drug, will be considered DLTs:

Hematologic:

- Grade 4 neutropenia
- Grade 3 neutropenic infection
- Grade 3 thrombocytopenia with bleeding
- Grade 4 thrombocytopenia

Non-Hematologic:

- Grade 3 or above toxicities, persisting after optimal treatment with standard medical therapy (eg, anti-emetics, anti-diarrheals)

- Drug-induced liver injury ([DILI], Hy's Law), as defined in Section 6.2.2.6.3

Investigators should always manage their patients according to their medical judgment which may include interruption of study drug based on the particular clinical circumstances.

3.1.1.3 DMC Recommendations

During scheduled meetings, the DMC will review relevant study data for safety or benefit-risk concern. During the MAD part of the study, the DMC may provide the following recommendations to the sponsor:

- Expanding a cohort at a specific dosing level, or repeating a lower dose in a subsequent cohort
- Continuing a dose level for a given cohort
- Escalating a dose level for a subsequent cohort
- Termination of current or previous cohort(s)

Further dosing in a given cohort will be halted if 2 or more DLTs are identified intra- and inter-patients dosed. For the POC portion, the DMC and Boston Pharmaceuticals will conduct a data review to determine which dose will be carried forward into the POC Phase 2 part of the study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2, and 3; this dose will not exceed doses tested during the MAD portion. The DMC will be reviewing all relevant data from Cohorts 1, 2, and 3 that is available 30 days after the last patient from Cohort 3 receives the third dose. Details are provided in the DMC Charter.

3.1.2 POC Phase 2

3.1.2.1 BOS161721 POC Dose Selection and Justification

The dose for the POC portion of the study is 120 mg administered SC monthly (a total of 7 doses). The rationale for the BOS161721-02 Phase 2 POC dose selection was based on cumulative safety, tolerability, immunogenicity, PK, and PD data available from an interim analysis (IA) performed during the MAD Phase 1b portion of the trial.

The data cut-off for this IA occurred on CCI [redacted] and included all 6 patients and 7 doses from Cohort 1 (20 mg), 12 patients and 6 doses from Cohort 2 (60 mg), and 12 patients and 4 doses from Cohort 3 (120 mg).

The safety analysis focused on incidence and severity of all AEs, SAEs, and pre-determined adverse events of special interest (see Section 6.2.2.6). The DMC and designated unblinded Boston Pharmaceuticals team met on CCI [redacted] and did not identify any untoward safety signals at any BOS161721 dose levels.

Because there were no safety, tolerability, or immunogenicity trends observed at the time of the IA, the Phase 2 POC dose selection was made based on available PK and PD data. pSTAT3 levels were assessed as the primary PD biomarker of IL-21R signaling levels. This is because IL-21R signaling, upon IL-21 binding, initially involves phosphorylation of JAK1/JAK3 which dissociate from the receptor complex, and phosphorylate STAT3 which translocates to the nucleus and drives IL-21-regulated gene expression. CCI [redacted]

The 120 mg dose will be communicated to site investigators participating in the POC Phase 2 portion, and to Institutional Review Boards (IRBs) and the Independent Ethics Committee (IEC).

3.1.2.2 POC Study Design

For the POC part of the study, approximately 156 additional patients will be randomized to active or placebo groups in a 2:1 ratio.

As in the MAD part of the study, each patient in the POC portion may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180. Assessments will be completed according to the Schedule of Assessments (Section 3.4).

DMC safety reviews will be conducted periodically throughout the study as described in the DMC charter.

3.2 Randomization and Blinding

This is a randomized, double-blind study.

Patients meeting all inclusion and exclusion criteria will be centrally randomized to either placebo or BOS161721 using an IWRS according to a randomization list generated by an independent, non-study statistician. Randomization will be performed separately for each study portion and separately for each cohort in the Phase 1b and 2 portions as follows:

Phase/Cohort	Number of Patients	Randomization Ratio BOS161721:Placebo
Phase 1b/Cohort 1	6	5:1
Phase 1b/Cohort 2	12	3:1
Phase 1b/Cohort 3	12	3:1
Phase 2	156*	2:1

*Additional patients may be enrolled to ensure sufficient numbers of patients are in the full analysis set (FAS).

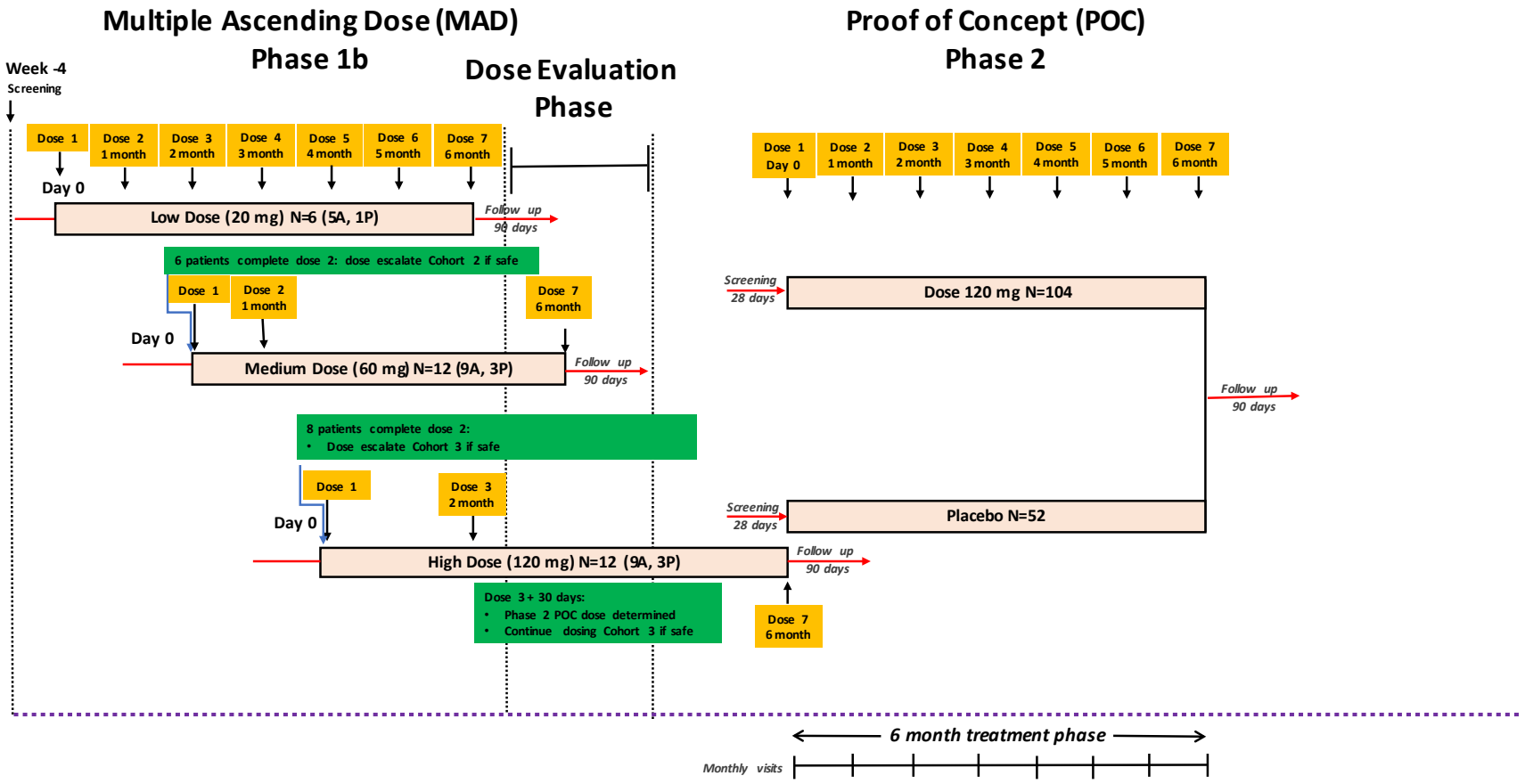
Eligible patients will be assigned to the study portion which is active at time of enrollment. Similarly, patients in the Phase 1b MAD will be assigned to the cohort which is active. Each patient will be assigned a unique randomization number which will not be reused.

All patients, investigators, and study team participants will be blinded to treatment assignment. An independent biostatistician not otherwise involved on the study will be unblinded and prepare materials for the IA, ad hoc analyses as needed, and the DMC safety reviews. The DMC will

review unblinded data during safety reviews and the IA. A limited team at Boston Pharmaceuticals will review unblinded results from the Phase 1b MAD portion during the IA to determine the dose that will be used for the Phase 2 POC portion of the study. Details regarding maintenance of the blinding and content of data reviews will be described in the DMC charter or related study documentation.

3.3 Study Schematic

Figure 2. Study Diagram for MAD Phase 1b and POC Phase 2



A = active drug (BOS161721); P = placebo

3.4 Schedule of Assessments

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
GENERAL ASSESSMENTS																
Informed consent	X															
Inclusion/Exclusion criteria	X															
Medical history	X															
Demographics	X															
SLICC Criteria for SLE	X															
Concomitant medication[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[c]		X														
BOS161721 or placebo dosing		X			X		X	X	X	X	X					
SAFETY ASSESSMENTS																
Full physical exam	X	X														
Chest x-ray[d]	X															
C-SSRS	X	X						X			X					
AEs and SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	X	X			X			X								X
Injection site reaction assessment		X[f]	X		X		X	X	X	X	X	X	X	X	X	X
Targeted physical examination				X	X	X	X	X	X	X	X			X	X	X
Vital signs (BP, HR, and temperature)[g]	X	X		X	X	X	X	X	X	X	X			X	X	X
EFFICACY ASSESSMENTS																
BILAG-2004 Index	X	X			X		X	X	X	X	X			X	X	X

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
SLEDAI-2K[h]	X	X			X		X	X	X	X	X			X	X	X
PGA of disease activity	X	X			X		X	X	X	X	X			X	X	X
ACR-28 joint count	X	X			X		X	X	X	X	X			X	X	X
CLASI	X	X			X		X	X	X	X	X			X	X	X
CCI		X			X		X	X	X	X	X			X	X	X
SLICC/ACR Damage Index		X									X					
CCI		X			X		X	X	X	X	X			X	X	X
LABORATORY ASSESSMENTS																
CD4+ count	X	X		X	X	X		X			X					
Clinical laboratory assessments (hematology and clinical chemistry)[i]	X	X			X	X	X	X	X	X	X			X	X	X
Coomb's test direct[j]	X	X			X		X	X	X	X	X			X	X	X
Total IgG and IgM	X	X		X	X	X		X			X					
Plasma CCI	X	X			X		X	X	X	X	X			X	X	X
Plasma CCI & CCI		X		X	X		X	X			X					
Whole blood for leukocyte immunophenotype		X		X	X		X	X			X					
ADA[k]		X		X	X		X	X			X					X
nAb[l]								X			X					
pSTAT3[m]		X			X	X	X	X								
CCI		X		X				X			X					X
CCI		X														

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
CCI [redacted]	X	X			X		X	X	X	X	X			X[n]	X[n]	X[n]
CRP	X							X								X
Serum pregnancy test (women)	X															
FSH (postmenopausal women)	X															
Urine pregnancy test (women)[o]		X			X		X	X	X	X	X					X
TB test (QuantiFERON-TB Gold In-Tube)[d]	X															
Serology (hepatitis B and C, HIV-1/2 combination)	X															
Stool sample[p]	X															
Spot urine for protein/creatinine ratio	X	X			X		X	X	X	X	X			X	X	X
Urinalysis	X	X			X		X	X	X	X	X			X	X	X

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
PK Labs																
Predose		X			X		X	X	X	X	X					
Predose PK Window		60m			± 3d		± 3d	± 3d	± 3d	± 3d	± 3d					
Postdose		X[q]	X	X	X[q]						X[q]	X	X	X	X	X
Postdose PK Window		4h ± 30m 8h ± 45m 24h ± 60m	± 1d	± 3d	4h ± 30m 8h ± 45m 24h ± 60m						4h ± 30m 8h ± 45m 24h ± 60m	± 3d	± 3d	± 3d	± 3d	± 3d

Abbreviations: ACR = American College of Rheumatology; ADA= anti-drug antibody; AE = adverse event; CCI [redacted]; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; C = complement; CD4+ = cluster of differentiation 4; CLASI = Cutaneous Lupus Area and Severity Index; CRP = C-reactive protein; C-SSRS = Columbia Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; CCI [redacted]; FSH = follicle stimulating hormone; h = hour; HR = heart rate; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IL-21 = interleukin 21; IV = intravenous; m = minute; nAb = neutralizing antibody; PGA = Physician's Global Assessment; PK = pharmacokinetic; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; SAE = serious adverse event; SC = subcutaneous; CCI [redacted]; SLEDAI-2K = SLE Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; CCI [redacted]; TB = tuberculosis; TDAR = T-cell dependent antigen response.

[a] Screening assessments will be performed over more than 1 visit.

[b] Concomitant use of oral corticosteroids: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). See Section 4.6.1 for further details.

[c] Randomization should occur after patient eligibility has been confirmed by central eligibility review.

[d] If patients have had a TB test and chest x ray within 3 months prior to screening, then these assessments do not need to be repeated during screening. The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

[e] ECGs will be performed after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws.

[f] Injection site reaction assessments to be performed at 2 hours postdose.

[g] Vital signs will be assessed after the patient has been supine and at rest ≥ 5 minutes. Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours postdose, as well as on each of the scheduled outpatient days in the table above (excluding PK-only site visits at Days 7, 187, and 195). When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**

[h] SLEDAI-2K should be done before randomization and dosing on Day 0 as SLEDAI-2K < 6 is exclusionary.

[i] Clinical laboratory assessments will include a fasting glucose and lipid panel, with exception of screening (Visit 1) which will be nonfasting.

[j] When clinically indicated for hemolytic anemia.

[k] Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only assayed (analyzed) if the patient had a positive ADA on Day 90.

[l] nAb is collected for all patients, though will only be analyzed by central lab if patient is positive for ADA at Day 90.

[m] Predose (trough) samples only.

[n] Only CCI collected during safety follow-up visits.

[o] Urine pregnancy test will be collected on WOCBP prior to study drug administration on dosing visits.

[p] Cryptosporidium test is required at screening. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

[q] Postdose samples will be collected at 4, 8, and 24 hours after study drug administration on Days 0, 30, and 180.

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC)

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187[b] (± 3)**	**195[b] (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
GENERAL ASSESSMENTS														
Informed consent	X													
Inclusion/Exclusion criteria	X													
Medical history	X													
Demographics	X													
SLICC Criteria for SLE	X													
Concomitant medication[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[d]		X												
BOS161721 or placebo dosing		X		X	X	X	X	X	X					
SAFETY ASSESSMENTS														
Full physical exam	X	X												
Chest x-ray[e]	X													
C-SSRS	X	X				X			X					
AEs and SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[f]	X	X		X		X								X
Injection site reaction assessment		X[g]		X	X	X	X	X	X	X	X	X	X	X
Targeted physical examination			X	X	X	X	X	X	X			X	X	X
Vital signs (BP, HR, and temperature)[h]	X	X	X	X	X	X	X	X	X			X	X	X
EFFICACY ASSESSMENTS														
BILAG-2004 Index	X	X		X	X	X	X	X	X			X	X	X
SLEDAI-2K	X	X[i]		X	X	X	X	X	X			X	X	X
PGA	X	X		X	X	X	X	X	X			X	X	X
ACR-28 joint count	X	X		X	X	X	X	X	X			X	X	X
CLASI	X	X		X	X	X	X	X	X			X	X	X
CCI		X		X	X	X	X	X	X			X	X	X

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC)

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187[b] (± 3)**	**195[b] (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
SLICC/ACR Damage Index		X							X					
CCI		X		X	X	X	X	X	X			X	X	X
LABORATORY ASSESSMENTS														
CD4+ count	X	X	X	X		X			X					
Clinical laboratory assessments (hematology and clinical chemistry)[j]	X	X		X	X	X	X	X	X			X	X	X
Coomb's test direct[k]	X	X		X	X	X	X	X	X			X	X	X
Total IgG and IgM	X	X	X	X		X			X					
Plasma CCI	X	X		X	X	X	X	X	X			X	X	X
Plasma CCI & CCI		X	X	X		X			X					
Whole blood for leukocyte immunophenotype		X	X	X		X			X					
ADA[l]		X	X	X	X	X			X					X
nAb[m]						X			X					
CCI		X	X			X			X					X
CCI		X												
CCI	X	X		X	X	X	X	X	X			X[n]	X[n]	X[n]
CRP	X					X								X
Serum pregnancy test (women)	X													
FSH (postmenopausal women)	X													
Urine pregnancy test (women)[o]		X		X	X	X	X	X	X					X
TB test (QuantiFERON-TB Gold In-Tube)[e]	X													
Serology (hepatitis B and C, HIV-1/2 combination)	X													

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC)

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187[b] (± 3)**	**195[b] (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
Stool sample[p]	X													
Spot urine for protein/creatinine ratio	X	X		X	X	X	X	X	X			X	X	X
Urinalysis	X	X		X	X	X	X	X	X			X	X	X
PK Labs[b]														
Predose		X		X	X	X	X	X	X					
Postdose			X							X	X	X	X	X

Abbreviations: ACR = American College of Rheumatology; ADA= anti-drug antibody; AE = adverse event; CCI [redacted]; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; C = complement; CD4+ = cluster of differentiation 4; CLASI = Cutaneous Lupus Area and Severity Index; CRP = C-reactive protein; C-SSRS = Columbia Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; CCI [redacted]; FSH = follicle stimulating hormone; h = hour; HR = heart rate; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IL-21 = interleukin 21; IV = intravenous; m = minute; nAb = neutralizing antibody; PGA = Physician's Global Assessment; PK = pharmacokinetic; SAE = serious adverse event; SC = subcutaneous; CCI [redacted]; SLEDAI-2K = SLE Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; CCI [redacted]; TB = tuberculosis; TDAR = T-cell dependent antigen response.

[a] Screening assessments will be performed over more than 1 visit.

[b] PK samples will only be collected at the investigational sites that participate in the PK portion of the study. On PK only days (ie, Day 187 and Day 195 when no laboratory assessments are scheduled) samples will be collected at the investigational sites of the selected countries that participate in the PK portion of the study. Patients not participating in PK are not required to return for investigation site visits on Days 187 and 195.

[c] Concomitant use of oral corticosteroids: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). See Section 4.6.1 for further details.

[d] Randomization should occur after patient eligibility has been confirmed. The actual randomization procedure can be completed on Day -1 after eligibility confirmation or the morning of Day 0 prior to dosing for logistical purposes.

[e] If patients have had a TB test and chest x ray within 3 months prior to screening, then these assessments do not need to be repeated during screening. The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

[f] ECGs will be performed after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws.

[g] Injection site reaction assessments to be performed at 2 hours postdose.

[h] Vital signs will be assessed after the patient has been supine and at rest ≥ 5 minutes. Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours postdose, as well as on each of the scheduled outpatient days in the table above (excluding PK-only site visits at Days 187 and 195). When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC)

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187[b] (± 3)**	**195[b] (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**

[i] SLEDAI-2K should be done before randomization and dosing on Day 0 as SLEDAI-2K < 6 is exclusionary.

[j] Clinical laboratory assessments will include a fasting glucose and lipid panel, with exception of screening (Visit 1) which will be nonfasting.

[k] When clinically indicated for hemolytic anemia.

[l] Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only assayed (analyzed) if the patient had a positive ADA on Day 90.

[m] nAb is collected for all patients, though will only be analyzed by central lab if patient is positive for ADA at Day 90.

[n] Only CCI collected during safety follow-up visits.

[o] Urine pregnancy test will be collected on WOCBP prior to study drug administration on dosing visits.

[p] Cryptosporidium test is required at screening. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

3.5 End of Study

End of Study (Individual Patient): A patient is considered at the end of study if he/she has withdrawn, prematurely discontinued, or completed all of the study procedures including the last visit.

End of Study (End of trial): The end of the study is defined as the date of the last visit of the last patient in the study globally, or the date of which the last patient withdraws or discontinues if all prior enrolled patients have already completed/withdrawn.

4 POPULATION

4.1 Participant Recruitment

Advertisements approved by the IRB, and investigator databases, may be used as recruitment procedures for adult men and women with moderately to severely active SLE.

4.2 Number of Patients

Approximately 186 male and female patients are planned for enrollment, but may be adjusted upward according to the dropout (noncompliance) rate, which will be monitored in a blinded fashion in an ongoing basis. Approximately 30 patients will be randomized for the MAD Phase 1b portion, and approximately 156 additional patients will be randomized in the POC Phase 2 portion. Note that approximately 24 dropouts are assumed.

4.3 Patient Screening

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular individual. Patient eligibility will be reviewed and confirmed by the medical monitor or designee prior to randomization. Screening assessments (see the Schedule of Assessments [Section 3.4]) for this study must be performed between Day -28 and Day -1.

4.4 Inclusion Criteria

Patients who meet the following criteria will be considered eligible to participate in this clinical study:

1. Men and women, ages 18 to 70 years, inclusive
2. Patients must be mentally capable of giving consent and there must be evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study
3. Patients must have SLE as defined by meeting 4 of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE (with at least 1 clinical and 1

immunologic criterion or Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies), either sequentially or simultaneously

4. At screening, patients must have at least 1 of the following:
   a. Elevated ANA ≥ 1:80 via immunofluorescent assay at the central laboratory
   b. Positive anti-dsDNA or anti-Smith (Sm) above the normal level as determined by the central laboratory
   c. C3 or C4 levels below normal as determined by central lab
5. At screening, the SLE Disease Activity Index 2000 (SLEDAI-2K) must be ≥ 6, including points from at least 1 of the following clinical components:
   a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis
      i. Excluding parameters which require central laboratory results: hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia
      ii. Points from lupus headache and organic brain syndrome will also be excluded
6. On Day 0, the SLEDAI-2K must be ≥ 6, including points from at least 1 of the following clinical components:
   a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis
      i. Excluding parameters which require central laboratory results: hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia
      ii. Points from lupus headache and organic brain syndrome will also be excluded
7. Patients must have at least 1A or 2Bs from the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer:
   a. BILAG A or B score in the mucocutaneous body system
   b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis defined as follows:
      i. "BILAG A:" Severe Arthritis, (BILAG item number 41), manifested by observed active synovitis in ≥ 2 joints with marked loss of functional range of movements and significant impairment of basic activities of daily living that has been present on several days cumulatively over the past 30 days, including at the time of the screening visit. See APPENDIX 5 for additional detailed specifications.
         - Basic ADLs are defined as the following activities which require assistance or assistive devices, (at least 1 must be present and documented in source):

- Ambulation, toileting, grooming- including bathing and dressing; feeding oneself

ii. "BILAG B:" Moderate Arthritis, Tendonitis or Tenosynovitis, (BILAG item number 42), defined as tendonitis/tenosynovitis, or active synovitis in ≥ 1 joint, (observed or throughout history), with some loss of functional range of movements manifested by effects on instrumental ADLs such as:

- Cooking, driving, using the telephone or computer, shopping, cleaning, etc., and has been present on several days over the last 30 days, and is present at the time of the screening visit

If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in the other body systems for a total of 2 "B" BILAG body system scores

8. Patients must be currently receiving at least 1 of the following:
   a. Administration for a minimum of 12 weeks, and a stable dose for at least 56 days (8 weeks prior to signing consent) of the following permitted steroid-sparing agents:
      i. Azathioprine (AZA), mycophenolate mofetil or mycophenolic acid, chloroquine, hydroxychloroquine, or methotrexate (MTX)
   b. Prednisone (or prednisone-equivalent) cannot exceed 30 mg/day at screening for a patient to be eligible and must be stable at a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization) (see APPENDIX 3)
9. Women of childbearing potential (WOCBP; see Section 4.7 for full information regarding WOCBP, definition of menopause, and contraception):
   a. Must have a negative serum pregnancy test at screening. Urine pregnancy test must be negative prior to first dose
   b. Must not be breastfeeding
   c. Must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 52 weeks
10. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 52 weeks
11. Patients must demonstrate willingness and ability to comply with the scheduled study visits, treatment plans, laboratory tests, and other procedures

4.5 Exclusion Criteria

Patients presenting with any of the following will not be included in this study:

1. Drug-induced SLE, rather than "idiopathic" SLE

2. Other systemic autoimmune disease (eg, erosive arthritis, rheumatoid arthritis [RA], multiple sclerosis [MS], systemic sclerosis, or vasculitis not related to SLE)
    a. RA-Lupus overlap (Rupus), and secondary Sjögren syndrome are allowed
3. Any major surgery within 6 weeks of study drug administration, (Day 0), or any elective surgery planned during the course of the study
4. Any history or risk for tuberculosis (TB), specifically those with:
    a. Current clinical, radiographic, or laboratory evidence of active TB
    b. History of active TB
    c. Latent TB defined as positive QuantiFERON-TB Gold In-Tube (QFT-G) or other diagnostic test in the absence of clinical manifestations. Latent TB is not excluded if the patient has documented completion of adequate course of prophylactic treatment with regimen recommended by local health authority guideline, or the patient has started treatment with isoniazid, or other regimen recommended by local health authority guidelines for at least 1 month before Day 0 and continues to receive the prophylactic treatment during study until the treatment course is completed.
5. Active or unstable lupus neuropsychiatric manifestations, including but not limited to any condition defined by BILAG A criteria, with the exception of mononeuritis multiplex and polyneuropathy, which are allowed
6. Severe proliferative lupus nephritis, (WHO Class III, IV), which requires or may require induction treatment with cytotoxic agents or high dose CS
7. Concomitant illness that, in the opinion of the investigator, is likely to require additional systemic glucocorticosteroid therapy during the study, (eg, asthma), is exclusionary
    a. However, treatment for asthma with inhalational CS therapy is allowed
8. Use or planned use of concomitant medication outside of standard of baseline treatment for SLE from Day -1 or for any time during the study. (See Section 4.6 for prohibited concomitant medication)
9. Active and clinically significant infection (bacterial, fungal, viral, or other) within 60 days prior to first dose of study drug. Clinically significant is defined as requiring systemic parenteral antibiotics or hospitalization
10. A history of opportunistic infection, or a history of recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years
11. Chronic viral hepatitis including hepatitis B (HBV) and hepatitis C (HCV) unless patient received curative treatment for HCV and has a documented negative viral load, known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness
12. Cryptosporidium in the stool sample at screening
13. White blood cells (WBC) < 1,200/mm^3 (1.2×10^9/L) at screening
14. Absolute neutrophil count (ANC) < 500/mm^3 at screening

15. CD4+ count < 350/μL at screening
16. Platelets < 50,000/mm^3 (50 × 10^9/L) or < 35,000/ mm^3 (35 × 10^9/L) if related to SLE, at screening
17. Hemoglobin < 8 g/dL or < 7 g/dL at screening if related to SLE
18. Proteinuria > 3.0 g/day (3000 mg/day) at screening or equivalent level of proteinuria as assessed by protein/creatinine ratio (3 mg/mg or 339 mg/mmol)
19. Serum creatinine > 2.0 mg/dL at screening or creatinine clearance (CrCL) < 40 ml/minute based on Cockcroft-Gault calculation[39]:

    GFR = ([1 for male] or [0.85 for female]) × (140 – Age) × BW / (72 × Creatinine)

20. Serum ALT and/or serum AST > 2 × ULN at screening, unless explicitly related to lupus based on the investigator's judgment
21. Creatinine kinase (CK) > 3.0 × ULN at screening, unless it is related to lupus myositis
22. Direct bilirubin > 1.5 × ULN at screening (unless related to Gilbert's syndrome)
23. Any other laboratory test results that, in the opinion of the Investigator, might place a patient at unacceptable risk for participating in this study
24. History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody (eg, IgG protein) or molecules made of components of monoclonal antibodies
25. History substance and/or alcohol abuse or dependence within the past 1 year, at the investigator's judgment
26. History of cancer within the last 5 years (except for cutaneous basal cell or squamous cell cancer, or cervical cancer in situ resolved by excision)
27. Any other severe acute or chronic medical or psychiatric condition, including recent (within the past year) medical conditions (eg, cardiovascular conditions, respiratory illnesses) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study
28. Investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or patients who are employees of the sponsor or directly involved in the conduct of the trial
29. Currently participating in, or who have participated in other interventional (drug or device) clinical study within 30 days or 5 half-lives of baseline, whichever is longer
30. Recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4 or 5 on the C-SSRS
31. Current or pending incarceration

32. Current or pending compulsory detainment for treatment of either a psychiatric or physical (eg, infectious disease) illness

4.6 Concomitant Medications

Any medicinal product, prescribed or OTC, including herbal and other nontraditional remedies, is considered a concomitant medication. Patients should stay on stable regimen of other concomitant medications for the treatment of SLE (eg, analgesics, NSAIDs, statins, ACE inhibitors/ARBs and other antihypertensive drugs), unless changes in these treatments are clinically indicated. Use of any other drugs for non-SLE conditions, including over-the-counter medications and herbal preparations, should remain stable unless change or addition is clinically necessary. Discussion with the medical monitor prior to initiation of new medication is strongly recommended. Any concomitant therapies must be recorded on the eCRF. Prior and concomitant medication use will be recorded for the 30 days prior to screening until the last follow-up visit. In addition, historical treatment for SLE (including immunosuppressant, anti-malarial, corticosteroid, and/or biologic agent) will be recorded for the 48 weeks prior to screening in the eCRF.

4.6.1 Corticosteroid

Prior to randomization, oral CSs (prednisone or prednisone equivalent), may be used in accordance with the investigator's clinical judgment and best standard of care. See APPENDIX 3 for examples of equivalents.

A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day).

Tapering of steroids during the course of the study will be highly encouraged and should be evaluated at the protocol permitted visits (Day 0 through Day 60 and Day 120 through Day 150). Between Day 60 and Day 120, and between Day 150 and Day 210, oral CS doses must be held constant due to the endpoint evaluations occurring at Day 120 and Day 210.

- Once a patient has received the first dose of study drug (after Day 0), prednisone (or prednisone equivalent) dose is highly encouraged to continue tapering down as appropriate. The investigator should evaluate the prednisone dose at each visit and make the decision, within the protocol allowed windows.
    - Exception: Between Day 60 and Day 120, and between Day 150 and Day 210 (ie, within 60 days of primary and secondary endpoint assessments), oral CS doses must be held constant.

After Day 0 (first dose of study drug), a maximum of 1 oral CS "burst" for increased SLE disease activity will be allowed between Day 0 and Day 60, according to the following:

- The oral CS dose is allowed to increase to ≤ 40 mg/day of prednisone or equivalent, which must be tapered down to ≤ 10 mg/day within 2 weeks of initiation of the "burst"

- Alternatively, a single intramuscular (IM) dose of methylprednisolone (40 mg or equivalent) is permitted

- No increase of oral CS above baseline is permitted beyond Day 60

Treatment with inhalational CS therapy (eg, for asthma), or by any other route, but systemic administration, is allowed.

Treatment with intra-articular or intravenous CS is prohibited during the course of the study.

4.6.2 Other Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study drug administration and during the study are described below, and washout requirements are provided in APPENDIX 4. Medications taken within 30 days prior to screening must be recorded on the eCRF.

1. Prior exposure to BOS161721
2. Patients who have received treatment with anti-CD20 monoclonal antibodies within 24 weeks of screening; recovery of B cells (CD19+) must be documented (record absolute number of CD19+ B cells)
3. Patients who have received treatment with cyclophosphamide within the 24 weeks prior to screening
4. Patients who have received treatment with cyclosporine (with exception of ophthalmic use), any other calcineurin inhibitor or other immunosuppressive medication not specified in the inclusion criteria within 4 weeks for oral use or 8 weeks for topical use of screening
5. Patients who are currently receiving or are scheduled to receive plasmapheresis or lymphapheresis therapy, or have received such therapy within 24 weeks prior to screening
6. Patients who have received any live vaccines within 30 days of screening. Note: Furthermore, live vaccines should not be used during the course of the study and within the 2 months following last dose. Other inactivated vaccines such as tetanus, etc., may be used according to local guidelines during treatment period
7. Patients who are scheduled or anticipated to have elective surgery during the course of the study
8. Initiation of new immunosuppressant or anti-malarial agent is not permitted. Note: Dose reduction or replacement may be allowed due to intolerability or shortage for patients on a stable dose prior to study initiation

4.7 Women of Childbearing Potential

WOCBP is defined as any woman who has experienced menarche and who has not undergone surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) and is not postmenopausal.

See Section 4.7.2 for detailed information regarding contraceptive requirements for WOCBP.

4.7.1 Determination of Menopause

Menopause is defined as at least 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. Women under the age of 55 years must have a documented serum FSH level > 40 mIU/mL at screening to confirm menopause.

4.7.2 Contraception

WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 52 weeks, due to the mean terminal ½ life of the study drug.

Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 52 weeks, due to the mean terminal ½ life of the study drug.

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

At a minimum, patients must agree to the use of 1 method of highly effective contraception from the following:

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by patients who are WOCBP or a male patient's WOCBP partner. Women who are partner of men who are patients participating in the study may use hormone-based contraceptives as 1 of the acceptable methods of contraception since they will not be receiving study drug.
- IUDs, such as ParaGard®
- Vasectomy
- Complete abstinence, defined as complete avoidance of heterosexual intercourse, is an acceptable form of contraception. Women who are abstinent while participating in the study must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the patient chooses to forego complete abstinence.

Azoospermic men and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP must still undergo pregnancy testing.

4.8 Deviation from Inclusion/Exclusion Criteria

Deviation from the inclusion or exclusion criteria will not be allowed. If deviation of inclusion/exclusion criteria is discovered after randomization, the investigator should contact the medical monitor for discussion. A decision will be made whether to allow a patient to continue or withdrawal from the study medication.

See Section 6.8 for additional details.

4.8.1 Patient Withdrawal and Replacement

See Section 5.5 for reasons for removal from the trial. Withdrawn patients may be replaced during the MAD part of the study after discussion between the principal investigator or designee and sponsor.

5 STUDY PROCEDURES

Refer to the eCRF completion guidelines for data collection requirements and documentation of study assessments/procedures.

5.1 Screening

Screening will be the same for both the MAD and POC portions of the study.

Screening will take place from Day -28 to Day -1, and assessments may be performed over more than 1 visit. Confirmation that the most current IRB/IEC approved informed consent form (ICF) has been signed must occur before any study-specific screening procedures are performed. Procedures that are part of standard of care are not considered study-specific procedures and may be performed prior to informed consent and used to determine eligibility.

All screened patients will be assigned a unique screening number. The screening number will include a 3-digit site number and a 4-digit sequential number to identify patients from the time of screening. Only eligible patients who are confirmed by central review as meeting the inclusion/exclusion criteria, listed in Section 4.4 and Section 4.5 respectively, will be enrolled in the study. Screened patients who drop out of the clinical study before randomization will be recorded as screen failures. If rescreening occurs, the site will assign a new screening number.

Specific procedures at the screening visit will include:

- Medical history documentation
- Review of inclusion and exclusion criteria
  - Patient medical records must contain documentation of SLE diagnosis
  - C-SSRS
- Concomitant medication documentation
- Demographics
- Full physical examination
- Vital signs
- Chest x-ray (a prior x-ray can be used if taken within 12 weeks of screening date)
- Laboratory evaluations (non-fasting):
  - Hematology and clinical chemistry
  - Serology (Hepatitis B and C; HIV-1/2 combination)
  - TB test

- CRP
- Direct Coomb's test (if indicated for hemolytic anemia)
- CD4+ count, total IgG and IgM levels, plasma CCI , CCI [redacted]
- Serum pregnancy test (WOCBP)
- FSH (postmenopausal women under age 55 years)
- Spot urine for protein/creatinine ratio
- Urinalysis
- Stool sample

- 12-lead ECG
- SLE-related indices (BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, Physician's Global Assessment (PGA) of disease activity

Screening procedures are listed in the Schedule of Assessments (Section 3.4), and details are provided in Section 6.

5.1.1 Retesting During Screening Period

A single retesting of laboratory parameters and/or other assessments during the screening period is permitted (in addition to any parameters that require a confirmatory value) only if:

- medically indicated
- there is evidence a laboratory sample was mislabeled, indeterminate, inadequately processed, and/or deteriorated in transit to the central laboratory

Any new result will override the previous result (ie, the most current result prior to randomization) and is the value by which study inclusion/exclusion will be assessed, as it represents the patient's most current clinical state. This will also apply to patients who are being rescreened.

5.2 Enrollment/Randomization and Day 0 Treatment

Randomization should occur after patient eligibility for enrollment has been confirmed by the central eligibility review.

Prior to randomization, the study site should confirm that the patient still meets inclusion/exclusion criteria (especially SLE disease activity and treatment). The site will obtain a randomization number when registering the patient in IWRS. All patients will receive BOS161721 or placebo according to the kit number assigned by the IWRS randomization scheme.

After randomization, procedures include:

- PROs: CCI [redacted]
- C-SSRS
- Laboratory evaluations (fasting):

  - Hematology and clinical chemistry
  - Direct Coomb's test (if indicated for hemolytic anemia)
  - CD4+ count, total IgG and IgM levels, plasma CCI, plasma CCI and CCI whole blood for leukocyte immunophenotype
  - ADA
  - pSTAT3 (predose [trough] samples only in Phase 1b)
  - CCI
  - CCI
  - CCI
  - See Table 1 and Table 2 for details of PK sampling in the MAD and POC portions
  - Urine pregnancy test will be collected on WOCBP prior to study drug administration
  - Spot urine for protein/creatinine ratio
  - Urinalysis
- Concomitant medication documentation
- Documentation of AEs and SAEs (see Section 6.2.2.5 on SAE reporting requirements)
- Full physical examination
- Vital signs (prior to PK blood draw, predose, and at 1 and 2 hours postdose on Day 0)
- 12-lead ECG (prior to PK blood draw)
- SLE-related indices (BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, PGA)
- SLICC/ACR damage index
- Study drug administration:
  - Administration of BOS161721 or placebo will take place on-site, and is discussed in Section 7.3
- Injection site reaction assessment performed at 2 hours postdose

Procedures on Day 0 are listed in the Schedule of Assessments (Section 3.4), and details are provided in Section 6.

All patients who are enrolled, randomized, and receive study drug, or undergo study-specific procedures should reconsent with any updated versions of IRB/IEC approved informed consents during study participation as applicable and per institutional guidelines.

5.3 Treatment Period/Follow-Up Visits

The following procedures will be performed as indicated in the Schedule of Assessments (Table 1 and Table 2). See Schedule of Assessment tables for allowable windows for each visit.

- Targeted physical examination
- Vital signs (prior to PK blood draw)
- Concomitant medication documentation
- Documentation of AEs and SAEs (see Section 6.2.2.5 on SAE reporting requirements)
- PROs: CCI

- Urine pregnancy tests will be collected on WOCBP prior to study drug administration
- Injection site reaction assessments will be performed predose
- Direct Coomb's test (if indicated for hemolytic anemia)
- Spot urine for protein to creatinine ratio
- Urinalysis
- CCI
- Plasma CCI
- PGA, BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, and the CLASI will be completed
- SLICC/ACR Damage Index will be completed at Day 180
- C-SSRS
- ECGs prior to PK blood draw
- See Table 1 and Table 2 for details of PK sampling in the MAD and POC studies, respectively
- Fasting hematology and chemistry assessments
- The CD4+ count and total IgG and IgM levels
- Plasma CCI & CCI, ADA, and whole blood for leukocyte immunophenotype
- pSTAT3 (predose [trough] samples only Phase 1b)
- nAb will be analyzed by central lab if patient is positive for ADA
- CRP
- CCI

5.4 Safety Follow-Up Visits

Safety follow-up visits will take place at Days 210, 240, and 270. These visits will include the following assessments as indicated in the Schedule of Assessments (Table 1 and Table 2):

- PROs: CCI
- Documentation of AEs and SAEs (see Section 6.2.2.5 on SAE reporting requirements)
- Injection site reactions
- Targeted physical examination
- Vital signs (prior to PK blood draw)
- Spot urine for protein/creatinine ratio and urinalysis
- Concomitant medication documentation
- BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, and PGA
- Fasting clinical laboratory assessments (hematology and clinical chemistry)
- Direct Coomb's test (if indicated for hemolytic anemia)
- Plasma CCI
- CCI
- 12-lead ECG (prior to PK blood draw)

- CRP
- ADA
- CCI [redacted]
- Urine pregnancy test
- See Table 1 and Table 2 for details of PK sampling in the MAD and POC portions, respectively

5.5 Premature Discontinuation

While patients are encouraged to complete all study evaluations, they may withdraw from the study at any time and for any reason. Every effort will be made to determine why any patient withdraws from the study prematurely. If the patient is unreachable by telephone, a registered letter, at the minimum, should be sent to the patient requesting him/her to contact the clinic.

All patients who withdraw from the study with an ongoing AE or SAE must be followed until the end of study or until the event is resolved or deemed stable, respectively.

If a patient withdraws prematurely after dosing, an end of treatment (EOT) visit should be performed (Day 180) and a last follow-up visit 90 days after dosing should be scheduled (Day 270). Safety follow-up visit procedures based on the Schedule of Assessments (see Section 5.4).

Patient participation may be terminated prior to completing the study and the reason recorded as follows:

- AE/SAE
- Protocol deviation
- Lost to follow-up
- Patient withdraws consent at their own request
- Investigator decision
- Decision by sponsor (other than AE/SAE, protocol deviation, or lost to follow-up)

Withdrawn patients may be replaced after discussion between the investigator or designee and sponsor.

6 ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, which may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and wellbeing of the patient. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. All protocol violations are entered directly into the eCRFs.

6.1 Medical History, Demographic and Other Baseline Information

The medical history comprises:

- General medical history
- Documentation of SLE diagnosis
- Historical medication therapy for SLE

The following demographic information will be recorded:

- Age
- Ethnic origin (Hispanic/Latino or not Hispanic/not Latino)
- Race (White, American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black/African American)
- Height (without shoes, in cm)
- Body weight, without shoes (kg)
- Body mass index (BMI [kg/m^2])

Other baseline characteristics will be recorded as follows:

- Concomitant medication documentation (see Section 4.6)
- Status of child bearing potential and contraception

6.2 Safety Assessments

6.2.1 Laboratory Assessments

Laboratory tests will be performed at times defined in the Schedule of Assessments (Section 3.4). Patient eligibility will be determined based on these tests at screening. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

A central laboratory will be used (with the exception of urine pregnancy tests) to ensure accuracy and consistency in test results. Laboratory/analyte results that could unblind the study (ie, biomarker results) will not be reported to investigative sites. Urinalysis will be performed on midstream, clean catch specimens. Some biomarkers listed above will not be drawn at some sites due to geographical logistical challenges. See the laboratory manual for details.

Endpoint analyses will be based on changes from baseline assessments at Days 120 and 210.

Table 3. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other Safety Tests
Hemoglobin	BUN	pH	Spot urine for protein/creatinine ratio
Hematocrit	Creatinine	Glucose (qual)	FSH[b]
RBC count	Glucose (fasting)	Protein (qual)	Urine pregnancy test[c]
RDW	Calcium	Blood (qual)	QuantiFERON®-TB Gold In-Tube test

Table 3. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other Safety Tests
MCV	Sodium	Ketones	(QFT-G)[d]
MCH	Potassium	Nitrites	Serology[d] (Hepatitis B and C; HIV-1/2 combination)
MCHC	Chloride	Leukocyte esterase	
Platelet count	Total CO_2 (bicarbonate)	Urobilinogen	Stool sample[e]
WBC count	AST, ALT	Urine bilirubin	Serum pregnancy test
CD4+ count	Total bilirubin	Microscopy[a]	
Total neutrophils (Abs)	Alkaline phosphatase		
	Creatine kinase		
Eosinophils (Abs)	Uric acid		
Monocytes (Abs)	Albumin		
Basophils (Abs)	Total cholesterol (fasting)		
Lymphocytes (Abs)	LDL-C (fasting)		
	HDL-C (fasting)		
	Triglycerides (fasting)		
	Total protein		
	PT/INR		

	Additional Tests[f] (potential Hy's Law)	Immunogenicity, PD and other Biomarker Tests
	AST, ALT (repeat)	ADA
	Total bilirubin (repeat)	nAb[g]
	Albumin (repeat)	pSTAT3 (predose [trough] samples only in Phase 1b)
	Alkaline phosphatase (repeat)	Total IgG & IgM
	Direct bilirubin	Plasma CCI
	Indirect bilirubin	Plasma CCI & CCI
	GGT	Whole blood for leukocyte immunophenotype
	Prothrombin time/international normalized ratio (repeat)	CCI
	Creatine kinase (repeat)	CCI
		CCI
		CRP
		Direct Coomb's test[h]

Abbreviations: Abs = absolute; ADA = anti-drug antibody; ALT = alanine aminotransferase; CCI ; CCI ; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C = complement; CD4+ = cluster of differentiation 4; CRP = C-reactive protein; dsDNA = double-stranded deoxyribonucleic acid;; FSH = follicle stimulating hormone; GGT = gamma-glutamyltransferase; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ration; IL-21 = interleukin 21; LDL-C = low-density lipoprotein cholesterol; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = Mean corpuscular volume; nAb = neutralizing antibody; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; PT = prothrombin time; qual = qualitative; RBC = red blood cell; RDW = RBC distribution width; SAE = serious adverse event; SC = subcutaneous; CCI ; TB = tuberculosis.

a. On all urine samples.
b. At screening only, in women who are amenorrheic for at least 12 consecutive months and under 55 years old.
c. For WOCBP.

Table 3. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other Safety Tests

[d.] Screening only.
[e.] At screening, and if a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.
[f.] Additional testing for potential Hy's Law cases only (See Section 6.2.2.6.3).
[g.] If patient is positive for ADA.
[h.] If clinically indicated for hemolytic anemia.

6.2.1.1 Pregnancy testing

For WOCBP, a serum pregnancy test will be performed at screening. Following a negative serum pregnancy result at screening, appropriate contraception must be commenced or continued and a further negative urine pregnancy test results will then be required at the baseline visit before the patient may receive the investigational product. Urine pregnancy tests will also be routinely repeated at study drug administration visits prior to study drug administration, at the last follow up visit day (Day 270) and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive pregnancy test or confirmed pregnancy, the patient will be discontinued from study drug, an EOT visit should be performed (Day 180), and a last follow-up visit 90 days after last dose should be scheduled (Day 270). Safety follow-up visit procedures (see Section 5.4) are specified in the Schedule of Assessments (see Section 3.4).

See Section 6.2.2.7.1 for information on reporting of pregnancies as AEs/SAEs during the study.

6.2.1.2 Tuberculosis Screening

During the screening period, it must be determined and documented that a patient does not have evidence of active or latent or inadequately treated TB per the exclusion criteria (Section 4.5). The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

6.2.1.2.1 Mycobacterium Tuberculosis Testing Using QuantiFERON Test[40]

QuantiFERON®-TB Gold In-Tube (QFT-G) is an *in vitro* diagnostic test using a peptide cocktail simulating ESAT-6, CFP-10, and TB 7.7 proteins to stimulate cells in heparinized whole blood. Detection of INFγ performed by enzyme-linked immunosorbent assay (ELISA) is used to identify *in vitro* responses to these peptide antigens that are associated with Mycobacterium tuberculosis infection. QFT-G is an indirect test for M. tuberculosis infection (including disease) and is intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.

Test results will be reported as positive, negative, or indeterminate. A negative QFT-G test result is required to meet the inclusion criterion. In the case of an indeterminate result, repeat tests should be permitted for the purpose of determining eligibility of patients to enroll in this study. If a repeat test is indeterminate again, the patient is a screen failure. The procedure for

using this test and interpreting the results will be described fully in the laboratory manual, which will be provided to investigators.

6.2.2 Adverse Events

6.2.2.1 Definitions

An AE is defined as any untoward medical occurrence experienced by a study patient, whether or not considered drug related by the principal investigator.

AEs are unfavorable changes in a general condition, subjective or objective signs or symptoms, worsening of pre-existing concomitant disease, and clinically significant abnormality in laboratory parameters observed in a patient in the course of a clinical study.

Non-serious SLE manifestations or abnormal laboratory results related to SLE disease activity would not be recorded as AEs unless they meet the definition for SAEs (Section 6.2.2.5).

6.2.2.2 Recording of Adverse Events

AEs should be collected and recorded for each patient from the date of the first dose of study drug until the end of their participation in the study, including the safety follow up period.

AEs may be volunteered spontaneously by the study patient, or discovered by the study staff during physical examinations or by asking an open, nonleading question such as 'How have you been feeling since you were last asked?' All AEs and any required remedial action will be recorded on the Adverse Events eCRF and Safety Adverse Event Form. The details of the AE, date of AE onset, date of AE outcome, and action taken for the AE will be documented together with the principal investigator's assessment of the seriousness of the AE and causal relationship to the study drug and/or the study procedure.

All AEs should be recorded individually, using diagnostic terms where possible. If the diagnosis is not established, individual symptoms may be reported. The AEs will subsequently be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

6.2.2.3 Severity of Adverse Events

Each AE will be assessed by the principal investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03 criteria. [41] When changes in the severity (grade) of an AE occur more frequently than once a day, the maximum severity for the event should be noted for that day. Any change in severity of signs and symptoms over a number of days will be captured by recording a new AE, with the amended severity grade and the date (and time, if known) of the change.

6.2.2.4 Causality of Adverse Events

The principal investigator will assess the causal relationship between BOS161721 or placebo and the AE. One of the following categories (Table 4) should be selected based on medical judgment, considering the definitions below and all contributing factors.

Table 4. Causality Definitions

Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment (dechallenge[a]) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge[b] procedure if necessary.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (eg, concomitant disease, environmental factors, or other drugs or chemicals).

[a] Dechallenge: Upon discontinuation of a drug suspected of causing an AE, the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation (positive dechallenge), or the symptoms continue despite withdrawal of the drug (negative dechallenge). Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists (for example, as in bone marrow suppression, fixed drug eruptions, or tardive dyskinesia).

[b] Rechallenge: Upon re-administration of a drug suspected of causing an AE in a specific patient in the past, the AE recurs upon exposure (positive rechallenge), or the AE does not recur (negative rechallenge).

An unexpected adverse drug event is any adverse drug event for which the specificity or severity is not consistent with the current IP.

6.2.2.5 Seriousness of Adverse Events

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

- Results in death
- Is life threatening; this means that the patient was at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires hospitalization or prolongation in existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly or birth defect
- Is other important medical event (see below)

Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in inpatient hospitalization
- Development of drug dependency or drug abuse

Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (eg, elective surgery for a pre-existing condition that has not worsened) need not be considered SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'nonserious' according to the usual criteria.

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are associated with the use of the drug and are serious and unexpected.

6.2.2.6 Adverse Events of Special Interest

AEs of special interest in this study include the following:

1. Anaphylaxis and serious allergic reactions
2. Grades 2 to 5 injection site reaction, including erythema, pain, and induration (See APPENDIX 6)
3. Drug Induced Liver Injury (DILI) assessed following Hy's Law
4. Malignancy (not including basal cell carcinoma or squamous cell carcinoma of skin)
5. Opportunistic infections such as disseminated histoplasmosis, cryptococcosis, disseminated herpes simplex, disseminated tuberculosis, *Aspergillus* sp., *Candida albicans*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Cytomegalovirus*, *Histoplasma capsulatum*, *Isospora belli*, and *Polyomavirus JC polyomavirus*
6. Cryptosporidiasis

6.2.2.6.1 Anaphylaxis and Serious Allergic Reactions

Anaphylaxis will be defined according to the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria.[42] In the event of anaphylactic reaction or severe/serious hypersensitivity/allergic reaction, the patient must discontinue IP and emergency resuscitation measures implemented. In case of other mild to moderate hypersensitivity reaction, depending on the severity, the investigator may manage in accordance with the standard-of-care.

Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus, or flushing, swollen lips-tongue-uvula) and at least 1 of the following:
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
   a. Systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from the patient's baseline

6.2.2.6.2 Injection Site Reactions

Injection site reactions are to be captured and reported as AEs. These will include Grades 2 to 5 injection site erythema, pain, and induration (see APPENDIX 6), which are also captured as Adverse Events of Special Interest (See Section 6.2.2.6). The investigator should provide a clear description of the observed or reported AE including location and severity. All concomitant treatments used to treat injection site reactions should be recorded and captured in the eCRF, together with the AE of injection site reactions.

6.2.2.6.3 Potential Drug-Induced Liver Injury

Abnormal values in AST and/or ALT levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of DILI, and as potential Hy's Law cases, and should always be considered important medical events. If symptoms compatible with DILI precede knowledge of serum chemical test abnormalities, liver enzyme measurements should be made immediately, regardless of when the next visit or monitoring interval is scheduled. In some cases, symptoms may be an early sign of injury and although typically less sensitive than serum enzyme elevations, they may indicate a need for prompt serum testing. An increase in liver enzymes should be confirmed by a repeated test within 48 to 72 hours following the initial test, prior to reporting of a potential DILI event. Patients will continue to have weekly or biweekly liver enzyme measurements until resolution or levels return to baseline.

All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.2.2.7.2 for reporting details).

Potential DILI is defined as:

1. ALT or AST elevation > 3 × ULN

AND

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

AND

3. No other immediately apparent possible causes of ALT or AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

The patient should return to the investigational site and be evaluated as soon as possible, include laboratory tests, detailed history, and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, CK, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/International Normalized Ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

Study drug discontinuation is considered if there is marked serum AST or ALT elevation or evidence of functional impairment (as indicated by rising bilirubin or INR, which represent substantial liver injury) that is related to study drug. Discontinuation of treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5× ULN for more than 2 weeks

Discontinuation of treatment must occur if:

- ALT or AST >3 × ULN and (total bilirubin > 2 × ULN or INR > 1.5)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

6.2.2.6.4 Malignancy

The identification of a malignancy event will be made by the study site and communicated to the sponsor or designee. AEs should be reported as serious per the criteria in Section 6.2.2.5.

After the first dose of study drug, when there is a decision to biopsy a potentially malignant tumor, lymph node, or other tissue (with the exception of suspected basal cell/squamous cell), the investigator and/or consultant(s) should contact the sponsor clinicians or designee to discuss the issue and any decisions as soon as possible. Basal cell carcinoma or squamous cell carcinoma of skin is not considered an AE of special interest.

6.2.2.6.5 Specific Infections

Any diagnosis or suggested diagnosis of opportunistic infections such as disseminated histoplasmosis, cryptococcosis, disseminated herpes simplex, disseminated tuberculosis, *Aspergillus* sp., *Candida albicans*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Cytomegalovirus*, *Histoplasma capsulatum*, *Isospora belli*, or *Polyomavirus JC polyomavirus* will be recorded as AEs of special interest.

Cryptosporidiosis is also considered an AE of special interest. Patients will be evaluated for cryptosporidium in the stool at screening, and as clinically indicated (eg, watery diarrhea) during the study. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

6.2.2.7 Reporting of Adverse Events

AE reporting will be carried out in accordance with applicable local regulations, including regulatory agency and IRB reporting requirements.

Each AE is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate, and is further outlined in Section 6.2.2.7.2.

6.2.2.7.1 Reporting of Pregnancy

As information is available, a pregnancy diagnosed during the study will be reported within 24 hours to the sponsor via the Pregnancy Notification and Outcome Form, including pregnancy in female patients who received study drug and female partners of male study patients who received study drug. The pregnancy should be followed to term and/or outcome and this outcome should also be reported to the sponsor via the Pregnancy Notification and Outcome Form. Pregnancy itself is not regarded as an AE or SAE unless there is complication.

In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an AE or SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious

adverse events when the investigator assesses the neonatal death as related or possibly related to exposure to investigational product.

6.2.2.7.2 Reporting of Serious Adverse Events

The principal investigator is responsible for providing notification to the sponsor of any SAE via the Safety Adverse Event Form, whether deemed study drug related or not, that a patient experiences during their participation in this study within 24 hours of becoming aware of the event.

If an SAE is fatal or life threatening, notification to the sponsor must be made aware immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding cases. In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

The principal investigator will review each SAE and evaluate the intensity and the causal relationship of the event to the study drug. All SAEs will be recorded from the time of first dose of study drug through the safety follow-up period (up to Day 270). SAEs occurring after the final follow-up visit and coming to the attention of the principal investigator must be reported only if there is (in the opinion of the principal investigator) reasonable causal relationship with the study drug.

As a minimum requirement, the initial notification should provide the following information:

- Study number
- Patient number
- Details of the SAE (verbatim details are sufficient for immediate notification)
- Criterion for classification as ‘serious’
- Causality assessment (which may be updated in a follow-up report when sufficient information is available to make this classification)

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (eg, hospital reports, consultant reports, autopsy reports, etc), with the study patient’s personal identifiers removed. All relevant information obtained by the principal investigator through review of these documents will be recorded and submitted to the sponsor within 24 hours of receipt of the information. If a new Safety Adverse Event Form is submitted, then the principal investigator must sign and date the form. The sponsor may also request additional information on the SAE, or clarification of omitted or discrepant information from the initial notification, which the principal investigator or an authorized delegate should submit to the sponsor within 24 hours of the request as possible.

6.2.2.7.3 Reporting of Adverse Events of Special Interest

AEs of special interest will be reported to safety immediately or within 24 hours of the site becoming aware of the event and recorded as such on the Adverse Events eCRF and Safety Adverse Event Form.

Potential DILI will be reported based on specifications mentioned in Section 6.2.2.6.3.

Each AE of special interest is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate, and is further outlined in Section 6.2.2.7.2.

6.2.2.8 Follow Up of Adverse Events

All AEs will be followed up through the safety follow-up visits. All SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the event has resolved, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the principal investigator and medical monitor, until there is a satisfactory explanation for the changes observed, or until the patient is lost to follow-up.

See Section 6.2.2.7.1 for details related to follow-up of pregnancy. See Section 6.2.2.6.3 for details related to follow-up of potential DILI. See Section 6.2.2.6.4 for details related to follow-up of malignancy.

6.2.3 Vital Signs

Vital signs (blood pressure, heart rate, and body temperature) will be assessed as specified in the Schedule of Assessments (Section 3.4). Vital signs will be assessed on Day 0 at predose and at Day 0, 1 and 2 hours postdose, as well as on each of the scheduled visit days during the study (excluding PK-only site visits). Supine BP and heart rate recordings will be made after the patient has been recumbent and at rest ≥ 5 minutes. When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

6.2.4 12-Lead Electrocardiograms

ECG will be assessed as specified in the Schedule of Assessments (Section 3.4). ECG recording will initiate after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws, though timing will be such that PK draws are collected on their scheduled times where possible.

The ECG will include all 12 standard leads and a Lead II rhythm strip on the bottom of the tracing. The ECG will be recorded at a paper speed of 25 mm/second. The following ECG parameters will be collected: PR interval, QRS interval, RR interval, QT interval, and QT interval corrected for heart rate using Fridericia's formula (QTcF).

All ECGs must be evaluated by a qualified physician or qualified designee for the presence of abnormalities and will be captured electronically and retained for future evaluation if required, up to the time of the clinical study report (CSR) completion.

6.2.5 Physical Examinations

The full physical examination will be completed at screening and Day 0. It includes an assessment of general appearance and evaluation of head, eyes, ears, nose, mouth, throat, neck, thyroid, lymph nodes, and extremities, and dermatologic, respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurologic, and psychiatric systems.

The targeted (limited) physical examination will be completed at all other visits as indicated in the Schedule of Assessments (Section 3.4). It includes evaluation of patient complaints and SLE disease-related issues, and will exclude the genitourinary system.

6.2.6 C-SSRS

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed by Columbia University researchers for the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment. It is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening.[43]

The C-SSRS evaluation will be performed as specified in the Schedule of Assessments (Section 3.4). Patients with recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4, or 5 is exclusionary at screening will be excluded from the study. Patients with recent or active suicidal ideation or behavior at subsequent study visits will have responses to the C-SSRS reviewed in detail to assess patient risk, and appropriate consultative mental health services will be provided.

6.2.7 Injection Site Reactions

Patients will be monitored for local injection site reactions as specified in the Schedule of Assessments (Section 3.4). Local injection site reactions will be assessed at 2 hours postdose at baseline, and predose for each injection after baseline. Injection site reactions should be managed according to the standard of care. Injection site reactions, Grades 2 to 5, are to be reported as AEs of special interest (see Section 6.2.2.7.3).

6.2.8 Immunogenicity

The serum samples to measure the presence of ADA will be collected as specified in the Schedule of Assessments (Section 3.4). Blood samples (4 mL) to provide approximately 1.5 mL of plasma for anti BOS161721 antibody analysis will be collected into appropriately labeled tubes containing K_2EDTA. The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods. Blood samples for ADA analysis will be

collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only analyzed by a central lab if the patient had a positive ADA on Day 90.

After the first dose, if a patient tests positive in the validated confirmatory ADA assay, a sample from this patient will be further analyzed in the neutralizing antibody (nAb) assay by a central lab.

6.3 Efficacy Assessments

All efficacy assessments will be performed at times defined in the Schedule of Assessments (Section 3.4).

6.3.1 SLEDAI-2K

The SLEDAI-2K is a validated instrument that measures disease activity in SLE patients at the time of the visit and in the previous 30 days. It is a global index and includes 24 clinical and laboratory variables that are weighted by the type of manifestation, but not by severity. The total score falls between 0 and 105, with higher scores representing increased disease activity. The SLEDAI-2K has been shown to be a valid and reliable disease activity measure in multiple patient groups. A SLEDAI -2K of 6 or more generally represents moderately to severely active disease.[44]

6.3.2 BILAG 2004

The BILAG-2004 index is an organ-specific 97-question assessment based on the principle of the doctor's intent to treat. Only clinical features attributable to SLE disease activity are to be recorded and based on the patient's condition in the last 4 weeks compared with the previous 4 weeks. It will be scored as not present (0), improved (1), the same (2), worse (3), or new (4). Disease activity is graded separately for 9 body systems to 5 different grades (A to E) as follows: A ("Active") is very active disease, B ("Beware") is moderate activity, C ("Contentment") is mild stable disease, D ("Discount") is inactive now but previously active, and E ("Excluded") indicates the organ was never involved.[44] A shift from BILAG-2004 Grade A or B to a lower grade indicates a clinically relevant change in disease activity as the BILAG-2004 grades mirror the decision points for treatment interventions.

Only investigators that complete BILAG-2004 training will be allowed to perform the BILAG-2004 assessments. Preferably, the same investigator should evaluate the patient at each BILAG-2004 assessment from screening to study completion. The investigator must maintain documentation with descriptive details supporting the BILAG-2004 scoring (eg, chart, worksheet, clinic notes, and labs) at each visit.

See APPENDIX 5 for detailed specifications.

6.3.3 PGA of Disease Activity

The PGA is used to assess investigator's general impression on the patient's overall status of SLE disease activity via visual analogue scale (100 mm) with 0 being "very good, asymptomatic

and no limitation of normal activities" with 100 mm being "most severe possible disease ever seen in all SLE patients". PGA worsening is defined as an increase of ≥ 30 mm from baseline.

When scoring the PGA, the assessor should always look back at the score from the previous visit.

6.3.4 Composite Endpoints: SRI-4, SRI-5, SRI-6, and BICLA Response

6.3.4.1 SRI-4 Response

The SRI-4 is a composite index of SLE disease improvement that consists of scores derived from the SLEDAI-2K and the BILAG 2004 Index. Response based on the SRI-4 is defined by:

1) ≥ 4-point reduction in SLEDAI-2K global score, 2) no new severe disease activity (BILAG A organ score) or more than 1 new moderate organ score (BILAG B), and 3) no deterioration from baseline in the PGA by ≥ 30 mm. The SRI-4 response in patients with moderate to severe SLE is associated with broad improvements in clinical and patient-reported outcomes.[45]

6.3.4.2 SRI-5 and SRI-6 Response

Like the SRI-4, the SRI-5 and SRI-6 are composite indices of SLE disease improvement that consists of scores derived from the SLEDAI-2K and the BILAG 2004 Index. However, the SRI-5 and SRI-6 are computed with a minimal five-point or six-point improvement in SLEDAI-2K being required, respectively.[46]

6.3.4.3 BICLA Response

The BICLA is a responder index developed to measure response to therapy, and it includes scores from the BILAG, SLEDAI-2K, and PGA. BICLA response is defined as 1) at least 1 gradation of improvement in baseline BILAG 2004 scores in all body systems with moderate disease activity at entry (eg, all B [moderate disease] scores falling to C [mild], or D [no activity]); 2) no new BILAG A or more than 1 new BILAG B scores; 3) no worsening of total SLEDAI-2K score from baseline; 4) ≤ 10% deterioration in PGA score and 5) no treatment failure.[44] It is driven primarily by the BILAG, and has been used in Phase 2 and 3 mAb studies.[47]

For the endpoints of BICLA response at Days 210, 240, and 270, patient scores will be completed and response determined.

6.3.5 CLASI Response

The CLASI is a comprehensive tool for assessment of disease activity and damage in cutaneous lupus, shown to be valid, reliable, and sensitive to changes in disease activity.[48] Response is defined as 50% improvement from baseline in "A" or "B" scores. This assessment will be applied to all patients as all are required to have cutaneous disease activity.

For the secondary efficacy endpoint of CLASI response at Day 210, patient scores on MAD and POC studies will be compared with baseline for 50% improvement.

6.3.6 ACR-28 Joint Count

The ACR-28 joint count will evaluate the number of tender and swollen joints in the shoulder, elbow, wrist, hand, knee joints. Joints of the feet are excluded.

6.4 Other Variables

6.4.1 SLICC/ACR Damage Index

The SLICC/ACR damage index is a validated instrument to assess damage, defined as irreversible impairment, continuously persistent for 6 months (ascertained by clinical assessment), occurring since the onset of lupus, and it is based on a weighted scoring system. This index records damage occurring in patients with SLE regardless of cause, with demonstrated content, face, criterion, and discriminant validity.[49] It will be performed on Days 0 and 180.

6.4.2 PROs

Patients should be encouraged to complete the PROs at the clinic at the beginning of the study visit prior to any clinical assessments. A member of the staff should be available if a patient requires further instruction and to review the PRO questionnaires for completeness prior to leaving the clinic. The PROs include the CCI and the CCI and will be assessed as specified in the Schedule of Assessments (Section 3.4).

CCI [redacted][50]

CCI [redacted].

6.5 Pharmacokinetic Assessments

During the MAD Phase 1b (all sites) and POC Phase 2 (select sites only) parts of the study, blood samples for PK analysis of BOS161721 or placebo concentration will be collected according to Table 1 and Table 2.

Plasma concentrations of BOS161721 will be measured using a validated immunoassay. The PK parameters will be calculated from the plasma concentration actual time profiles.

6.6 Pharmacodynamic Assessments

Blood samples for PD parameters (plasma) will be collected at times indicated in the Schedule of Assessments (Section 3.4) for each of the following parameters:

- pSTAT3 (predose [trough] samples only Phase 1b)
- Antibodies: CCI [redacted]
- Plasma complement (CCI)

- Plasma CCI and CCI
- Whole blood for leukocyte immunophenotype

6.7 Pharmacokinetic/Pharmacodynamic Relationship

Evidence of any PK/PD relationships will be evaluated between BOS161721 plasma concentrations and the available PD endpoints and biomarkers.

6.8 Protocol Deviations

Protocol deviations will be documented during the study.

7 STUDY DRUG MANAGEMENT

7.1 Description

7.1.1 Formulation

CCI

CCI

Additional information regarding dose preparation will be provided in a separate Pharmacy Manual.

7.1.2 Storage

All supplies of BOS161721 or placebo must be stored in accordance with the manufacturer's instructions. BOS161721 or placebo will be stored in a securely locked area, accessible to authorized persons only, until needed for dosing.

Information regarding storage and dose preparation will be provided in a separate Pharmacy Manual.

7.2 Packaging and Shipment

Investigational medicinal products will be supplied by Boston Pharmaceuticals, Inc. Investigational medicinal products will be packaged and labeled according to applicable local and regulatory requirements.

7.3 Dose and Administration

Details of dosing are provided in Section 3.1.

Each unit dose will be prepared by a qualified staff member. The vials of investigational product (IP) will appear identical and will have a "blinded" label on the vials that will state CCI mg or placebo. When the site goes into the IWRS to request the patient kit(s), the IWRS will assign the appropriate number of kits (regardless of assignment to placebo or active treatment) per the dose (ie, CCI [redacted]). If a patient is randomized to the placebo arm, they will receive the matching number of kits.

The designated staff member (or designee under the direction of the designated staff member) will dispense BOS161721 or placebo for each patient according to the protocol, randomization list, and Pharmacy Manual, if applicable.

After receiving sponsor approval in writing, the investigational site is responsible for returning all unused or partially used BOS161721 or placebo to the sponsor or designated third party or for preparing BOS161721 or placebo for destruction via incineration.

Further details are found in a separate Pharmacy Manual.

7.4 Accountability

The Principal Investigator or designee is responsible for maintaining accurate accountability records of BOS161721 or placebo throughout the clinical study. The drug accountability log includes information such as, randomization number, amount dispensed and amount returned to the pharmacy (if any). Products returned to the pharmacy will be stored under the same conditions as products not yet dispensed. The returned products should be marked as 'returned' and kept separate from the products not yet dispensed.

All dispensing and accountability records will be available for sponsor review after database lock procedures are completed. During safety monitoring, the drug accountability log will be reconciled with the products stored in the pharmacy.

7.5 Prohibited Concomitant Therapy

Prohibited concomitant medications are discussed in Section 4.6 and APPENDIX 4 and will be listed as protocol violations if taken when not permitted.

7.6 Compliance

Dosing will be performed by trained, qualified personnel designated by the principal investigator. The date and time of dosing will be documented on each dosing day. Comments will be recorded if there are any deviations from the planned dosing procedures.

8 STATISTICS

The following analyses are planned:

- An IA will be performed during the last cohort of the MAD portion to determine dose selection for the POC part of the study.

- An additional analysis may be performed for the MAD portion of the study when all MAD patients have completed the safety follow-up or withdrawn from the study, and prior to final analysis. Data from the POC part of the study will be excluded from this additional analysis.
- The final analysis will be performed when all patients have completed the POC safety follow-up or withdrawn from the study.
- Safety analyses will be performed for DMC reviews throughout the study to evaluate dose escalation decisions and accumulating safety data. The frequency and details of the content and format of the safety review meetings will be described in the SAP and/or DMC charter.

All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9 or higher.

The following standards will be applied for the analysis unless otherwise specified. Data will be summarized descriptively by treatment and overall for each study portion. For the MAD part of the study, BOS161721 will be summarized overall and by each dose level, and placebo patients from each cohort will be combined. Select parameters may be summarized using patients from both study parts. Statistical testing will be performed on data from the Phase 2 portion only.

Continuous data will be summarized using number, mean, standard deviation (SD), 25th and 75th percentiles, minimum, median, and maximum. Categorical data will be summarized by treatment group using frequency tables (number and percentage). Time to event data will be summarized using counts, medians, 25th and 75th percentiles, and standard error. All data will be listed for all patients.

Statistical inference will be based on a 2-tailed test with an overall 0.10 level of significance, unless stated otherwise.

The effects of noncompliance, background therapy use, treatment discontinuations, premature withdrawal from study and covariates will be assessed to determine the impact on the general applicability of results from this study. Exploratory analyses of the data will be conducted as deemed appropriate. Any deviations from the planned analyses will be described and justified in the final integrated CSR.

Protocol deviations and prohibited medications that define medication failures will be fully assigned and documented before database lock and unblinding.

Further details of the analysis, including the handling of missing data, transformations and other data handling procedures will be provided in the SAP.

8.1 Sample Size

Sample size in the Phase 1b part of the study is based on operational consideration.

The sample size in the Phase 2 portion is based on the primary endpoint, SRI-4 Response at Day 210. Approximately 156 additional patients will be randomized in a 2:1 ratio to BOS161721 versus placebo to achieve 132 evaluable patients in the FAS. This assumes

24 patients will drop prior to having received treatment and an evaluable post-baseline efficacy measure. Enrollment and randomization will be monitored in a blinded fashion and increased if needed to ensure at least 132 patients are randomized into the FAS.

A total of 132 patients randomized provides more than 80% power to detect a treatment difference of 25% in SRI-4 response rates at Day 210, based on a targeted 2-sided significance level of 10% and using a 2-sided Pearson's chi-squared test. This assumes of a response rate of 65% for BOS161721 and 40% for placebo, where missing data at Day 210 is carried forward from most recent non-missing result and patients are treated as a non-responder if a prohibited medication defined as a medication failure occurs.

8.2 Statistical Methods

8.2.1 Analysis Populations

The primary efficacy analysis will be based on the FAS, defined as all patients who receive at least 1 dose of study treatment and at have least 1 evaluable post-baseline efficacy evaluation. FAS analyses will be conducted on the basis of the randomized treatment.

A per protocol (PP) analysis set may be defined to exclude major protocol violations from the efficacy analysis. The PP Population will include all patients from the FAS except those with major violations to the protocol deemed to impact the analysis of the primary endpoint. These violations will be identified based on blinded data prior to study unblinding. PP analyses will be conducted on the basis of the randomized treatment.

Safety analyses will be based on the safety analysis set (SS), defined as all patients who receive at least 1 dose of study treatment. Safety analyses will be conducted on the basis of actual treatment received.

Pharmacokinetic analysis will be conducted on the PK analysis set, defined as the FAS with sufficient concentration data for the calculation of PK parameters.

8.2.2 Demographics and Baseline Characteristics

Baseline and patient characteristics will be summarized using all randomized patients.

8.2.3 Primary Efficacy Endpoint(s)

The proportion of patients who achieve a SRI-4 response at Day 210 will be assessed via Pearson's chi-squared analysis. The primary efficacy endpoint will be analyzed using the FAS and if needed repeated in the PP analysis set. Missing values will be addressed by employing a last observation carried forward (LOCF) analysis. Other imputation methods may be employed as a sensitivity analysis and will be described in the SAP. Additional analyses exploring impact of baseline factors such as baseline disease severity, race, and other characteristics may be performed.

Patients that received prohibited medications or unallowable CS usage as described in Section 4.6 will be considered "medication failures" and will be treated as non-responders for the

primary efficacy analysis. The determination of medication failures will be reviewed using blinded data and finalized prior to unblinding.

The superiority of BOS161721 relative to placebo will be evaluated. If the proportion of SRI-4 responders for the selected POC dose in BOS161721 arm is higher than that of the placebo arm, then BOS161721 will be considered superior to placebo if the 2-sided p-value is less than 0.10. Secondary and exploratory endpoints for this POC portion will be evaluated based on the same statistical hypothesis.

8.2.4 Secondary Efficacy Endpoint(s)

Binary efficacy endpoints will be assessed via Pearson's chi-squared analysis. Continuous efficacy endpoints will be assessed via analysis of variance (ANOVA) or analysis of covariance (ANCOVA) and treatment will be compared using the F-test. Repeated measures mixed models may be performed to evaluate data collected at each visit and overall. Time-to-event endpoints will be assessed via Kaplan-Meier methodology and treatment will be compared using the log-rank test. The secondary efficacy endpoints will be analyzed on the FAS and if needed repeated in the PP analysis set. Details including handling of missing data and "medication failures" will be available in the SAP.

8.2.5 Analysis of Safety

8.2.5.1 Safety Analysis

Safety analyses will be performed on the SS. AE data will be coded to system organ class and preferred term using MedDRA. The number and percentage of patients experiencing any treatment-emergent AE, overall, and by system organ class and preferred term, will be tabulated. Treatment-emergent AEs will also be summarized by severity and relationship.

Concomitant medications will be coded using the WHO Drug dictionary. Observed values and changes from baseline in vital signs, ECG readings, and hematology and clinical chemistry parameters will be summarized at each individual visit.

8.2.6 Pharmacokinetic and Pharmacodynamic Data

8.2.6.1 Analysis of Pharmacokinetic Data

PK parameters will be calculated from concentration data collected during the MAD Phase 1b portion of the study using non-compartmental analysis and include the following:

- C_{max}, T_{max}, AUC, $t_{½}$, CL, V_d

The PK parameter data will be listed and summarized descriptively in tabular format.

If data permit, the following analyses will be performed for plasma BOS161721 concentration data:

- A listing of all plasma BOS161721 concentrations by patient at actual times post dose;

- A descriptive summary of plasma BOS161721 concentrations. Summary statistics of geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum will be tabulated by study days with PK assessments.

8.2.6.2 Analysis of Pharmacodynamic Data

The PD parameter data will be listed and summarized descriptively in tabular format.

Exploratory analyses examining the relationship between PD parameters and PK concentration and PK parameters will be performed.

8.2.6.3 Population Pharmacokinetic Analysis or PK/PD Modeling

Plots of individual patient values for each relevant PD parameter on Y-axis and each relevant PK parameter on X-axis will be examined for relationship. If relationships are revealed by these diagnostic plots, PK and PD data from this study may be analyzed using modeling approaches to describe the relationship and may also be pooled with data from other studies to investigate any association between BOS161721 exposure and biomarkers or significant safety endpoints.

8.3 Interim Analysis and Power

One IA is planned for this study and will be conducted at the time of the POC decision for dose selection.

Since there is no IA during the POC part of the study, there is no impact on the type 1 error.

9 ETHICS AND RESPONSIBILITIES

9.1 Good Clinical Practice

The procedures set out in this protocol are designed to ensure that the sponsor and the principal investigator abide by the principles of the International Council for Harmonisation (ICH) guidelines on GCP and the Declaration of Helsinki (Version 2013). The clinical study also will be carried out in the keeping with national and local legal requirements (in accordance with US IND regulations [21 CFR 56]).

9.2 DMC

This study will use an external DMC. The DMC is an independent committee established to provide oversight of safety considerations in study and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of enrolled patients and those yet to be recruited to the trial as well as for the continuing validity and scientific merit of the study results. The DMC is charged with assessing such actions in light of an acceptable benefit/risk profile for BOS161721. The recommendations made by the DMC (ie, dose escalation, etc.) will be forwarded to the sponsor for final decision. The sponsor will forward such decisions, which may include summaries of safety data which are not endpoints, to regulatory authorities, as appropriate.

The sponsor will appoint a DMC for the periodic review of available study data. The DMC is an independent group of experts that advises the sponsor and the study investigators. The members of the DMC serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DMC are to (1) periodically review and evaluate the accumulated study data for participant safety, study conduct, and progress, (2) make recommendations to the sponsor concerning the continuation, modification, or termination of the study and (3) suggest dose for POC portion of the study as described in Section 3.1.1.3.

The DMC considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. The DMC is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking (unblinding), and voting procedures prior to initiating any data review. The DMC is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

The DMC will have access to unblinded treatment information during the clinical trial. Details regarding management and process of this committee are found in the DMC Charter.

The DMC may recommend termination of BOS161721 treatment arm or the entire BOS161721 MAD/POC trial for any safety concern that is felt to outweigh potential benefits. The recommendation must be supported by the sponsor as indicated in the DMC Charter.

9.3 Institutional Review Board/Independent Ethics Committee

Independent Ethics Committees/IRB must meet the guidelines set out by the U.S. Food and Drug Administration (FDA) and conform to local laws and customs where appropriate. Written IRB/IEC approval for the protocol and the signed ICF must be obtained and transmitted to Boston Pharmaceuticals or representative before the study can be initiated. The IRB/IEC must be informed of and approve all protocol amendments. The investigator will ensure that this study is conducted in full conformance with all applicable local and regional laws and regulations. The complete text of the World Medical Association Declaration of Helsinki is given in APPENDIX 2.

9.4 Informed Consent

Before each patient undergoes any protocol required assessments or procedure, the written informed consent will be obtained according to the regulatory and legal requirements of the participating country. As part of this procedure, the principal investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study patient should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. The principal investigator or designee will provide the sponsor with a copy of the IRB-approved ICF prior to the start of the study.

The informed consent document must be signed and dated; 1 copy will be handed to the patient and the principal investigator will retain a copy as part of the clinical study records. The principal investigator will not undertake any investigation specifically required for the clinical

study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

If the informed consent document is revised, it must be reviewed and approved by the responsible IRB/IEC. Patients currently enrolled may need to sign this revision (based on IRB/IEC requirements) and all future patients enrolled in the clinical study will be required to sign this revised ICF.

9.5 Records Management

The principal investigator will ensure the accuracy, completeness, and timeliness of the data reported to the sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The principal investigator or designee will cooperate with the sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The principal investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each patient receiving BOS161721 or placebo.

The principal investigator will allow sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB to have direct access to all documents pertaining to the study.

Electronic case report forms are required and should be completed for each randomized patient. It is the principal investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported on the patients' eCRF. Electronic case report forms should be completed in a timely fashion to support the study timelines. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status. The principal investigator or designated representative should complete and the principal investigator should verify the source documents as the information is collected. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The principal investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes.

9.6 Source Documentation

The documents that will form the source data for the clinical study (eg, patient charts, laboratory reports) must be defined and documented in the in-house study master file prior to the start of the study. Data on the eCRFs which will be checked against source data during monitoring visits must also be defined and documented in the in-house study master file including the percentage of each of the source data to be verified and the percentage of patients' eCRFs to be monitored.

9.7 Study Files and Record Retention

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of BOS161721. However, these documents should be retained for a longer period if required by the applicable legal requirements.

10 AUDITING AND MONITORING

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and on-site visits. The study will be routinely monitored to ensure compliance with the study protocol and the overall quality of data collected. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor may periodically request review of the investigator study file to assure the completeness of documentation in all respects of clinical study conduct. The study monitor will verify that each patient has proper consent documentation from the patient and/or patient's authorized representative for study procedures and for the release of medical records to the sponsor, FDA, other regulatory authorities, and the IRB. The study monitor will also verify that assent was obtained for patients not capable of providing informed consent or that documentation is provided by the investigator explaining why the patient was unable to provide assent. The investigator or appointed delegate will receive the study monitor during these on-site visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies. On completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

Throughout the course of the study, the medical monitor will determine eligibility of all screened patients, will address any medical issues that might arise, clarify medical questions, review patient safety data (eg, AE/SAE, laboratory, and ECG), and partner with the study team in the overall study management. The study medical monitoring plan will document additional details of the study medical oversight and monitoring.

11 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by Boston Pharmaceuticals. A protocol change intended to eliminate an apparent

immediate hazard to patients may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. Boston Pharmaceuticals will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, and/or Boston Pharmaceuticals, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the patient and/or has an impact on the patient's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for patients enrolled in the study before continued participation.

12 STUDY REPORT AND PUBLICATIONS

Boston Pharmaceuticals is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

By signing the protocol, the principal investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the competent authorities will be notified of the principal investigator’s name, address, qualifications, and extent of involvement.

The principal investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted and obtained approval from the sponsor in advance.

13 STUDY DISCONTINUATION

Both Boston Pharmaceuticals and the principal investigator reserve the right to terminate the study at the investigator’s site at any time. Should this be necessary, Boston Pharmaceuticals or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the principal investigator will inform the IRB/IEC of the same. In terminating the study Boston Pharmaceuticals and the principal investigator will assure that adequate consideration is given to the protection of the patients’ interests.

14 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Boston Pharmaceuticals, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial or to comply with regulatory requirements. However, authorized regulatory officials, IRB/IEC personnel, Boston Pharmaceuticals, and its authorized representatives are allowed full access to the records.

Identification of patients and eCRFs shall be by initials, birthdate, or patient number. Documents that identify the patient (eg, the signed informed consent document) must be

maintained in confidence by the principal investigator. If required, the patient's full name may be made known to an authorized regulatory agency or other authorized official.

15 REFERENCES

1 Urowitz MB, Gladman DD. How to improve morbidity and mortality in systemic lupus erythematosus. Rheumatology 2000;39:238-44.

2 Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Morbidity and Mortality in Systemic Lupus Erythematosus During a 10-Year Period. Medicine 2003;82(5):299-308.

3 Pons-Estel GJ, Alarcón GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. Semin Arthritis Rheum. 2010;39(4):257. Epub 2009 Jan 10.

4 Kanta H, Mohan C. Three Checkpoints in lupus development: central tolerance in adaptive immunity, peripheral amplification by innate immunity, and end-organ inflammation. Genes and Immunity 2009;10:390-6.

5 Dall'Aqua WF, Kiener PA, Wu H. Properties of Human IgG1s Engineered for Enhanced Binding to the Neonatal Fc Receptor (FcRn). J Biol Chem. 2006 Aug 18, 281(33):23514-24.

6 Spolski R, Leonard WJ. The Yin and Yang of interleukin-21 in allergy, autoimmunity and cancer. Curr Opin Immunol. 2008a;20:295-301.

7 Asao H, Okuyama C, Kumaki S, Ishii N, Tsuchiya S, Foster D, et al. Cutting edge: the common gamma-chain is an indispensable subunit of the IL-21 receptor complex. J Immunol. 2001;167:1-5.

8 Habib T, Senadheera S, Weinberg K, Kaushansky K. The common gamma chain (gamma c) is a required signaling component of the IL-21 receptor and supports IL-21-induced cell proliferation via JAK3. Biochemistry. 2002;41:8725-31.

9 Spolski R, Leonard WJ. Interleukin-21: basic biology and implications for cancer and autoimmunity. Annu Rev Immunol. 2008b;26:57-79.

10 Puga I, Cols M, Barra CM, He B, Cassis L, Gentile M, et al. B-cell-helper neutrophils stimulate the diversification and production of immunoglobulin in the marginal zone of the spleen. Nat Immunol. 2011;13(2):170-80.

11 Costanzo A, Chimenti MS, Botti E, Caruso R, Sarra M, Monteleone G. IL-21 in the pathogenesis and treatment of skin diseases. J Dermatol Sci. 2010;60(2):61-6.

12 Avery DT, Bryant VL, Ma CS, de Waal Malefy R, Tangye SG. IL-21-induced isotype switching to IgG and IgA by human naive B cells is differentially regulated by IL-4. J Immunol. 2008;181:1767-79.

13 Rasmussen TK, Andersen T, Bak, RO, Yiu G, Sorensen CM, Stengaard-Pedersen K, et al. Overexpression of microRNA-155 increases IL-21 mediated STAT3 signaling and IL-21 production in systemic lupus erythematosus. Arthritis Research & Therapy 2015;17(154)

14 Ettinger R, Kuchen S, Lipsky PE. The role of IL-21 in regulating B-cell function in health and disease. Immunol Rev. 2008;223:60-86.

15 Caprioli F, Sarra M, Caruso R, Stolfi C, Fina D, Sica G, et al. Autocrine regulation of IL-21 production in human T lymphocytes. J Immunol. 2008;180(3):1800-7.

16 Yang L, Anderson DE, Baecher-Allan C, Hastings WD, Bettelli E, Oukka M, et al. IL-21 and TGF-beta are required for differentiation of human T(H)17 cells. Nature. 2008;454(7202):350-2.

17 Tangye SG, Ma CS, Brink R, Deenick EK. The good, the bad and the ugly - TFH cells in human health and disease. Nat Rev Immunol. 2013;13(6):412-26.

18 Fantini MC, Rizzo A, Fina D, Caruso R, Becker C, Neurath MF, et al. IL-21 regulates experimental colitis by modulating the balance between Treg and Th17 cells. Eur J Immunol. 2007;37(11):3155-63.

19 Peluso I, Fantini MC, Fina D, Caruso R, Boirivant M, MacDonald TT, et al. IL-21 counteracts the regulatory T-cell-mediated suppression of human CD4+ T lymphocytes. J Immunol. 2007;178(2):732-9.

20 Hippen KL, Bucher C, Schirm DK, Bearl AM, Brender T, Mink KA, et al. Blocking IL-21 signaling ameliorates xenogeneic GVHD induced by human lymphocytes. Blood. 2012;119(2):619-28.

21 Davis ID, Skrumsager BK, Cebon J, Nicholaou T, Barlow JW, Moller NP, et al. An open-label, two-arm, phase I trial of recombinant human interleukin-21 in patients with metastatic melanoma. Clin Cancer Res. 2007;13:3630-6.

22 Frederiksen KS, Lundsgaard D, Freeman JA, Hughes SD, Holm TL, Skrumsager BK, et al. IL-21 induces in vivo immune activation of NK cells and CD8(+) T-cells in patients with metastatic melanoma and renal cell carcinoma. Cancer Immunol Immunother. 2008;57(10):1439-49.

23 Karrich JJ, Jachimowski LC, Nagasawa M, Kamp A, Balzarolo M, Wolkers MC, et al. IL-21- stimulated human plasmacytoid dendritic cells secrete granzyme B, which impairs their capacity to induce T-cell proliferation. Blood. 2013;121(16):3103-11.

24 Lindner S, Dahlke K, Sontheimer K, Hagn M, Kaltenmeier C, Barth TF, et al. Interleukin-21-induced granzyme B-expressing B-cells infiltrate tumors and regulate T-cells. Cancer Res. 2013;73(8):2468-79.

25 Monteleone G, Caruso R, Fina D, Peluso I, Gioia V, Stolfi C, et al. Control of matrix metalloproteinase production in human intestinal fibroblasts by interleukin 21. Gut. 2006;55(12):1774-80.

26 Nakou M, Papadimitraki ED, Fanouriakis A, Bertsias GK, Choulaki C, Goulidaki N, et al. Interleukin-21 is increased in active systemic lupus erythematosus patients and contributes to the generation of plasma B-cells. Clin Exp Rheumatol. 2013;31(2):172-9.

27 Li Q, Liu Z, Dang E, Jin L, He Z, Yang L, et al. Follicular helper T-cells (Tfh) and IL-21 involvement in the pathogenesis of bullous pemphigoid. PLoS One. 2013;8(7):e68145.

28 Liu R, Wu Q, Su D, Che N, Chen H, Geng L, et al. A regulatory effect of IL-21 on T follicular helper-like cell and B-cell in rheumatoid arthritis. Arthritis Res Ther. 2012;14(6):R255.

29 Kang KY, Kim HO, Kwok SK, Ju JH, Park KS, Sun DI, et al. Impact of interleukin-21 in the pathogenesis of primary Sjögren's syndrome: increased serum levels of interleukin-21 and its expression in the labial salivary glands. Arthritis Res Ther. 2011;13(5):R179.

30 Terrier B, Geri G, Chaara W, Allenbach Y, Rosenzwajg M, Costedoat-Chalumeau N, et al. Interleukin-21 modulates Th1 and Th17 responses in gianT-cell arteritis. Arthritis Rheum. 2012a;64(6):2001-11.

31 Terrier B, Costedoat-Chalumeau N, Garrido M, Geri G, Rosenzwajg M, Musset L, et al. Interleukin 21 correlates with T-cell and B-cell subset alterations in systemic lupus erythematosus. J Rheumatol. 2012b;39(9):1819-28.

32 International Conference on Harmonisation. Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6 (R1). 2011.

33 Wang W, Wang EQ, Balthasar JP. Monoclonal Antibody Pharmacokinetics and Pharmacodynamics. Clin Pharm & Ther 2008; 84(5):548-58.

34 Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. Journal of Allergy and Clinical Immunology 2006;117:391–7.

35 Elsaesser H, Sauer K, Brooks DG. IL-21 is required to control chronic viral infection. Science. 2009;324(5934):1569-72

36 Kotlarz D, Zietara N, Uzel G, Weidemann T, Braun CJ, Diestelhorst J, et al. Loss-of-function mutations in the IL-21 receptor gene cause a primary immunodeficiency syndrome. J Exp Med. 2013;210(3):433-43.

37 Hunter PR, Nichols G. Epidemiology and clinical features of Cryptosporidium infection in immunocompromised patients. Clinical microbiology reviews. 2002;15(1):145-54.

38 Desjardins M, Mazer BD. B-cell memory and primary immune deficiencies: interleukin-21 related defects. Curr Opin Allergy Clin Immunol. 2013;13(6):639-45.

39 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.

40 Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, US: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a4.htm.

41 NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, available at https://evs.nci.nih.gov/ftp1/CTCAE/About.html.

42 Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. Journal of Allergy and Clinical Immunology 2006;117:391–7.

43 Posner K, Melvin G a, Stanley B, Oquendo M a, Gould M. Factors in the assessment of suicidality in youth. *CNS Spectr*. 2007;12(2):156-162.

44 Castrejon I, Tani C, Jolly M, Huang A, Mosca M. Indices to assess patients with systemic lupus erythematosus in clinical trials, long-term observational studies, and clinical care. Clin Exp Rheumatol 2014; 32(85):S85-95.

45 Furie R, Wang L, Drappa J, Illei G. Systemic Lupus Erythematosus (SLE) Responder Index [SRI(4)] Response Is Associated with Global Benefit in Patients with Moderate to Severe SLE [abstract]. *Arthritis Rheumatol.* 2016; 68 (suppl 10).

46 Thanou A, Chakravarty E, James JA, Merrill JT. Which outcome measures in SLE clinical trials best reflect medical judgment? Lupus Science & Medicine 2014;1:e000005. doi:10.1136/lupus-2013-000005.

47 Wallace DJ, Kalunian K, Petri MA, Strand V, Houssiau FA, Pike M,*et al.* Efficacy and safety of epratuzumab in patients with moderate/severe active systemic lupus erythematosus: results from EMBLEM, a phase IIb, randomised, double-blind, placebo-controlled, multicentre study. *Ann Rheum Dis* 2014;73:183-90.

48 Albrecht J, Taylor L, Berlin JA, Dulay S, Ang G, Fakharzadeh S. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): An Outcome Instrument for Cutaneous Lupus Erythematosus. J Invest Derm. 2005;125(5):889-94.

49 Stoll T, Seifert B, Isenberg DA. SLICC/ACR Damage Index is Valid, and Renal and Pulmonary Organ Scores are Predictors of Sever Outcome in Patients with Systemic Lupus Erythematosus. Br J Rheumatol. 1996;35:248-54.

50 CCI [redacted]

16 APPENDICES

APPENDIX 1 NAMES OF STUDY PERSONNEL

Sponsor:	Boston Pharmaceuticals 55 Cambridge Parkway Suite 400 Cambridge, MA 02142, USA
Medical Monitor:	PPD PPD PPD
Clinical Research Organizations:	PPD PPD PPD
Bioanalytical Laboratory:	PPD
Central Laboratory:	PPD PPD

APPENDIX 2 DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles
For
Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subject."

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic, and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility, and quality.

In current medical practice and in medical research, most prophylactic, diagnostic, and therapeutic procedures involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Research investigators should be aware of the ethical, legal, and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal, or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any SAEs. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a subject of the research, even though the subject has given consent.

Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the

subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

The subjects must be volunteers and informed participants in the research project.

The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the subject's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining

informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic, or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the subjects who are research subjects.

The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists.

At the conclusion of the study, every subject entered into the study should be assured of access to the best-proven prophylactic, diagnostic, and therapeutic methods identified by the study.

The physician should fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study must never interfere with the subject-physician relationship.

In the treatment of a subject, where proven prophylactic, diagnostic, and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the subject, must be free to use unproven or new prophylactic, diagnostic, and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health, or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

APPENDIX 3 COMMONLY USED CORTICOSTEROID EQUIVALENTS

Medication	Prednisone Dose Equivalence
Prednisone	1 mg
Cortisone	5 mg
Hydrocortisone	4 mg
Prednisolone	1 mg
Methylprednisolone	0.8 mg
Triamcinolone	0.8 mg
Budesonide	0.25 mg
Dexamethasone	0.16 mg
Bethamethasone	0.16 mg

APPENDIX 4 MEDICATION WASHOUT PERIODS

WASHOUT TIMES OF MEDICATIONS BASED ON 5 HALF-LIVES

Medication	**Discontinuing Prior to Signing Consent**
Abatacept (CTLA4Ig)	24 weeks
Alefacept	12 weeks
AMG 623 (blisibimod)	24 weeks
Anifrolumab	12 weeks
Atacicept (TACI-Ig)	12 weeks
Belimumab	24 weeks
Cyclophosphamide	24 weeks
Cyclosporine (except for CSA eye drops)	4 weeks for oral and 8 weeks for topical
Danazol	4 weeks
Dapsone	4 weeks
Eculizumab	12 weeks
Efalizumab	12 weeks
Epratuzumab	24 weeks
Intravenous globulin	4 weeks
Leflunomide	8 weeks (4 weeks for washout with cholestyramine)
Lenalidomide with cholestiramine	8 weeks
Lupuzor	12 weeks
Memantine	4 weeks
Natalizumab	24 weeks
Ocrelizumab	48 weeks (or 24 weeks with recovery of B cell)
Pimecrolimus	4 weeks
Plasmapheresis	24 weeks
Retinoids (oral or topical)	4 weeks
Rituximab	48 weeks (or 24 weeks with recovery of B cell)
Sirolimus	4 weeks
Tacrolimus	4 weeks
Thalidomide	8 weeks
Tocilizumab	12 weeks

APPENDIX 5 BILAG-2004 (STUDY-SPECIFIC MODIFIED CRITERIA)

CCI

APPENDIX 6 INJECTION SITE REACTION GRADING SCALE

Adverse event Injection site reaction	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection	Tenderness with or without associated symptoms (eg, warmth, erythema, itching)	Pain; Lipodystrophy; Edema; phlebitis	Ulceration or necrosis; Severe tissue damage; Operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	-
Rash maculopapular/Erythema /Induration Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally, and associated with pruritus.	Macules/papules covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness) Erythema covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness)	Macules/papules covering 10% - 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL; Erythema 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering > 30% BSA with or without associated symptoms; limiting self-care ADL Erythema covering > 30% BSA with or without associated symptoms; limiting self-careADL	-	-

ADL = active daily living

APPENDIX 7 PROTOCOL SUMMARY OF CHANGES

The protocol summary of changes was moved to the end of the protocol for easier readability.

Significant changes are described in the table below. Changed text is displayed for the first major occurrence only. Deleted text is presented in strikethrough format, and added text is presented in bold format.

Section	Description of Changes	Rationale
Global	Replace: Protocol Date and Version: 27 July 2018; V4.0 With: Protocol Date and Version: **23 January** 2019**;** V**5**.0	Administrative
Global	Change: Changed Version number from V4.0 (Amendment 3) to V**5**.0 (Amendment **4**) and Version date from 27 July 2018 to **23 January 2019**.	Administrative
Global	Made administrative and editorial (formatting, typographical, and grammatical) updates.	Administrative
PROTOCOL SUMMARY, Objectives and Endpoints, MAD Phase 1b, Secondary Objectives Section 2.1, Study Objectives and Endpoints, Phase 1b Multiple Ascending Dose, Secondary Objectives	Replace: • To characterize the PK of BOS161721 and select the optimal dose of BOS161721 based on safety, PK, and PD effects in patients with mild to moderate SLE. With: • To characterize the PK of BOS161721 and select the optimal dose of BOS161721 based on safety, PK, and PD effects in patients with moderate**ly to severely active** SLE.	Error in the previous protocol; text updated to "moderately to severely active."
PROTOCOL SUMMARY, Objectives and Endpoints, POC Phase 2, Safety Objectives Section 2.2, Study Objectives and Endpoints, Phase 2 Proof of Concept,	Replace: • To assess safety and tolerability of repeat doses of BOS161721 (20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment With: • To assess safety and tolerability of repeat doses of BOS161721 **at the chosen dose** administered SC in adult patients with moderately to severely active SLE on limited background standard	Error in the previous protocol; text updated to reflect the POC study and not the 3 doses used in the MAD Phase 1b study.

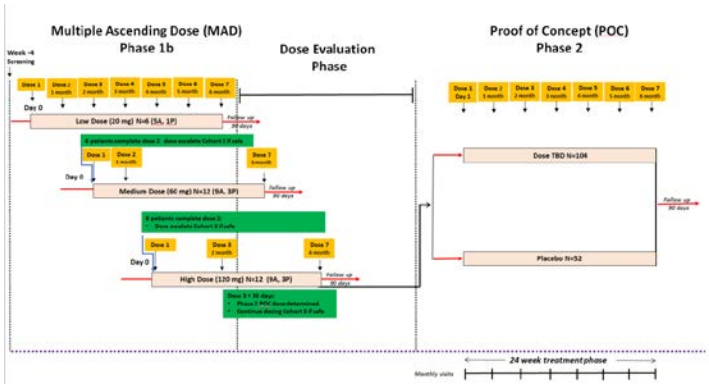
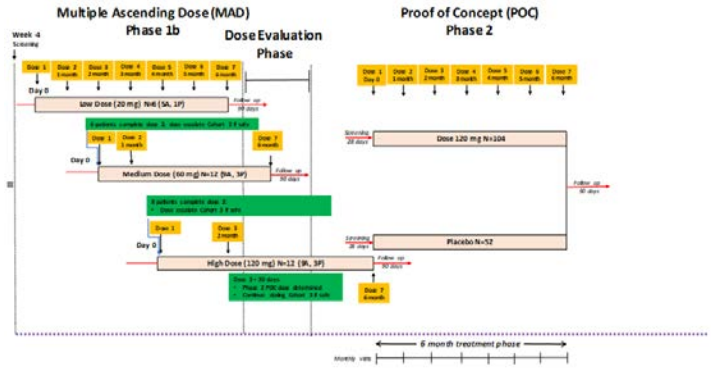
Section	Description of Changes	Rationale
Safety Objectives	of care treatment	
PROTOCOL SUMMARY, Objectives and Endpoints, POC Phase 2, Exploratory Objectives Section 2.2, Study Objectives and Endpoints, Phase 2 Proof of Concept, Exploratory Objectives	Replace: • CCI [redacted] With: • CCI [redacted]	CCI [redacted]
PROTOCOL SUMMARY, Study Design, Paragraph 5	Replace: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). One oral CS "burst" for increased SLE disease activity may occur during the study between Day 0 and Day 60. Tapering of steroids during the course of the study will be encouraged and should be evaluated at all visits. Tapering may occur after randomization except within 60 days of the primary (Day 210) and secondary (Day 120) endpoint assessments. Between Day 60 and Day 120, and between Day 150 and Day 210, oral CS doses must be held constant. With: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). One oral CS "burst" for increased SLE disease activity may occur during the study between Day 0 and Day 60. **Tapering of steroids during the course of the study will be highly encouraged and should be evaluated at the protocol permitted visits (Day 0 through Day 60 and Day 120 through Day 150). Between Day 60 and Day 120, and between Day 150 and Day 210, oral CS doses must be held constant due to the endpoint evaluations occurring at Day 120 and Day 210.**	Protocol clarification; text was reworded to better explain the importance of tapering when allowed and to reiterate when it is not.
PROTOCOL SUMMARY, Main Criteria for Inclusion and Exclusion, Inclusion Criteria, criteria 9, c and 10 Section 4.4, Inclusion Criteria, criteria 9, c	Replace: 9. Women of childbearing potential (WOCBP; see Section 4.7 for full information regarding WOCBP, definition of menopause, and contraception): c. Must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS161721 plus 30 days (duration of ovulatory cycle) for a total of 36 weeks after treatment completion	Protocol clarification.

Section	Description of Changes	Rationale
and 10	10. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of BOS161721 plus 90 days (duration of sperm turnover) for a total of 44 weeks after treatment completion With: 9. Women of childbearing potential (WOCBP; see Section 4.7 for full information regarding WOCBP, definition of menopause, and contraception): c. Must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus **52 weeks** 10. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus **52 weeks**	
PROTOCOL SUMMARY, Main Criteria for Inclusion and Exclusion, Exclusion Criteria criterion 2 Section 4.5, Exclusion Criteria, criterion 2	Replace: 2. Other systemic autoimmune disease (eg, erosive arthritis, rheumatoid arthritis [RA], multiple sclerosis [MS], systemic scleroderma, or vasculitis not related to SLE) With: 2. Other systemic autoimmune disease (eg, erosive arthritis, rheumatoid arthritis [RA], multiple sclerosis [MS], systemic **sclerosis**, or vasculitis not related to SLE)	Protocol clarification.
PROTOCOL SUMMARY, Statistical Considerations, Paragraph 2	Add: Two analyses are planned: 1) an interim analysis to select the POC dose based on the MAD data, and 2) a final analysis at study completion. Additionally, DMC safety analyses will be performed for each MAD cohort and throughout the POC to monitor patient safety as described in the DMC charter. **An additional analysis may be performed for the MAD portion of the study when all MAD patients have completed the safety follow-up, or withdrawn from the study, and prior to the final analysis. Data from the POC part of the study will be excluded from this additional analysis.**	Protocol clarification; text added to clarify that additional analysis would allow for flexibility if sponsor wanted to add an IA to review MAD only data.
Section 1.2.2.3, Clinical Studies, Paragraph 2	Replace: PK data from the SAD study demonstrates BOS161721 has an extended $t_{½}$ (provisional single dose data indicates this to be approximately 42-46 days) which supports evaluation of monthly dosing. With: **Final** PK data from the SAD study demonstrates BOS161721 has **a mean $t_{½}$ ranging from 80 to 87 days for doses of ≥ 30 mg in healthy subjects**.	Updated to reflect that terminal elimination half-life ($t_{½}$) is due to a full Healthy Volunteer Single Ascending Dose dataset.

Section	Description of Changes	Rationale
Section 1.2.3, Study Dose Selection, Paragraph 3	Replace: This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2 and 3 from the MAD portion (see Section 3.1.1.1). With: This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2 and 3 from the MAD portion (see **Section 3.1.2.1 for the chosen POC dose and justification).**	Respective added section to be referenced.
Section 1.2.5.1, Anaphylaxis and Serious Allergic Reactions, Paragraph 3	Delete: Based on the ~~limited~~ Phase 1 SAD study (BOS161721-01), anaphylaxis and serious allergic reactions in subjects who received BOS161721 was not observed.	Updated to reflect that all of the data is now acquired and 'limited' no longer applies; there were no changes to the safety results.
Section 1.2.5.3, Immune Complex Disease, Paragraph 2	Delete: Based on the ~~limited~~ Phase 1 SAD study (BOS161721-01), immune complex disease in subjects who received BOS161721 was not observed.	Updated to reflect that all of the data is now acquired and 'limited' no longer applies; there were no changes to the safety results.
Section 1.2.5.4, Infections, Paragraph 7	Delete: Based on the ~~limited~~ Phase 1 SAD study (BOS161721-01), infections in subjects who received BOS161721 was not observed.	Updated to reflect that all of the data is now acquired and 'limited' no longer applies; there were no changes to the safety results.

Section	Description of Changes	Rationale
Section 1.2.5.5, Malignancy	Delete: Based on the ~~limited~~ Phase 1 SAD study (BOS161721-01), malignancy in subjects who received BOS161721 was not observed.	Updated to reflect that all of the data is now acquired and 'limited' no longer applies; there were no changes to the safety results.
Section 1.2.5.6, Hepatic Function Abnormality, Paragraph 2	Delete: Based on the ~~limited~~ Phase 1 SAD study (BOS161721-01), hepatic function abnormality in subjects who received BOS161721 was not observed.	Updated to reflect that all of the data is now acquired and 'limited' no longer applies; there were no changes to the safety results.
Section 1.2.5.7, Failure of Vaccination, Paragraph 2	Replace: The effect of BOS161721 was evaluated in *in vivo* single dose studies in Cynomolgus monkey in which the animals received vaccination to T-cell dependent KLH antigen to stimulate a TDAR. These *in vivo* studies demonstrated that BOS161721 significantly inhibited B-cell proliferation and IgG antibody responses to the KLH protein antigen; however, it is worth noting that BOS161721 administration did not produce any remarkable changes in anti-KLH antibody data for IgM, IgG1, IgG3, and IgG4 or anti-tetanus toxoid (TT) antibody data for IgM, IgG, IgG1, or IgE during the dosing phase in the same study. With: The effect of BOS161721 was evaluated in *in vivo* single dose studies in Cynomolgus monkey in which the animals received vaccination to T-cell dependent KLH antigen to stimulate a TDAR. **These *in vivo* studies demonstrated that BOS161721 significantly inhibited B-cell proliferation and IgG antibody responses to the KLH protein antigen in a dose-dependent fashion; however, BOS161721 administration did not affect anti-tetanus toxoid antibody data for IgM, IgG, IgG1, or immunoglobulin E (IgE) during the dosing phase in the same study.**	Protocol clarification; text added for specificity.
Section 3.1.2.1, BOS161721 POC Dose Selection and Justification	Replace: 3.1.2.1 BOS161721 Dose The optimal dose is chosen based on MAD Phase 1b safety, tolerability, immunogenicity, and PK and PD data. The dose will be	Added text for POC dose and justification.

Section	Description of Changes	Rationale
	communicated by a letter to site investigators participating in the POC Phase 2 portion, and to the IRB/IEC. With: 3.1.2.1 BOS161721 **POC** Dose **Selection and Justification** **The dose for the POC portion of the study is 120 mg administered SC monthly (a total of 7 doses). The rationale for the BOS161721-02 Phase 2 POC dose selection was based on cumulative safety, tolerability, immunogenicity, PK, and PD data available from an interim analysis (IA) performed during the MAD Phase 1b portion of the trial.** **The data cut-off for this IA occurred on CCI and included all 6 patients and 7 doses from Cohort 1 (20 mg), 12 patients and 6 doses from Cohort 2 (60 mg), and 12 patients and 4 doses from Cohort 3 (120 mg).** **The safety analysis focused on incidence and severity of all AEs, SAEs, and pre-determined adverse events of special interest (see Section 6.2.2.6). The DMC and designated unblinded Boston Pharmaceuticals team met on CCI and did not identify any untoward safety signals at any BOS161721 dose levels.** **Because there were no safety, tolerability, or immunogenicity trends observed at the time of the IA, the Phase 2 POC dose selection was made based on available PK and PD data. pSTAT3 levels were assessed as the primary PD biomarker of IL-21R signaling levels. This is because IL-21R signaling, upon IL-21 binding, initially involves phosphorylation of JAK1/JAK3 which dissociate from the receptor complex, and phosphorylate STAT3 which translocates to the nucleus and drives IL-21-regulated gene expression. CCI** **The 120 mg dose will be communicated to site investigators participating in the POC Phase 2 portion, and to Institutional Review Boards (IRBs) and the Independent Ethics Committee (IEC).**	
Section 3.1.2.2, POC Study Design, Paragraph 2	Delete: As in the MAD part of the study, each patient in the POC portion may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180. Assessments will be completed according to the Schedule of Assessments (Section 3.4). ~~Dose selection will be based on the DMC and sponsor's assessment of safety, tolerability, immunogenicity, and PK and PD data from the MAD portion of 30~~	Remove text to reduce redundancy with Section 3.1.2.1

Section	Description of Changes	Rationale
	~~patients treated with BOS161721/placebo.~~	
Section 3.2, Randomization and blinding, Paragraph 4	Replace: An independent biostatistician not otherwise involved on the study will be unblinded and prepare materials for the interim analysis (IA) and the DMC safety reviews. With: An independent biostatistician not otherwise involved on the study will be unblinded and prepare materials for the IA**, ad hoc analyses as needed,** and the DMC safety reviews.	Added in order to allow for ongoing analysis of the data in the IAs.
Section 3.3, Study Schematic	Replace:  With: 	Protocol clarification.
Section 3.4, Schedule of Assessments, Table 1, Footnote	Add: Table[6]1. → Schedule of Assessments – Phase 1b – Multiple Ascending Dose |	Screen[a]	Enroll[b]	Treatment Period Follow-Up											Safety Follow-Up		
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Days	-28 to -1	0	7 (±3)	15 (±3)	30 (±3)	44 (±3)	60 (±3)	90 (±3)	120 (±3)	150 (±3)	180 (±3)	187 (±3)	195 (±3)	210 (±3)	240 (±3)	270 (±3)
Visit Number	1	2	--	3	4	5	6	7	8	9	10	--	--	11	12	13
SLEDAI-2K[h]	X	X			X		X	X	X	X	X			X	X	X | **h** **SLEDAI-2K should be done before randomization and**	Footnote added for protocol clarification. All subsequent footnotes after 'h' were re-lettered accordingly.

Section	Description of Changes	Rationale
	dosing on Day 0 as SLEDAI-2K < 6 is exclusionary.	
Section 3.4, Schedule of Assessments, Table 2, Footnote	Add: Table 2. Schedule of Assessments – Phase 2 Proof of Concept (POC) Screen[a] (-28 to -1) | Enroll (0) | Treatment Period Follow-up: 15 (±3), 30 (±3), 60 (±3), 90 (±3), 120 (±3), 150 (±3), 180 (±3), 187[n] (±3), 195[n] (±3) | Safety Follow-Up: 210 (±3), 240 (±3), 270 (±3) Days: -28 to -1 | 0 | 15 (±3) | 30 (±3) | 60 (±3) | 90 (±3) | 120 (±3) | 150 (±3) | 180 (±3) | 187[n] (±3) | 195[n] (±3) | 210 (±3) | 240 (±3) | 270 (±3) Visit Number: 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | -- | -- | 10 | 11 | 12	Footnote added for protocol clarification.
Section 3.4, Schedule of Assessments, Table 2, Footnote	Replace: o PK samples will only be collected at the investigational sites that will be participating in the PK portion of the study. With: b PK samples will only be collected at the investigational sites that **participate** in the PK portion of the study. **On PK only days (ie, Day 187 and Day 195 when no laboratory assessments are scheduled) samples will be collected at the investigational sites of the selected countries that participate in the PK portion of the study. Patients not participating in PK are not required to return for investigation site visits on Days 187 and 195.**	Footnote added for protocol clarification. All subsequent footnotes after 'b' were re-lettered accordingly.
Section 3.4, Schedule of Assessments, Table 2, Footnote	Add: Table 2. Schedule of Assessments – Phase 2 Proof of Concept (POC) Screen[a] (-28 to -1) | Enroll (0) | Treatment Period Follow-up: 15 (±3), 30 (±3), 60 (±3), 90 (±3), 120 (±3), 150 (±3), 180 (±3), 187[n] (±3), 195[n] (±3) | Safety Follow-Up: 210 (±3), 240 (±3), 270 (±3) Days: -28 to -1 | 0 | 15 (±3) | 30 (±3) | 60 (±3) | 90 (±3) | 120 (±3) | 150 (±3) | 180 (±3) | 187[n] (±3) | 195[n] (±3) | 210 (±3) | 240 (±3) | 270 (±3) Visit Number: 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | -- | -- | 10 | 11 | 12 EFFICACY ASSESSMENTS SLEDAI-2K[i]: X | X | - | X | X | X | X | X | X | - | - | X | X | X i **SLEDAI-2K should be done before randomization and dosing on Day 0 as SLEDAI-2K < 6 is exclusionary.**	Footnote added for protocol clarification.
Section 3.4, Schedule of Assessments, Table 2, Predose and Postdose PK Window rows	Delete: Screen[a] (-28 to -1) | Enroll (0) | Treatment Period Follow-up: 15 (±3), 30 (±3), 60 (±3), 90 (±3), 120 (±3), 150 (±3), 180 (±3), 187[n] (±3), 195[n] (±3) | Safety Follow-Up: 210 (±3), 240 (±3), 270 (±3) Days: -28 to -1 | 0 | 15 (±3) | 30 (±3) | 60 (±3) | 90 (±3) | 120 (±3) | 150 (±3) | 180 (±3) | 187[n] (±3) | 195[n] (±3) | 210 (±3) | 240 (±3) | 270 (±3) Visit Number: 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | -- | -- | 10 | 11 | 12 PK Labs[b]: Predose: - | X | - | X | X | X | X | X | X | - | - | - | - | - ~~Predose PK Window~~: - | 60m | - | ~~-3d~~ | ~~-3d~~ | ~~-3d~~ | ~~-3d~~ | ~~-3d~~ | ~~-3d~~ | - | - | - | - | - Postdose: - | - | X | - | - | - | - | - | - | X | X | X | X | X ~~Predose PK Window~~: - | - | ~~-3d~~ | - | - | - | - | - | - | ~~-3d~~ | ~~-3d~~ | ~~-3d~~ | ~~-3d~~ | ~~-3d~~	Removed Predose and Postdose PK Window rows to reduce redundancy as these are the same as visit window rows.
Section 4.4, Inclusion Criteria, criterion 7, b, item ii	Delete: ii. "BILAG B:" Moderate Arthritis, Tendonitis or Tenosynovitis, (BILAG item number 42), defined as tendonitis/tenosynovitis, or active synovitis in ≥ 1 joint, (observed or throughout history), with some loss of functional range of movements ~~which lead to some loss of functional range of motion as~~ manifested by effects on instrumental ADLs such as:	Repetitive text removed.
Section 4.6.1,	Replace:	Revised to reduce

Section	Description of Changes	Rationale
Corticosteroid	4.6.1 Oral Corticosteroid Dose Prior to randomization, oral CSs (prednisone or prednisone equivalent), may be used in accordance with the investigator's clinical judgment and best standard of care. See APPENDIX 3 for examples of equivalents. A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). After Day 0 (after initiation of study therapy), no up-titration above 10 mg/day is allowed except for up to 1 CS burst for increased disease activity. Tapering of steroids during the course of the study will be encouraged and should be evaluated at all visits. • Once a patient has received the first dose of study drug, prednisone (or prednisone equivalent) may be tapered down at the discretion of the investigator. o Tapering is allowed after randomization except within 60 days of the primary (Day 210) and secondary (Day 120) endpoint assessments. Between Day 60 and Day 120, and between Day 150 and Day 210, oral CS doses must be held constant. A maximum of 1 oral CS "burst" for increased SLE disease activity will be allowed during the study between Day 0 and Day 60, according to the following: • An oral CS "burst" between Day 0 and Day 60; (an increase of ≤ 40 mg/day of prednisone or equivalent), which must be tapered down to a maximum of 10 mg/day within 2 weeks of initiation of the "burst" o Alternatively, a single intramuscular (IM) dose of methylprednisolone (40 mg or equivalent) is permitted o The course of the oral CS "burst" is not permitted to extend beyond Day 60 Treatment with inhalational CS therapy (eg, for asthma), or by any other route, is allowed. Other concomitant medications for SLE need to be taken at stable doses as per the inclusion criteria (Section 4.4). With: 4.6.1 Corticosteroid Prior to randomization, oral CSs (prednisone or prednisone equivalent), may be used in accordance with the investigator's clinical judgment	redundancy and improve clarity. Text revised to clarify the meaning of "any other route" and added to address the use of CS for non-SLE conditions. Text regarding other medications not applicable to CS were removed.

Section	Description of Changes	Rationale
	and best standard of care. See APPENDIX 3 for examples of equivalents. A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). **Tapering of steroids during the course of the study will be highly encouraged and should be evaluated at the protocol permitted visits (Day 0 through Day 60 and Day 120 through Day 150). Between Day 60 and Day 120, and between Day 150 and Day 210, oral CS doses must be held constant due to the endpoint evaluations occurring at Day 120 and Day 210.** • Once a patient has received the first dose of study drug **(after Day 0)**, prednisone (or prednisone equivalent) **dose is highly encouraged to continue tapering** down **as appropriate**. **T**he investigator **should evaluate the prednisone dose at each visit and make the decision, within the protocol allowed windows.** o **Exception:** Between Day 60 and Day 120, and between Day 150 and Day 210 **(ie, within 60 days of primary and secondary endpoint assessments)**, oral CS doses must be held constant. **After Day 0 (first dose of study drug), a** maximum of 1 oral CS "burst" for increased SLE disease activity will be allowed between Day 0 and Day 60, according to the following: • **The oral CS dose is allowed to increase to** ≤ 40 mg/day of prednisone or equivalent, which must be tapered down to ≤ 10 mg/day within 2 weeks of initiation of the "burst" o Alternatively, a single intramuscular (IM) dose of methylprednisolone (40 mg or equivalent) is permitted o **No increase of** oral CS **above baseline** is permitted beyond Day 60 Treatment with inhalational CS therapy (eg, for asthma), or by any other route, **but systemic administration,** is allowed. **Treatment with intra-articular or intravenous CS is prohibited during the course of the study.**	
Section 4.7.2, Contraception, Paragraphs 1, 2, and 5	Replace: WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS161721 plus 30 days (duration of ovulatory cycle) for a total of 36 weeks after treatment completion.	Protocol clarification.

Section	Description of Changes	Rationale
	Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS161721 plus 90 days (duration of sperm turnover) for a total of 44 weeks after treatment completion. Azoospermic men and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing. With: WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus **52 weeks, due to the mean terminal ½ life of the study drug**. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus **52 weeks, due to the mean terminal ½ life of the study drug**. Azoospermic men and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, **WOCBP** must still undergo pregnancy testing.	
Section 5.1, Screening	Add: • Laboratory evaluations (non-fasting): ○ FSH (postmenopausal women **under age 55 years**)	Protocol clarification.
Section 6.2.2.5, Seriousness of Adverse Events	Delete: • Is ~~an~~other important medical event (see below)	Revised for clarity.
Section 6.2.2.6, Adverse Events of Special Interest	Replace: 4. Malignancy 5. Opportunistic infections such as disseminated histoplasmosis, cryptococcosis, and disseminated tuberculosis With: 4. Malignancy **(not including basal cell carcinoma or squamous cell carcinoma of skin)** 5. Opportunistic infections such as disseminated histoplasmosis, cryptococcosis, **disseminated herpes simplex,** disseminated tuberculosis**,** ***Aspergillus* sp., *Candida albicans*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Cytomegalovirus*, *Histoplasma capsulatum*, *Isospora belli*, and *Polyomavirus JC polyomavirus*****	Text added 1) to clarify that basal cell carcinoma is not a neoplasia associated with immune suppression, but rather secondary to sun exposure and 2) to clarify specific opportunistic infections of special interest in this study.
Section 6.2.2.6.4, Malignancy,	Add:	Revised to align with text for

Section	Description of Changes	Rationale
Paragraph 2	After the first dose of study drug, when there is a decision to biopsy a potentially malignant tumor, lymph node, or other tissue **(with the exception of suspected basal cell/squamous cell),** the investigator and/or consultant(s) should contact the sponsor clinicians or designee to discuss the issue and any decisions as soon as possible. **Basal cell carcinoma or squamous cell carcinoma of skin is not considered an AE of special interest.**	AEs of special interest.
Section 6.2.2.6.5, Special Infections	Replace: Any diagnosis or suggested diagnosis of opportunistic infections such as disseminated histoplasmosis, cryptococcosis, shingles, disseminated herpes simplex, or disseminated tuberculosis will be recorded as AEs of special interest. With: Any diagnosis or suggested diagnosis of opportunistic infections such as disseminated histoplasmosis, cryptococcosis, disseminated herpes simplex, disseminated tuberculosis**, *Aspergillus* sp., *Candida albicans*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Cytomegalovirus*, *Histoplasma capsulatum*, *Isospora belli*, or *Polyomavirus JC polyomavirus*** will be recorded as AEs of special interest.	Revised to align with text for AEs of special interest.
Section 8, Statistics	Add: • **An additional analysis may be performed for the MAD portion of the study when all MAD patients have completed the safety follow-up or withdrawn from the study, and prior to final analysis. Data from the POC part of the study will be excluded from this additional analysis.**	Analysis added to allow the sponsor to perform another interim evaluation of the MAD only data after all subjects complete or discontinue if wanted.
Section 8.2.3, Primary Efficacy Endpoint(s)	Delete: Patients that received prohibited medications or unallowable CS usage as described in Section 4.6 will be considered "medication failures" and will be treated as non-responders for the primary efficacy analysis. ~~Patients that received an allowable CS burst but having missing data at Day 210 will considered a medication failure and will be treated as non-responders for the primary efficacy analysis.~~ The determination of medication failures will be reviewed using blinded data and finalized prior to unblinding.	Correction of error in previous version; text is not applicable to the primary efficacy analysis.
Appendix 1, Names of Study Personnel, Central Laboratory	Add: PPD PPD	Protocol clarification.

Section	Description of Changes	Rationale
	Industriepark Zwijnaarde 3b B-9052 Gent, Belgium	
Appendix 3	Replace: | Medication	Dose Equivalence
---	---
Prednisone	20 mg
Cortisone	100 mg
Hydrocortisone	80 mg
Prednisolone	20 mg
Methylprednisolone	16 mg
Triamcinolone	16 mg
Budesonide	4 mg
Dexamethasone	3 mg
Bethamethasone	2.4 mg | With: | Medication	**Prednisone** Dose Equivalence
---	---
Prednisone	**1** mg
Cortisone	**5** mg
Hydrocortisone	**4** mg
Prednisolone	**1** mg
Methylprednisolone	**0.8** mg
Triamcinolone	**0.8** mg
Budesonide	**0.25** mg
Dexamethasone	**0.16** mg
Bethamethasone	**0.16** mg	Revised to clarify 1:1 equivalence to prednisone.
Appendix 5, Paragraph 1	Replace: CCI [redacted] With: CCI [redacted]	Protocol clarification.
Appendix 5, bullet b, item ii	Delete: ii. CCI [redacted]	Protocol clarification.

A RANDOMIZED DOUBLE-BLIND PHASE 1b/2 COMBINED STAGGERED MULTIPLE DOSE ESCALATION STUDY OF BOS161721 IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS ON A BACKGROUND OF LIMITED STANDARD OF CARE

SPONSOR	Boston Pharmaceuticals, Inc. 55 Cambridge Parkway, Suite 400 Cambridge, MA 02142 United States of America (USA)
INVESTIGATIONAL COMPOUND:	BOS161721
PROTOCOL NUMBER:	BOS161721-02
PHASE	Phase 1b/2
INVESTIGATIONAL NEW DRUG (IND) NUMBER:	131796
ORIGINAL PROTOCOL DATE:	06 October 2017
VERSION NUMBER:	V4.0 (Amendment 3)
VERSION DATE:	27 July 2018

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care **Study Number: BOS161721-02**	
Version	**Date**
Original Protocol	06 October 2017
Protocol Version 2.0 (Amendment 1)	14 November 2017
Protocol Version 3.0 (Amendment 2)	21 March 2018
Protocol Version 4.0 (Amendment 3)	27 July 2018

This study protocol was subject to critical review and has been approved by sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (APPENDIX 2), and principles of Good Clinical Practices (GCP) as described in 21 Code of Federal Regulations (CFR) parts 50, 54, 56 and 312 and according to applicable local requirements.

The investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

I agree with these statements and indicate my approval by signature for this protocol:

Name and Title	**Signature and Date**
PPD , MD, PhD Chief Medical Officer Boston Pharmaceuticals	
PPD , MD, FACR Vice President, Clinical Development Boston Pharmaceuticals	
PPD Clinical Operations Lead Boston Pharmaceuticals	
PPD , MD, PhD Vice President, Clinical Development and Safety Officer Boston Pharmaceuticals	

BOS161721-02

A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to BOS161721 are the confidential and proprietary information of Boston Pharmaceuticals, Inc., and except as may be required by federal, state, or local laws or regulation, may not be disclosed to others without prior written permission of Boston Pharmaceuticals, Inc.

I have read the protocol (Version 4.0, dated 27 July 2018), including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Council for Harmonisation (ICH) guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Boston Pharmaceuticals, Inc., or specified designees. I will discuss the material with them to ensure that they are fully informed about BOS161721 and the study.

_____ _____

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

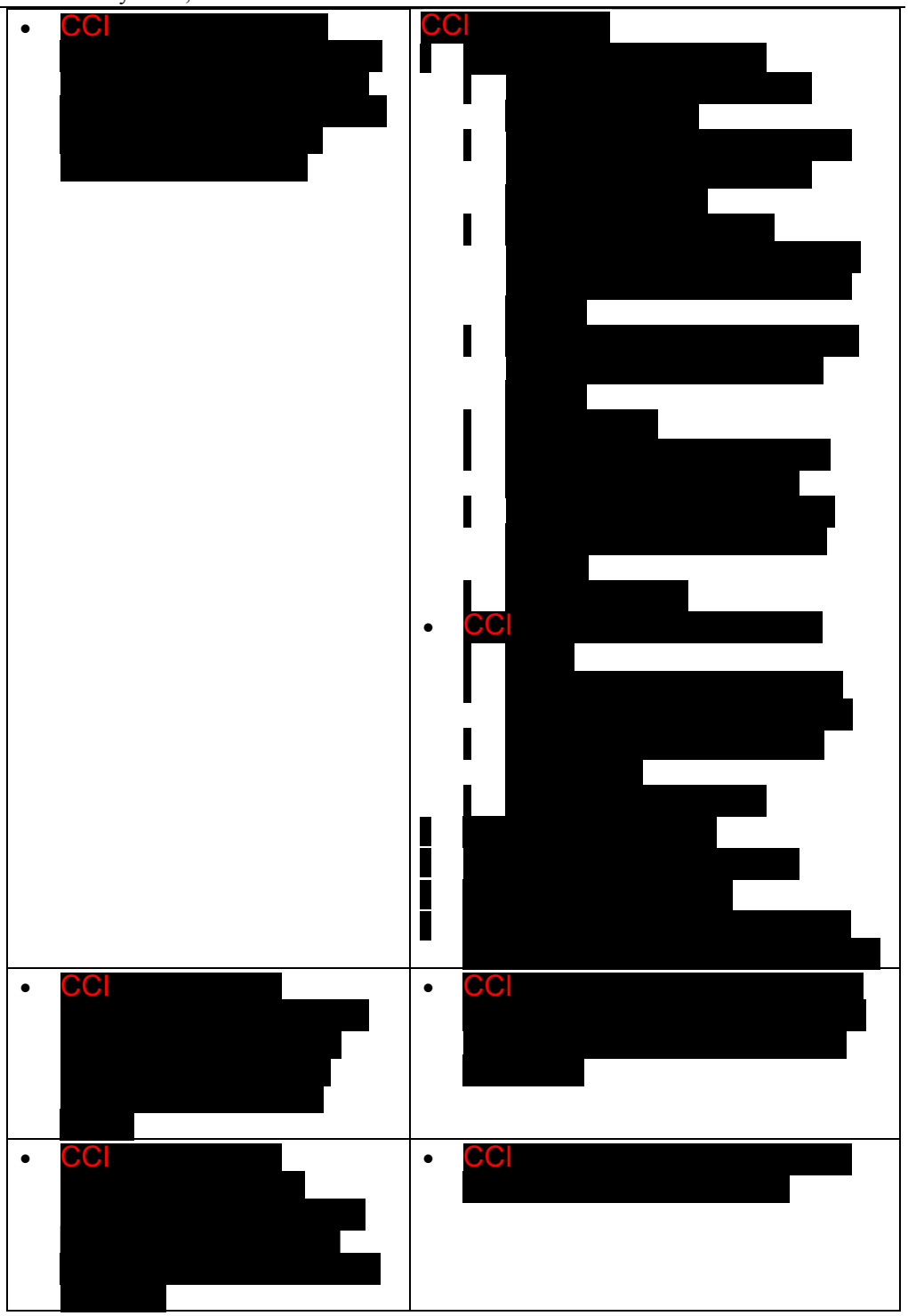
PROTOCOL SUMMARY

Title:	A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care
Indication	Adults with moderately to severely active SLE
Background and Rationale	SLE is a chronic systemic autoimmune disease with considerable heterogeneity in clinical manifestations and disease course. There is evidence that B- and T-cells are critical to the development of the disease, and that T-cell-derived cytokines such as interleukin-21 (IL-21) are involved in the SLE-associated inflammatory pathological response. BOS161721 is a humanized immunoglobulin G1 (IgG1) triple mutation monoclonal antibody (mAb) intended to have an extended terminal elimination half-life ($t_{1/2}$) that selectively binds to and neutralizes IL-21, which acts on multiple cell types that drive inflammation and autoimmunity. In vivo, BOS161721 inhibits T-cell dependent antigen responses of B-cells and is being developed as a potential treatment for adults with moderately to severely active SLE. Nonclinical studies have evaluated the toxicity, pharmacodynamics (PD), toxicokinetics (TK), pharmacokinetics (PK), and immunogenicity of BOS161721 administered intravenously (IV) and subcutaneously (SC). The no observed adverse effect level (NOAEL) in Cynomolgus monkeys was determined to be 100 mg/kg (SC and IV), the highest dose tested. There were no injection site reactions in animals dosed subcutaneously. In a Phase 1 single ascending dose (SAD) study, BOS161721 was administered IV and SC to healthy male and female adult subjects. This double-blind, placebo-controlled study evaluated 8 ascending dose levels (1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg) for safety, tolerability, PK, PD and immunogenicity. Overall, there were no clinically significant safety or tolerability findings from this study. Results from the Phase 1 SAD study informed the dose regimens used for the multiple ascending doses (MAD) Phase 1b portion of this trial. The MAD portion will involve 3 cohorts. The Phase 2 portion will be a proof of concept (POC) part, where dose selection will be based on the data monitoring committee (DMC) and sponsor's assessment of safety, tolerability, immunogenicity, and PK and PD data from the MAD portion of 30 patients treated with BOS161721/placebo. The purpose of the study is to establish a safe and effective dosage for adult patients with moderately to severely active SLE.

Objectives and Endpoints:

MAD Phase 1b

OBJECTIVES	ENDPOINTS
Primary	
• To assess safety, tolerability, and immunogenicity of repeat doses of BOS161721 (20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment, in order to estimate the optimal dose.	Safety Endpoints • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • Columbia Suicide Severity Rating Scale (C-SSRS) • 12-lead electrocardiograms (ECGs) parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from baseline • Physical examinations changes from baseline • Anti-drug antibodies (ADAs) • Study drug exposure/compliance
Secondary	
• To characterize the PK of BOS161721 and select the optimal dose of BOS161721 based on safety, PK, and PD effects in patients with mild to moderate SLE.	Pharmacokinetic Endpoints • BOS161721 concentration by visit and time point • Maximum observed concentration (C_{max}), first time to maximum concentration (T_{max}), area under the concentration-time curve (AUC), $t_{½}$, systematic clearance (C_L), volume of distribution (V_d) Pharmacodynamic Endpoints • Results and changes (or shifts) from baseline to each visit in phosphorylated signal transducer and activator of transcription 3 (pSTAT3), C3 and C4 levels, and leukocyte immunophenotype • Results and changes (or shifts) from baseline in anti-double-stranded DNA (dsDNA), antinuclear antibodies (ANA), anti-Sjögren syndrome A and B (SSA, SSB), Smith (Sm), and antiphospholipid (APL) autoantibodies at each visit • Results and changes (or shifts) from baseline in abrogation of IL-21 gene signature at each indicated visit
Exploratory	


CCI
CCI
CCI
CCI
CCI
CCI
CCI

POC Phase 2

OBJECTIVES	ENDPOINTS
Primary	
• To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on the SLE Responder Index 4 (SRI-4)	Primary Efficacy Endpoint • The proportion of patients with a SRI-4 response at Day 210 (see Section 6.3.4.1)
Secondary	
• To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on clinical indicators of SLE activity, in adult patients with moderately to severely active SLE on limited background standard of care treatment	Secondary Efficacy Endpoints • The proportion of patients with: - SRI-4 response at each visit - SRI-5 and SRI-6 response at each visit (Section 6.3.4.2) - a sustained reduction of oral corticosteroid (CS) (≤ 10 mg/day and ≤ Day 0 dose) between Day 120 and Day 210 - new BILAG A flare or > 1 BILAG B flares relative to baseline through Day 210 - PGA worsening - a BICLA response - a CLASI response - medication failures • Results and changes from baseline in: - CLASI - swollen and tender joints ACR-28 - SLEDAI-2K - SLICC/ACR damage index • Time to medication failure • Duration of longest SRI-4 response • Time to first SRI-4 response • Time to BILAG A flare or > 1 BILAG B flare compared to baseline through Day 210
Safety	
• To assess safety and tolerability of repeat doses of BOS161721 (20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment	Safety Endpoints • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • C-SSRS • 12-lead ECGs parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from

	baseline • Physical examinations changes from baseline • ADAs • Study drug exposure/compliance
Exploratory	
• CCI [redacted]	CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

Study Design: This is a Phase 1b/2 combined, randomized, multicenter, double-blind, placebo-controlled trial to study the clinical efficacy, safety, and PK of multiple SC doses of BOS161721 in adult patients with moderately to severely active SLE. After successfully completing a screening phase, eligible patients will be randomized to a specified dose of BOS161721 or placebo. The dosing schedule will be monthly. The trial will consist of 2 double-blinded portions: MAD Phase 1b and POC Phase 2. Patients may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180, followed by safety follow-up visits at Days 210, 240, and 270.

The MAD Phase 1b portion of the study design will consist of 3 cohorts, with Cohort 1 containing 6 patients, where 5 of these patients will receive BOS161721 (active), and 1 will receive placebo. Cohorts 2 and 3 will each contain 12 patients, including 9 active and 3 placebo patients. Dose selection for each cohort is based on 90-day safety, tolerability, PK, and PD data review from the Phase 1 SAD study (BOS161721-01) in healthy subjects. Each of the 3 doses (20, 60, and 120 mg) selected for the MAD portion are projected not to exceed the mean exposure of that achieved in the SAD study following the single 240 mg SC dose. Each patient may receive a total of

7 SC monthly doses on Days 0, 30, 60, 90, 120, 150, and 180.

The MAD portion design is staggered, where after the 6 patients in Cohort 1 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 2 begins dosing (after the DMC evaluates the safety and tolerability data from Cohort 1). Similarly, after 8 of the 12 patients in Cohort 2 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 3 begins dosing after the DMC evaluation of the safety and tolerability data from Cohort 2 and Cohort 1. Thirty days after the last patient in Cohort 3 receives the third dose, the DMC and Boston Pharmaceuticals will conduct a data review to determine which dose will be carried forward into the POC part of the study. This dose will not exceed doses tested during the MAD portion.

For the POC portion, approximately 156 additional patients will be randomized to active or placebo groups in a 2:1 ratio. As in the MAD portion, each patient in the POC portion may receive a total of 7 SC monthly doses on Days 0, 30, 60, 90, 120, 150, and 180.

A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). One oral CS "burst" for increased SLE disease activity may occur during the study between Day 0 and Day 60. Tapering of steroids during the course of the study will be encouraged and should be evaluated at all visits. Tapering may occur after randomization except within 60 days of the primary (Day 210) and secondary (Day 120) endpoint assessments. Between Day 60 and Day 120, and between Day 150 and Day 210, oral CS doses must be held constant.

DMC safety reviews will be conducted periodically throughout the study as described in the DMC charter.

Main Criteria for Inclusion and Exclusion

Inclusion Criteria:

1. Men and women, ages 18 to 70 years, inclusive

2. Patients must be mentally capable of giving consent and there must be evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study

3. Patients must have SLE as defined by meeting 4 of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE (with at least 1 clinical and 1 immunologic criterion OR Lupus nephritis as the sole clinical criterion in the presence of antinuclear antibodies [ANA] or anti- double-stranded deoxyribonucleic acid [dsDNA] antibodies), either sequentially or simultaneously

4. At screening, patients must have at least 1 of the following:

    a. Elevated ANA ≥ 1:80 via immunofluorescent assay at the central laboratory

    b. Positive anti-dsDNA or anti-Smith (Sm) above the normal level as determined by the central laboratory

    c. C3 or C4 levels below normal as determined by the central lab

5. At screening, the SLEDAI-2K must be ≥ 6, including points from at least 1 of the following clinical components:

    a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis

        i. Excluding parameters which require central laboratory results: (hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia)

        ii. Points from lupus headache and organic brain syndrome will also be excluded

6. On Day 0, the SLEDAI-2K must be ≥ 6, including points from at least 1 of the following clinical components:

    a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis

        i. Excluding parameters which require central laboratory results: hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA,

decreased complement, thrombocytopenia, and leukopenia

ii. Points from lupus headache and organic brain syndrome will also be excluded

7. Patients must have at least 1A or 2Bs from the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer:

   a. BILAG A or B score in the mucocutaneous body system

   b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis as defined in the protocol Section 4.4

   If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in the other body systems for a total of 2 "B" BILAG body system scores

8. Patients must be currently receiving at least 1 of the following:

   a. Administration for a minimum of 12 weeks, and a stable dose for at least 56 days (8 weeks prior to signing consent) of the following permitted steroid-sparing agents:

      i. Azathioprine (AZA), mycophenolate mofetil or mycophenolic acid, chloroquine, hydroxychloroquine, or methotrexate (MTX)

   b. Prednisone (or prednisone-equivalent) cannot exceed 30 mg/day at screening for a patient to be eligible and must be stable at a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization)

9. Women of childbearing potential (WOCBP; see Section 4.7 for full information regarding WOCBP, definition of menopause, and contraception):

   a. Must have a negative serum pregnancy test at screening. Urine pregnancy test must be negative prior to first dose

   b. Must not be breastfeeding

   c. Must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS161721 plus 30 days (duration of ovulatory cycle) for a total of 36 weeks after treatment completion

10. Men who are sexually active with WOCBP must agree to follow

instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of BOS161721 plus 90 days (duration of sperm turnover) for a total of 44 weeks after treatment completion

11. Patients must demonstrate willingness and ability to comply with the scheduled study visits, treatment plans, laboratory tests, and other procedures

Exclusion Criteria

Patients presenting with any of the following will not be included in this study:

1. Drug-induced SLE, rather than "idiopathic" SLE
2. Other systemic autoimmune disease (eg, erosive arthritis, rheumatoid arthritis [RA], multiple sclerosis [MS], systemic scleroderma, or vasculitis not related to SLE)
    a. RA-Lupus overlap (Rupus), and secondary Sjögren syndrome are allowed
3. Any major surgery within 6 weeks of study drug administration, (Day 0), or any elective surgery planned during the course of the study
4. Any history or risk for tuberculosis (TB), specifically those with:
    a. Current clinical, radiographic, or laboratory evidence of active TB
    b. History of active TB
    c. Latent TB defined as positive QuantiFERON-TB Gold In-Tube (QFT-G) or other diagnostic test in the absence of clinical manifestations. Latent TB is not excluded if the patient has documented completion of adequate course of prophylactic treatment with regimen recommended by local health authority guideline, or the patient has started treatment with isoniazid, or other regimen recommended by local health authority guidelines for at least 1 month before Day 0 and continues to receive the prophylactic treatment during study until the treatment course is completed
5. Active or unstable lupus neuropsychiatric manifestations, including but not limited to any condition defined by BILAG A criteria, with the exception of mononeuritis multiplex and polyneuropathy, which are allowed
6. Severe proliferative lupus nephritis, (WHO Class III, IV), which requires or may require induction treatment with cytotoxic agents or high dose CS
7. Concomitant illness that, in the opinion of the investigator, is likely to require additional systemic glucocorticosteroid therapy during the study, (eg, asthma), is exclusionary

a. However, treatment for asthma with inhalational CS therapy is allowed

8. Use or planned use of concomitant medication outside of standard of baseline treatment for SLE from Day -1 or for any time during the study
9. Active and clinically significant infection (bacterial, fungal, viral, or other) within 60 days prior to first dose of study drug. Clinically significant is defined as requiring systemic parenteral antibiotics or hospitalization
10. A history of opportunistic infection, or a history of recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years
11. Chronic viral hepatitis including hepatitis B (HBV) and hepatitis C (HCV) unless patient received curative treatment for HCV and has a documented negative viral load, known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness
12. Cryptosporidium in the stool sample at screening
13. White blood cells (WBC) < 1,200/mm^3 (1.2×10^9/L) at screening
14. Absolute neutrophil count (ANC) < 500/mm^3 at screening
15. CD4+ count < 350/μL at screening
16. Platelets < 50,000/mm^3 (50×10^9/L) or < 35,000/ mm^3 (35×10^9/L) if related to SLE, at screening
17. Hemoglobin < 8 g/dL or < 7 g/dL at screening if related to SLE
18. Proteinuria > 3.0 g/day (3000 mg/day) at screening or equivalent level of proteinuria as assessed by protein/creatinine ratio (3 mg/mg or 339 mg/mmol)
19. Serum creatinine > 2.0 mg/dL at screening or creatinine clearance (CrCL) < 40 ml/minute based on Cockcroft-Gault calculation
20. Serum alanine aminotransferase (ALT) and/or serum aspartate aminotransferase (AST) > 2 × the upper limit of normal (ULN) at screening, unless explicitly related to lupus based on the investigator's judgment
21. Creatinine kinase (CK) > 3.0 × ULN at screening unless related to lupus myositis
22. Direct bilirubin > 1.5 × ULN at screening (unless related to Gilbert's syndrome)
23. Any other laboratory test results that, in the opinion of the Investigator, might place a patient at unacceptable risk for participating in this study
24. History of allergic or anaphylactic reaction to any therapeutic or diagnostic mAb (eg, IgG protein) or molecules made of components of

mAbs

25. History substance and/or alcohol abuse, or dependence within the past 1 year, at the investigator's judgment
26. History of cancer within the last 5 years (except for cutaneous basal cell or squamous cell cancer, or cervical cancer in situ resolved by excision
27. Any other severe acute or chronic medical or psychiatric condition, including recent (within the past year) medical conditions (eg, cardiovascular conditions, respiratory illnesses) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study
28. Investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or patients who are employees of the sponsor or directly involved in the conduct of the trial
29. Currently participating in, or who have participated in other interventional (drug or device) clinical study within 30 days or 5 half-lives of baseline, whichever is longer
30. Recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4, or 5 on the C-SSRS
31. Current or pending incarceration
32. Current or pending compulsory detainment for treatment of either a psychiatric or physical (eg, infectious disease) illness

Statistical Considerations

Below is a summary of the statistical methods. Further details can be found in Section 8.

Two analyses are planned: 1) an interim analysis to select the POC dose based on the MAD data, and 2) a final analysis at study completion. Additionally, DMC safety analyses will be performed for each MAD cohort and throughout the POC to monitor patient safety as described in the DMC charter.

Unless stated otherwise, statistical testing will only be performed on the POC data and will be done using 2-sided overall alpha of 0.10. Data will be summarized descriptively by treatment and overall for each study phase. For the MAD portion, BOS161721 will be summarized overall and by each dose level and placebo patients from each cohort will be combined.

The descriptive summaries for the categorical data will include number and percentage. The descriptive summaries for the continuous data will include number, mean, median, standard deviations (SD), 25th and 75th percentiles, minimum, median, and maximum. Counts, medians, 25th and 75th percentiles,

and standard error will be presented for time-to-event data.

All safety analyses will be performed using the safety analysis set (SS), defined as all patients who receive at least 1 dose of study treatment. All efficacy analyses will be performed using the full analysis set (FAS), defined as all patients who receive at least 1 dose of study treatment and have at least 1 evaluable post-baseline efficacy evaluation. Select efficacy analyses may also be performed on the per protocol (PP) set.

Binary efficacy endpoints, including the primary efficacy endpoint, will be assessed via Pearson's chi-squared analysis.

Continuous efficacy endpoints will be assessed via analysis of variance (ANOVA) or analysis of covariance (ANCOVA) when applicable, adjusting for the baseline value. Repeated measures mixed models may be performed to evaluate data collected at each visit and overall. Time-to-event endpoints will be assessed via Kaplan-Meier methodology and treatment will be compared using the log-rank test.

Adverse event data will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients experiencing any treatment-emergent AE, overall, and by system organ class and preferred term will be tabulated. Treatment-emergent AEs will also be summarized by severity and relationship.

Concomitant medications will be summarized, based on coded terms, using frequency and percentage of patients. Observed values and changes from baseline in vital signs, ECG readings, and hematology and clinical chemistry parameters, will be summarized at each individual visit.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADA	anti-drug antibody
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANC	absolute neutrophil count
ANOVA	analysis of variance
ANCOVA	analysis of covariance
APL	antiphospholipid
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AZA	azathioprine
BICLA	BILAG-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BP	blood pressure
BUN	blood urea nitrogen
BW	body weight
C	complement
CS	corticosteroids
C-SSRS	Columbia Suicide Severity Rating Scale
CD	cluster of differentiation
CK	creatine kinase
C_L	systematic clearance
CLASI	Cutaneous Lupus Erythematosus Area and Severity Index
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CS	corticosteroids
CSR	clinical study report
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
dsDNA	double-stranded deoxyribonucleic acid
ECG	electrocardiogram
EOT	end of treatment
eCRF	electronic case report form
F	female
CCI	[redacted]
FAS	full analysis set

Fc	fragment crystallizable
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
eGFR	estimated glomerular filtration rate
GLP	Good Laboratory Practice
GWAS	genome-wide association studies
γc	gamma chain
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCl	hydrochloride
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IL	interleukin
IL-21R	interleukin 21 receptor
IM	intramuscular
INFγ	interferon gamma
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
IVRS	interactive voice response system
JAK	Janus kinase
kg	kilogram
KLH	keyhole limpet hemocyanin
LOCF	last observation carried forward
M	male
mAb	monoclonal antibody
MAD	multiple ascending dose
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary of Regulatory Activities
MS	multiple sclerosis
MTX	methotrexate

NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIAID/FAAN	National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network
NK	natural killer
NOAEL	no observed adverse event level
NO	nitric oxide
OTC	over-the-counter
PD	pharmacodynamics
PEF	peak expiratory flow
PGA	Physician's Global Assessment
PK	pharmacokinetics
POC	proof of concept
PP	per protocol
PR	(interval) from onset of the p-wave to the end of the r-wave
pSS	primary Sjögren's syndrome
pSTAT3	phosphorylated signal transducer and activator of transcription 3
PT	preferred term
QRS	(interval) from the onset of the q-wave to the end of the s-wave
QT	(interval) from onset of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
QFT-G	QuantiFERON-TB Gold In-Tube
RA	rheumatoid arthritis
RR	(interval) from the onset of the r-wave to the onset of the next consecutive r-wave
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SDMT	safety data monitoring board
CCI	[redacted]
SLE	systemic lupus erythematosus
SLEDAI-2K	SLE Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
Sm	Smith
SOC	system organ class
SRI-4	SLE Responder Index 4
SRI-5	SLE Responder Index 5
SRI-6	SLE Responder Index 6
SS	safety analysis set
SSA	Sjögren syndrome-A (Ro)
SSB	Sjögren syndrome-B (La)

STAT3	signal transducer and activator of transcription 3
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
TB	tuberculosis
TDAR	T-cell dependent antibody response
Tfh	T-follicular helper
Th	T-helper
TK	toxicokinetics
T_{max}	first time to maximum concentration
Treg	regulatory T-cell
TT	tetanus toxoid
ULN	upper limit of normal
US	United States
Vd	volume of distribution
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
YTE	triple mutation

1. INTRODUCTION AND RATIONALE

1.1 Indication

BOS161721 is a humanized monoclonal antibody (mAb), which binds to and inhibits interleukin-21 (IL-21) bioactivity, and is being developed for the treatment of moderately to severely active systemic lupus erythematosus (SLE) in adults.

1.2 Background and Rationale

1.2.1 Overview of the Disease State

SLE is a chronic inflammatory autoimmune disease that has variable manifestations in multiple organ systems and follows a relapsing and remitting course. The disease process includes abnormal immune responses mediated by tissue-binding autoantibodies and immune complex deposition, giving rise to tissue damage often resulting in end organ disease and even mortality. Survival of SLE has improved due to earlier detection, improved overall medical care, and standardized SLE treatment with corticosteroids (CS), immunosuppressants, and cytotoxic agents.[1] However, some of the morbidity in patients with SLE is related to its treatment. Comparison of early and late outcomes in patients with SLE demonstrate that death in early disease is most commonly due to infections and active SLE causing multi-system organ damage, while thromboses were the most common cause of death during later disease.[2]

The reported prevalence of SLE in the United States (US) is 20 to 70 cases per 100,000 people.[3] More than 90% of cases of SLE occur in women, frequently starting at childbearing age. Women of color are disproportionately affected by SLE. This suggests multiple genetic and environmental factors are at play. Accordingly, a multifactorial view of the immunopathogenesis of SLE suggests more than 1 area of interest, including breach in central tolerance in the adaptive arm of the immune system, peripheral amplification of the autoimmune response by the innate immune system, and local processes in the target organ that facilitate end-organ disease.[4]

1.2.2 BOS161721 Development

Boston Pharmaceuticals is developing BOS161721 for the treatment of SLE. BOS161721 is a humanized immunoglobulin G1 (IgG1) mAb with extended half-life directed against human IL-21.

Murine mAb 19E3, the progenitor of BOS161721, was generated using mouse hybridoma technology. 19E3 has subpicomolar (pM) affinity to human IL-21 and was selected for its potent neutralization of IL-21 bioactivity. BOS161721 was generated by the humanization of mAb 19E3 where its complementarity-determining regions were grafted onto a human IgG1 kappa backbone. The fragment crystallizable (Fc) portion of BOS161721 contains a YTE (M252Y/S254T/T256E triple mutation) in the constant domain of the IgG1 heavy chain that was introduced into the parental molecule, 19E3, intended to prolong the in vivo terminal elimination half-life ($t_{1/2}$) of the mAb.[5] Thus, BOS161721 retains sub-pM binding to IL-21 and prevents IL-21 from binding to the IL-21 receptor (IL-21R), inhibiting IL-21 bioactivity.

BOS161721 binds to human IL-21 and Cynomolgus monkey IL-21, which are highly homologous, and neutralizes the bioactivity of both. BOS161721 is specific for IL-21 as it does not bind to or inhibit the other gamma-chain (γc) family of cytokines, and acts to specifically neutralize the IL-21 pathway. In *in vitro* studies, BOS161721 inhibited downstream IL-21-induced signaling, IL-21-induced plasma cell differentiation, and IL-21-induced natural killer (NK) cell activation. In *in vivo* studies, BOS161721 significantly inhibited the T-cell dependent antibody response (TDAR) to immunization with a protein antigen as well as B-cell expansion following a second protein antigen immunization in Cynomolgus monkeys.

1.2.2.1 Interleukin-21

IL-21 is an inflammatory cytokine, which belongs to a family of cytokines that also includes IL-2, IL-4, IL-7, IL-9, and IL-15, all of which bind to private receptors in complex with the common cytokine receptor γc.[6] Most cytokines in this family are critically important for both the maintenance and function of T-cell and B-cell responses. IL-21 signals through a receptor complex consisting of its own private receptor, the IL-21R and γc.[6,7] Engagement of the IL-21R/γc complex leads to the activation of several signaling pathways, including the Janus kinase/signal transducer and activator of transcription, mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase pathways.[8] IL-21 is produced mainly by T-cells and NK T-cells, but neutrophils have also been reported to produce IL-21.[9,10] The IL-21R is expressed on a broad array of cell types, including B-cells, T-cells, NK-cells, macrophages and dendritic cells, as well as other hematopoietic and nonhematopoietic cells such as fibroblasts, keratinocytes, and intestinal epithelial cells.[9,11] Activation of signal transducer and activator of transcription 3 (STAT3) via phosphorylation is critical in regulating human B-cell responses to IL-21[12]; phosphorylated STAT3 (pSTAT3) forms a homodimer, which translocates to the nucleus where it initiates transcription of the IL-21 gene, forming an autocrine loop for IL-21 production via STAT3 phosphorylation.[13] In addition, IL-21 has been shown to upregulate expression of its own receptor[14] and induces an autocrine feedback loop.[15]

IL-21 modulates various aspects of immune function. It promotes cluster of differentiation 4 (CD4+) T-cell differentiation and promotes the generation of T-helper (Th)17[16] and T-follicular helper (Tfh) cells.[15,17] In mice, IL-21 has been shown to regulate the balance between Th17 and regulatory T-cell (Treg), in that it increases Th17, while inhibiting Treg differentiation.[18] Less is understood with regards to human Tregs, although IL-21 has been reported to counteract Treg suppression of human effector T-cells[19] and blockade of IL-21 promotes Treg generation in a murine model of graft versus host disease induced by human T-cells.[20] IL-21 upregulates CD8+ T-cell and NK-cell expansion and cytolytic activity by increasing granzyme B and perforin.[21,22] IL-21 also has been reported to increase granzyme B in plasmacytoid dendritic cells and B-cells resulting in inhibition of T-cell responses.[23,24] IL-21 also has a variety of effects on nonhematopoietic cells, such as stromal cells and induces inflammation through matrix metalloproteinase release by gut intestinal fibroblasts.[25]

One principal non-redundant role of IL-21 is the promotion of B-cell activation, differentiation, or death during humoral immune responses.[14] Furthermore, increased IL-21 production is characteristic of several autoimmune diseases and is likely to contribute to autoantibody production as well as pathologic features of autoimmune disease.[26] The critical role of IL-21 in promoting humoral and other immune responses makes it an important focus of potential

therapeutic interventions in conditions characterized by overproduction of pathogenic autoantibodies. IL-21 production by Tfh cells in humans is believed to play a major role in driving the autoantibody production through its role in plasma cell differentiation. Importantly, Tfh cell populations are expanded in patients with autoimmune diseases such as lupus, bullous pemphigoid, rheumatoid arthritis (RA) and primary Sjögren's syndrome (pSS) and have been reported to correlate with IL-21 levels, autoantibodies, and disease severity.[26,27,28,29] Furthermore, loss of number and functionality of Tregs has been associated with autoimmune diseases such as SLE and giant cell arteritis, which IL-21 is expected to modulate.[30,31] Thus, neutralization of IL-21 in settings of autoimmunity is expected to impact several cell populations believed to be involved in the pathogenesis of autoimmune disorders including SLE.

BOS161721 selectively binds IL-21 with high affinity to neutralize IL-21, and due to its pleiotropic nature, neutralization of IL-21 is expected to impact several cell populations believed to be involved in the pathogenesis of SLE. Importantly, patients with SLE have elevated IL-21 plasma levels that correlate with the severity of the disease. Recently, genome-wide association studies (GWAS) have provided convincing evidence that the chromosomal 4q 27 region harbors the IL-21 genes and is associated with chronic inflammatory disorders, including SLE.[29]

1.2.2.2 Preclinical Studies

The pharmacokinetics (PK) of BOS161721 were characterized following single-dose intravenous (IV) administration of BOS161721 (0.01 to 30 mg/kg) in male Cynomolgus monkeys or repeat, every 2 weeks IV administration (15 to 100 mg/kg) and subcutaneous (SC) administration (50 mg/kg) in male and female Cynomolgus monkeys. Systemic exposure was approximately dose-proportional within the tested dose range. SC bioavailability was determined to be 64.3%. CCI [redacted]

Two single-dose (IV) non-good laboratory practice (GLP) studies conducted in Cynomolgus monkeys evaluated the toxicity, pharmacodynamics (PD), toxicokinetics (TK), and immunogenicity of BOS161721. Following a single IV administration (slow bolus), there were no BOS161721-related adverse changes, resulting in a no-observed-adverse-effect-level (NOAEL) value of 30 mg/kg, the highest dose tested among 2 studies. CCI [redacted]

In a repeat-dose GLP toxicology study in Cynomolgus monkeys, BOS161721 was administered every 2 weeks by IV or SC (50 mg/kg) administration for 3 months (a total of 7 doses). CCI [redacted]

CCI [redacted] The NOAEL was determined to be 100 mg/kg (SC and IV), the highest dose tested.

An additional GLP, repeat-dose toxicity study was conducted in Cynomolgus monkeys (4 males and 4 females per dose group) following every 2 weeks (Q2W) administration by SC (10, 30, and 100 mg/kg) injection for a total of 14 doses. CCI [redacted] There were no BOS161721-related effects on survival, clinical signs, male body weights, ophthalmologic parameters, electrocardiogram (ECG) findings, clinical pathology, macroscopic observations, organ weights, or microscopic observations. CCI [redacted] The 100 mg/kg/dose was the NOAEL CCI [redacted]

1.2.2.3 Clinical Studies

BOS161721-01 was a double-blind, Phase 1, single ascending dose (SAD) study to assess the safety, PK, and PD of BOS161721 in healthy subjects. The primary objective of the study was to characterize the safety and tolerability of IV and SC SADs of BOS161721 in an otherwise healthy subject population without concomitant illnesses, immune abnormalities, or concomitant medications. Secondary objectives included characterization of the PK and immunogenicity of BOS161721, and exploratory objectives included the evaluation of the effect of BOS161721 on TDAR to keyhole limpet hemocyanin (KLH) (primary and secondary immunizations) in healthy subjects, the effects of BOS161721 on plasma levels of IL-21 (free and bound), and the evaluation of the effect of BOS161721 on IL-21 gene expression (via gene signature) in blood. This study consisted of 8 cohorts. Subjects were randomized in a 3:1 ratio (BOS161721: placebo) and received either a single dose of BOS161721 (1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg) or placebo, with safety follow-up. For the first cohort, after the first 2 subjects were dosed (1 active and 1 placebo), there was a minimum gap of 48 hours before the remaining subjects from that cohort were dosed, to allow for an initial review of any emerging safety and tolerability data. For all cohorts, escalation to the next dose was not

sooner than 8 days after all the subjects in the prior cohort had been dosed and were based on a review of at least 7 days of safety and tolerability data by the Safety Data Monitoring Team (SDMT).

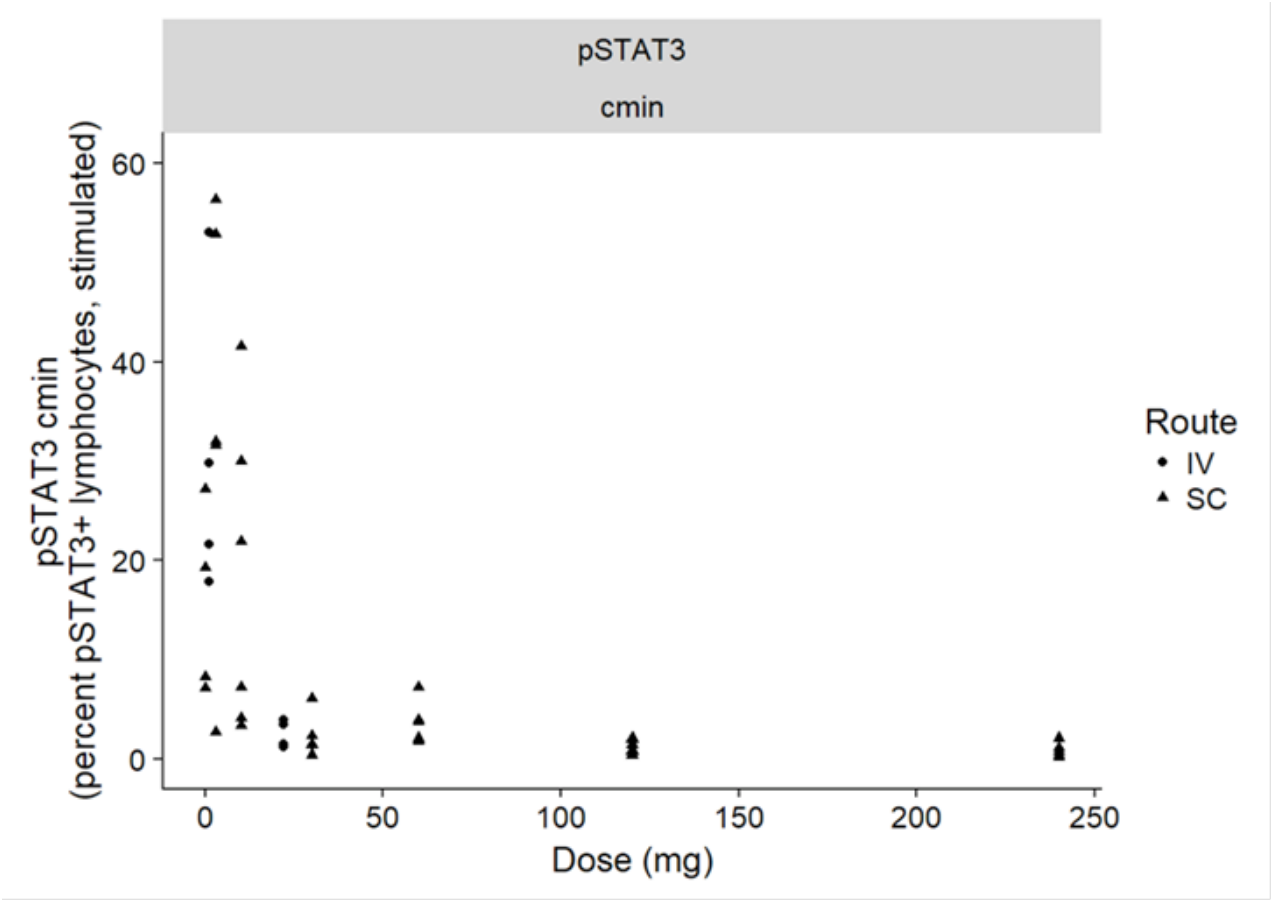
Blood samples were collected at every in-house study visit for BOS161721 concentration determinations. Blood samples were also collected for determination of IL-21 plasma levels (free and total). Safety was assessed based on the occurrence of treatment-emergent AEs, hepatic function abnormality, and acute and delayed hypersensitivity reactions. Other safety variables included ECGs, vital signs (blood pressure [BP], heart rate, and temperature), safety laboratory assessments, blood sampling for ADAs, total IgG and immunoglobulin M (IgM) levels, CD4+ count, and full and targeted physical examinations. Overall, there were no clinically significant findings from this study. Adverse events reported as related to the study drug, particularly infections, were expected for the compound, and there were no clinically relevant changes in laboratory and ECG results or vital signs. There was 1 serious adverse event (SAE; death due to pulmonary embolism) that occurred 127 days after a single administration of 240 mg SC dose of BOS161721. The causality of this single SAE was not attributed to study drug and further information can be found in the Investigator's Brochure. PK data from the SAD study demonstrates BOS161721 has an extended $t_{1/2}$ (provisional single dose data indicates this to be approximately 42-46 days) which supports evaluation of monthly dosing.

1.2.3 Study Dose Selection

Doses have been selected for the multiple ascending dose (MAD) Phase 1b portion based on a 90-day safety, tolerability, PK, and PD data review from the Phase 1 SAD study (BOS161721-01); the SDMT reviewed the blinded safety data from subjects for each dose cohort (8 cohorts, evaluating 1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg), along with the accumulated safety and available PK/PD data from all subjects in the previous dose cohorts, to make a decision on whether to proceed to the next higher dose level, repeat a dose level, or stop dose escalation. Overall, there were no clinically significant safety or tolerability findings from this study.

Based on the Day-90 interim cut of the PK and biomarker data in the BOS161721-01 study, the recommended doses for evaluation in the MAD portion of this study are 20, 60, and 120 mg SC monthly. This dose recommendation is supported by evidence of linear PK with BOS161721 resulting in a median first time to maximum concentration (T_{max}) of 6 days and an apparent terminal half-life of 44 days. Furthermore, pSTAT3 suppression, a marker of IL-21 target engagement, follows a similar time course of the mAb levels, with maximal and sustained suppression apparent with doses greater than 30 mg SC (Figure 1).

Figure 1. Individual pSTAT3 C_{min} Levels Versus Dose



IV = intravenous, pSTAT3 = phosphorylated signal transducer and activator of transcription 3; SC = subcutaneous

All doses selected for the MAD portion are projected not to exceed the mean exposure of that achieved following the highest single dose of 240 mg SC administered in the Phase 1 SAD study. Cohort 1 will include randomized treatment to the 20 mg dose. Based on the staggered study design, the data monitoring committee (DMC) will perform a scheduled review of safety data and sequentially consider dose escalation for Cohorts 2 and 3. In addition, the DMC and Boston Pharmaceuticals will conduct a data review to determine which dose will be carried forward into the proof of concept (POC) Phase 2 portion. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2 and 3 from the MAD portion (see Section 3.1.1.1).

1.2.4 Risk-Benefit Assessment

The available preclinical data on BOS161721, the findings in clinical study BOS161721-01, and existing clinical information on IL-21 inhibitors suggest that the present clinical study has an acceptable risk-benefit ratio. In this study, the risk-benefit assessment of BOS161721 in adult patients with moderately to severely active SLE will be ongoing, with step-wise evaluations during the staggered MAD portion. The DMC used in this study is charged with assessing such actions in light of an acceptable benefit-risk profile for BOS161721 as an anti-IL-21 mAb.

Formal DMC monitoring meetings will occur as described in the DMC Charter. Two weeks after Cohort 1 has received a second dose of study drug, the DMC will evaluate the safety and tolerability data from Cohort 1 to determine the recommended dose for Cohort 2. Two weeks after 8 patients in Cohort 2 receive a second dose, the DMC will determine if dose escalation to Cohort 3 can proceed. Thirty days after the last patient in Cohort 3 receives the third dose, the DMC and Boston Pharmaceuticals will conduct a data review to determine which dose will be carried forward into the POC part of the study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2 and 3 during the MAD part of study. Thereafter, DMC safety reviews will be conducted periodically throughout the study as described in the DMC charter. With the agreement of the DMC and sponsor, this schedule may be modified depending on the rate of patient accrual. Additional details can be found in the DMC Charter.

The benefit of participation for all patients in this study is close monitoring of their medical condition and safety of their treatment. Those randomized to the active treatment arm may potentially experience improvement in their SLE disease. Those randomized to the placebo (in combination with standard of care) arm are not expected to obtain any additional benefit, beyond those of their background treatment, though close monitoring of their medical condition and safety may itself be associated with improving their SLE.

1.2.5 Potential Risks

Potential risks based on the mechanism of action of BOS161721 include infections, risks associated with the administration of any foreign protein or biologic agent, including injection site reaction, anaphylaxis, serious allergic reaction, and development of ADAs. ADAs could result in immune complex disease (with manifestations such as arthralgias, serum-sickness, and vasculitis), or altered BOS161721 levels or activity. Further details can be found in the current Investigator's Brochure (IB) for BOS161721, which contains comprehensive toxicology, preclinical and clinical information on BOS161721.

Two investigational drug products are considered to be in the same pharmacological class as BOS161721 based on interruption of signaling through the IL-21 signaling pathway. No potential risk generalizable across the class has been observed with these investigational products. Based on the clinical Phase 1 SAD study (BOS161721-01), AEs reported as related to the study drug, particularly infections (flu-like symptoms, etc), were expected for the compound, and there were no clinically relevant changes in laboratory and ECG results or vital signs.

The majority of IgG elimination occurs via intracellular catabolism, following fluid-phase or receptor-mediated endocytosis. This type of endocytosis and elimination is a form of target-mediated disposition where the interaction of the drug and its pharmacological target (eg, a target receptor) serves as a significant contributor to the kinetics of antibody distribution and elimination. Renal elimination, which is a primary pathway of clearance of small-molecule drugs, is relatively unimportant for IgG, as its large size prevents efficient filtration through the glomerulus. Secretion into the bile is an important pathway of elimination of IgA antibodies, but this route is not a significant contributor to the elimination of IgG antibodies. Thus, risk to renal and hepatic systems due to metabolism of BOS161721 is low.[33]

1.2.5.1 Anaphylaxis and Serious Allergic Reactions

As with the administration of any foreign protein and/or other biological agents, acute hypersensitivity reactions, including acute anaphylactic/hypersensitivity, severe allergic, and anaphylactoid reactions may follow infusion of mAbs and can be caused by various mechanisms. These acute hypersensitivity reactions may be severe and result in death.

Anaphylaxis will be defined according to the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria,[34] and are discussed in Section 6.2.2.6.1.

Based on the limited Phase 1 SAD study (BOS161721-01), anaphylaxis and serious allergic reactions in subjects who received BOS161721 was not observed.

Patients with a known history of allergy or severe hypersensitivity reaction to any component of BOS161721 formulation or patients with a history of anaphylaxis to any other biological therapy such as mAbs will be excluded from studies with BOS161721. In addition, appropriate drugs and medical equipment to treat acute hypotensive, bronchoconstrictive, or anaphylactic reactions will be immediately available at the unit and study personnel will be trained to recognize and treat these reactions.

1.2.5.2 Injection Site Reactions

In a repeat-dose GLP toxicology study in Cynomolgus monkeys, BOS161721 was administered every 2 weeks by IV or SC for 3 months (a total of 7 doses). There were no injection site reactions in animals dosed subcutaneously. Further, there were no reports of injection site reactions in the 26-week GLP toxicology study in Cynomolgus monkeys.

Based on the Phase 1 SAD study (BOS161721-01), incidence of injection site reactions in subjects who received BOS161721 was similar to placebo.

Patients will be monitored for local injection site reactions in this study. See Section 6.2.7.

1.2.5.3 Immune Complex Disease

The potential risk of immune complex disease for BOS161721 is theoretical, based on the known risks associated with mAbs. The administration of a mAb can result in the formation of ADAs. Administration of the mAb in the presence of ADA may result in the formation of circulating antibody-antigen complexes potentially resulting in altered BOS161721 levels or activity or deposition of the complexes in microvasculature. Complement is frequently involved in the latter setting, and the breakdown products of complement attract polymorphonuclear leukocytes to the site of deposition where they can provoke local tissue damage through specific or nonspecific release of enzymes. Two of the more common end-organ targets are the blood vessels (vasculitis) and kidney (nephritis). These clinical manifestations represent immune complex disease or Type III hypersensitivity. Although BOS161721 is a humanized mAb, ADAs may develop; however, the likelihood of occurrence of immune complex disease with BOS161721 is low. The findings of immune complex disease are typically reversible when mAb administration stops and the antibody-antigen complexes are cleared from the body.

Based on the limited Phase 1 SAD study (BOS161721-01), immune complex disease in subjects who received BOS161721 was not observed.

1.2.5.4 Infections

BOS161721 is expected to diminish the activity of T-cell, B-cell and NK-cell lines. Like other medications modulating immune response, BOS161721 may increase the potential risk for infection, including serious infections. IL-21 produced by CD4+ Th cells is required to sustain the anti-viral function of CD8+ T-cells against chronic viral infections. Nonclinical evidence suggests that the risk of chronic viral infection recurrence or increased severity may occur with IL-21 inhibition.[35]

These conditions will be fully characterized with clinical descriptions and routine laboratory and/or specialty testing and treated where indicated with appropriate local standard of care.

Patients with a history of opportunistic infection, including recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years, or any other underlying pathology predisposing to serious infection, are excluded from studies with BOS161721 (for further details please refer to the current IB for BOS161721).

Patients will be assessed for hepatitis B, and C, and HIV-1/2 combination, at screening.

Cryptosporidium Infection

Cryptosporidium infection was noted in patients with an IL-21 receptor loss-of-function gene mutation and similar findings of cryptosporidium infection have been observed in immunosuppressed liver transplant and human immunodeficiency virus patients.[36,37] Since BOS161721 is expected to diminish the immunosurveillance activity of T-cell, B-cell, and NK-cell lines, a similar risk is biologically plausible with prolonged exposure to BOS161721.

Since the risk of opportunistic cryptosporidium infection increases with low levels of CD4+ T-cells,[37] patients with a CD4+ count < 500 cell/mm^3 were excluded from the Phase 1 SAD study (BOS161721-01), and CD4 + < 350 cells/mm^3 will be excluded from the MAD/POC parts of the study. Patients exposed to investigational product who develop diarrhea during the course of the study should immediately undergo an assessment for opportunistic infection including stool for ova and parasites and stool examination for cryptosporidium. Positive cryptosporidium in stool sample at screening is an exclusion. Treatment by the investigator where indicated should be guided by findings and be consistent with local standard of care.

Based on the limited Phase 1 SAD study (BOS161721-01), infections in subjects who received BOS161721 was not observed.

1.2.5.5 Malignancy

The stimulatory effect of IL-21 on NK cells and CD8+ T-cells suggests the cytokine may have anti-tumor activity. Nonclinical studies have demonstrated significant anti-tumor effects of IL-21 in a number of tumor models. IL-21 therapy of human metastatic melanoma and renal cell carcinoma has demonstrated POC with significant increases in levels of perforin, granzyme B,

and interferon gamma (IFNγ) expression in CD8+ T-cells and NK T-cells. Clinical response has been limited in these generally unmanageable diseases.

The impact of treatment with anti-IL-21 therapy on the development or growth of malignancies is not known; however, as with other immunomodulatory biologic agents, treatment with BOS161721 may result in an increase in the risk of malignancies. NK cell suppression by IL-21 neutralization may represent a biological mechanism for a potential risk for malignancy. Patients with a history or current diagnosis of cancer within the past 5 years, with the exception of non-melanoma skin cancer or cervical cancer in situ treated with apparent success with curative therapy, are excluded from the study.

Based on the limited Phase 1 SAD study (BOS161721-01), malignancy in subjects who received BOS161721 was not observed.

1.2.5.6 Hepatic Function Abnormality

There is no substantial evidence suggesting BOS161721 is associated with liver function abnormality. However, as a precaution, patients with a history of abnormal alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), or bilirubin at screening (ALT/AST > 2 × upper limit of normal [ULN]; total bilirubin > 1.5 × [ULN] and judged by the investigator to be clinically significant) were excluded from the Phase 1 SAD study (BOS161721-01), and will be excluded from this trial. Patients with a positive hepatitis B or C test or a history of alcohol dependence will also be excluded.

Based on the limited Phase 1 SAD study (BOS161721-01), hepatic function abnormality in subjects who received BOS161721 was not observed.

1.2.5.7 Failure of Vaccination

IL-21 is a key cytokine in development of B-cells into immunoglobulin-secreting plasma cells. Abnormal signaling through the IL-21R/Janus Kinase (JAK)3/signal transducer and activator of transcription (STAT3) pathway leads to defective humoral immune responses to both T-dependent and T-independent antigens and impairs the establishment of long-lasting B-cell memory. Abnormal signaling through the pathway has been related to decreased specific antibody responses following vaccination, and to increased susceptibility to encapsulated bacterial infections.[38]

The effect of BOS161721 was evaluated in in vivo single dose studies in Cynomolgus monkey in which the animals received vaccination to T-cell dependent KLH antigen to stimulate a TDAR. These in vivo studies demonstrated that BOS161721 significantly inhibited B-cell proliferation and IgG antibody responses to the KLH protein antigen; however, it is worth noting that BOS161721 administration did not produce any remarkable changes in anti-KLH antibody data for IgM, IgG1, IgG3, and IgG4 or anti-tetanus toxoid (TT) antibody data for IgM, IgG, IgG1, or IgE during the dosing phase in the same study.

1.2.5.8 Potential for Drug-Drug Interactions

Drug-drug interactions were not evaluated in the Phase 1 SAD study (BOS161721-01), which included only healthy adult subjects. Use of prescription medications (with the exceptions of oral contraceptives), and over-the-counter (OTC) treatments including herbal supplements such as St John's Wort (except multivitamins), in the 2 weeks prior to screening was prohibited in the SAD study.

See Section 4.5 for other specific exclusion criteria which support lowered risk of interactions, and Section 4.6.1 for corticosteroid (CS) dosing. In addition, Section 1.2.5.6 describes considerations for hepatic function for this study.

1.2.5.9 Potential Risk to Fetal Development

No data on preclinical reproductive toxicity are available at the time of this study.

2 STUDY OBJECTIVES AND ENDPOINTS

This trial has separate objectives and endpoints for the MAD Phase 1b and POC Phase 2 portions of the study. The primary, secondary, and exploratory objectives for each phase, as applicable, are described below with their corresponding endpoints.

2.1 Phase 1b Multiple Ascending Dose

OBJECTIVES	ENDPOINTS
Primary	
• To assess safety, tolerability, and immunogenicity of repeat doses of BOS161721 (20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment, in order to estimate the optimal dose.	Safety Endpoints • Incidence and severity of AEs and SAEs, related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • Columbia Suicide Severity Rating Scale (C-SSRS) • 12-lead ECGs parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from baseline • Physical examinations changes from baseline • ADAs • Study drug exposure/compliance
Secondary	
• To characterize the PK of BOS161721 and select the optimal dose of BOS161721 based on safety, PK, and PD effects in patients with mild to moderate SLE.	Pharmacokinetic Endpoints • BOS161721 concentration by visit and time point • Maximum observed concentration (C_{max}), T_{max}, area under the concentration-time curve (AUC), terminal elimination half-life ($t_{½}$), systematic clearance (C_L), volume of distribution (V_d)

	Pharmacodynamic Endpoints • Results and changes (or shifts) from baseline to each visit in phosphorylated signal transducer and activator of transcription 3 (pSTAT3), C3 and C4 levels, and leukocyte immunophenotype • Results and changes (or shifts) from baseline in anti-double-stranded DNA (dsDNA), antinuclear antibodies (ANA), anti-Sjögren syndrome A and B (SSA, SSB), Smith (Sm), and antiphospholipid (APL) autoantibodies at each visit • Results and changes (or shifts) from baseline in abrogation of IL-21 gene signature at each indicated visit
Exploratory	
• CCI	• CCI • CCI
• CCI	• CCI
• CCI	• CCI

2.2 Phase 2 Proof of Concept

OBJECTIVES	ENDPOINTS
Primary	
• To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on the SRI-4	Primary Efficacy Endpoint • The proportion of patients with a SRI-4 response at Day 210 (see Section 6.3.4.1)
Secondary	
To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on clinical indicators of SLE activity, in adult patients with moderately to severely active SLE on limited background standard of care treatment	Secondary Efficacy Endpoints • The proportion of patients with: - SRI-4 response at each visit - SRI-5 and SRI-6 response at each visit (Section 6.3.4.2) - a sustained reduction of oral corticosteroid (CS) (≤ 10 mg/day and ≤ Day 0 dose) between Day 120 and Day 210 - new BILAG A flare or > 1 BILAG B flares relative to baseline through Day 210 - PGA worsening - a BICLA response - a CLASI response - medication failures • Results and changes from baseline in**:** - CLASI - swollen and tender joints ACR-28 - SLEDAI-2K - SLICC/ACR damage index • Time to medication failure • Duration of longest SRI-4 response • Time to first SRI-4 response • Time to BILAG A flare or > 1 BILAG B flare compared to baseline through Day 210
Safety	
• To assess safety and tolerability of repeat doses of BOS161721 (20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment	Safety Endpoints • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • C-SSRS • 12-lead ECGs parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from baseline • Physical examinations changes from baseline • ADAs • Study drug exposure/compliance
Exploratory	

• CCI	CCI
• CCI	• CCI
• CCI	• CCI

3 STUDY PLAN

3.1 Study Design

This is a Phase 1b/2 combined, randomized, multicenter, double-blind, placebo-controlled trial to study the clinical efficacy, safety, and PK of SC doses of BOS161721 in adult patients with moderately to severely active SLE. After successfully completing a screening phase, eligible patients will be randomized to a specified dose of BOS161721 or placebo. The dosing schedule will be monthly.

The trial will consist of 2 double-blinded portions: MAD Phase 1b and POC Phase 2. Patients may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180, followed by safety follow-up visits at Days 210, 240, and 270.

SLE disease activity assessment data will be centrally reviewed by medical monitor and sponsor to ensure the scores are clinically meaningful and compliant with specific definition. The scope of responsibility includes, but is not limited to, review and confirmation of "A" and "B" BILAG system organ disease, confirmation of clinical components of the SLEDAI-2K score at screening and during the study, and cross-validation of the instruments used in this study to assess the disease activity. Further details on the content and methods of data reports by the medical monitor and sponsor will be outlined in the Medical Data Review Plan along with the processes and procedures that will be followed.

3.1.1 Multiple Ascending Dose Phase 1b

The MAD portion will consist of 3 cohorts:

- Cohort 1 (20 mg SC) will include 6 patients

- 5 patients will receive BOS161721 (active group) and 1 patient will receive placebo (placebo group)

- Cohorts 2 (60 mg SC) and 3 (120 mg SC) will include 12 patients each
  - 9 patients in the active group and 3 in the placebo group

Doses selected for each of the 3 cohorts is based on a 90-day safety, tolerability, PK and PD data review from the Phase 1 SAD study (BOS161721-01) in healthy subjects. All doses selected for the MAD part of the study are projected not to exceed the mean exposure of that achieved in the SAD study.

3.1.1.1 Dose Escalation for the MAD Portion

The MAD portion of the study design is staggered, where after the 6 patients in Cohort 1 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 2 begins dosing (after the DMC evaluation of the safety and tolerability data from Cohort 1). Similarly, after 8 of the 12 patients in Cohort 2 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 3 begins dosing after the DMC evaluation of the safety and tolerability data from Cohorts 1 and 2. Each cohort will continue at their assigned dose level through their respective 6-month treatment periods (See Study Schematic, Section 3.1). If patients discontinue the study in a cohort prior to adequate safety follow-up, he/she may be replaced.

Criteria for dose escalation are further described in the DMC Charter. See Section 3.1.1.2 for additional details about DLTs.

3.1.1.2 Dose Limiting Toxicity (DLT)

Severity of adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. For the purpose of dose escalation, any of the following AEs occurring after study drug administration, which are attributable to the study drug, will be considered DLTs:

Hematologic:

- Grade 4 neutropenia
- Grade 3 neutropenic infection
- Grade 3 thrombocytopenia with bleeding
- Grade 4 thrombocytopenia

Non-Hematologic:

- Grade 3 or above toxicities, persisting after optimal treatment with standard medical therapy (eg, anti-emetics, anti-diarrheals)

- Drug-induced liver injury ([DILI], Hy's Law), as defined in Section 6.2.2.6.3

Investigators should always manage their patients according to their medical judgment which may include interruption of study drug based on the particular clinical circumstances.

3.1.1.3 DMC Recommendations

During scheduled meetings, the DMC will review relevant study data for safety or benefit-risk concern. During the MAD part of the study, the DMC may provide the following recommendations to the sponsor:

- Expanding a cohort at a specific dosing level, or repeating a lower dose in a subsequent cohort
- Continuing a dose level for a given cohort
- Escalating a dose level for a subsequent cohort
- Termination of current or previous cohort(s)

Further dosing in a given cohort will be halted if 2 or more DLTs are identified intra- and inter-patients dosed. For the POC portion, the DMC and Boston Pharmaceuticals will conduct a data review to determine which dose will be carried forward into the POC Phase 2 part of the study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2, and 3; this dose will not exceed doses tested during the MAD portion. The DMC will be reviewing all relevant data from Cohorts 1, 2, and 3 that is available 30 days after the last patient from Cohort 3 receives the third dose. Details are provided in the DMC Charter.

3.1.2 POC Phase 2

3.1.2.1 BOS161721 Dose

The optimal dose is chosen based on MAD Phase 1b safety, tolerability, immunogenicity, and PK and PD data. The dose will be communicated by a letter to site investigators participating in the POC Phase 2 portion, and to the IRB/IEC.

3.1.2.2 POC Study Design

For the POC part of the study, approximately 156 additional patients will be randomized to active or placebo groups in a 2:1 ratio.

As in the MAD part of the study, each patient in the POC portion may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180. Assessments will be completed according to the Schedule of Assessments (Section 3.4). Dose selection will be based on the DMC and sponsor's assessment of safety, tolerability, immunogenicity, and PK and PD data from the MAD portion of 30 patients treated with BOS161721/placebo.

DMC safety reviews will be conducted periodically throughout the study as described in the DMC charter.

3.2 Randomization and Blinding

This is a randomized, double-blind study.

Patients meeting all inclusion and exclusion criteria will be centrally randomized to either placebo or BOS161721 using an IWRS according to a randomization list generated by an independent, non-study statistician. Randomization will be performed separately for each study portion and separately for each cohort in the Phase 1b and 2 portions as follows:

Phase/Cohort	Number of Patients	Randomization Ratio BOS161721:Placebo
Phase 1b/Cohort 1	6	5:1
Phase 1b/Cohort 2	12	3:1
Phase 1b/Cohort 3	12	3:1
Phase 2	156*	2:1

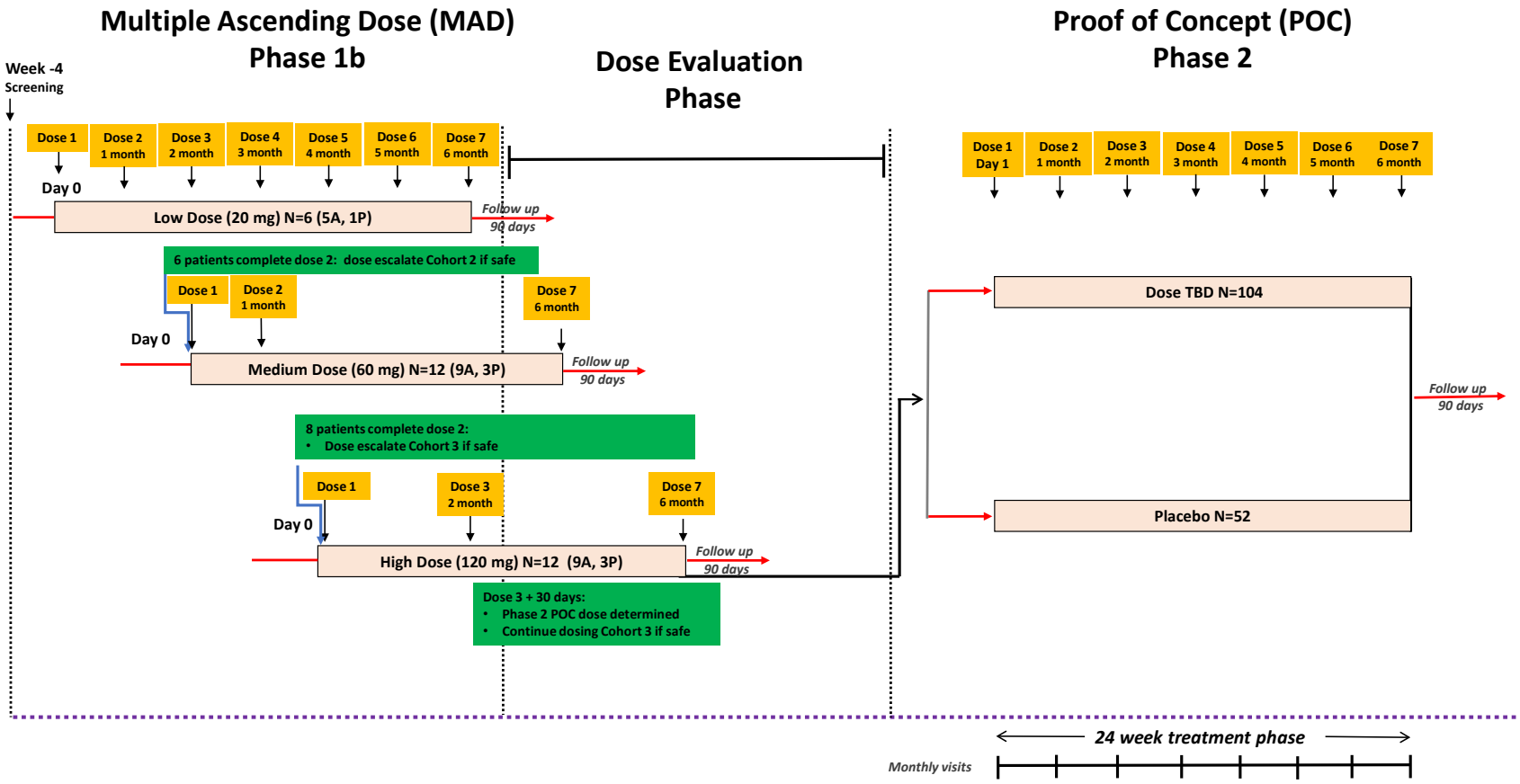
*Additional patients may be enrolled to ensure sufficient numbers of patients are in the full analysis set (FAS).

Eligible patients will be assigned to the study portion which is active at time of enrollment. Similarly, patients in the Phase 1b MAD will be assigned to the cohort which is active. Each patient will be assigned a unique randomization number which will not be reused.

All patients, investigators, and study team participants will be blinded to treatment assignment. An independent biostatistician not otherwise involved on the study will be unblinded and prepare materials for the interim analysis (IA) and the DMC safety reviews. The DMC will review unblinded data during safety reviews and the IA. A limited team at Boston Pharmaceuticals will review unblinded results from the Phase 1b MAD portion during the IA to determine the dose that will be used for the Phase 2 POC portion of the study. Details regarding maintenance of the blinding and content of data reviews will be described in the DMC charter or related study documentation.

3.3 Study Schematic

Figure 2. Study Diagram for MAD Phase 1b and POC Phase 2



A = active drug (BOS161721); P = placebo

3.4 Schedule of Assessments

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
GENERAL ASSESSMENTS																
Informed consent	X															
Inclusion/Exclusion criteria	X															
Medical history	X															
Demographics	X															
SLICC Criteria for SLE	X															
Concomitant medication[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[c]		X														
BOS161721 or placebo dosing		X			X		X	X	X	X	X					
SAFETY ASSESSMENTS																
Full physical exam	X	X														
Chest x-ray[d]	X															
C-SSRS	X	X						X			X					
AEs and SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	X	X			X			X								X
Injection site reaction assessment		X[f]	X		X		X	X	X	X	X	X	X	X	X	X
Targeted physical examination				X	X	X	X	X	X	X	X			X	X	X
Vital signs (BP, HR, and temperature)[g]	X	X		X	X	X	X	X	X	X	X			X	X	X
EFFICACY ASSESSMENTS																
BILAG-2004 Index	X	X			X		X	X	X	X	X			X	X	X

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
SLEDAI-2K	X	X			X		X	X	X	X	X			X	X	X
PGA of disease activity	X	X			X		X	X	X	X	X			X	X	X
ACR-28 joint count	X	X			X		X	X	X	X	X			X	X	X
CLASI	X	X			X		X	X	X	X	X			X	X	X
CCI		X			X		X	X	X	X	X			X	X	X
SLICC/ACR Damage Index		X									X					
CCI		X			X		X	X	X	X	X			X	X	X
LABORATORY ASSESSMENTS																
CD4+ count	X	X		X	X	X		X			X					
Clinical laboratory assessments (hematology and clinical chemistry)[h]	X	X			X	X	X	X	X	X	X			X	X	X
Coomb's test direct[i]	X	X			X		X	X	X	X	X			X	X	X
Total IgG and IgM	X	X		X	X	X		X			X					
Plasma CCI	X	X			X		X	X	X	X	X			X	X	X
Plasma CCI & CCI		X		X	X		X	X			X					
Whole blood for leukocyte immunophenotype		X		X	X		X	X			X					
ADA[j]		X		X	X		X	X			X					X
nAb[k]								X			X					
pSTAT3[l]		X			X	X	X	X								
CCI		X		X				X			X					X
CCI		X														

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
CCI [redacted]	X	X			X		X	X	X	X	X			X[m]	X[m]	X[m]
CRP	X							X								X
Serum pregnancy test (women)	X															
FSH (postmenopausal women)	X															
Urine pregnancy test (women)[n]		X			X		X	X	X	X	X					X
TB test (QuantiFERON-TB Gold In-Tube)[d]	X															
Serology (hepatitis B and C, HIV-1/2 combination)	X															
Stool sample[o]	X															
Spot urine for protein/creatinine ratio	X	X			X		X	X	X	X	X			X	X	X
Urinalysis	X	X			X		X	X	X	X	X			X	X	X

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
PK Labs																
Predose		X			X		X	X	X	X	X					
Predose PK Window		60m			± 3d		± 3d	± 3d	± 3d	± 3d	± 3d					
Postdose		X[p]	X	X	X[p]						X[p]	X	X	X	X	X
Postdose PK Window		4h ± 30m 8h ± 45m 24h ± 60m	± 1d	± 3d	4h ± 30m 8h ± 45m 24h ± 60m						4h ± 30m 8h ± 45m 24h ± 60m	± 3d	± 3d	± 3d	± 3d	± 3d

Abbreviations: ACR = American College of Rheumatology; ADA= anti-drug antibody; AE = adverse event; CCI [redacted]; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; C = complement; CD4+ = cluster of differentiation 4; CLASI = Cutaneous Lupus Area and Severity Index; CRP = C-reactive protein; C-SSRS = Columbia Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; CCI [redacted]; FSH = follicle stimulating hormone; h = hour; HR = heart rate; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IL-21 = interleukin 21; IV = intravenous; m = minute; nAb = neutralizing antibody; PGA = Physician's Global Assessment; PK = pharmacokinetic; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; SAE = serious adverse event; SC = subcutaneous; CCI [redacted]; SLEDAI-2K = SLE Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; CCI [redacted]; TB = tuberculosis; TDAR = T-cell dependent antigen response.

[a] Screening assessments will be performed over more than 1 visit.

[b] Concomitant use of oral corticosteroids: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). See Section 4.6.1 for further details.

[c] Randomization should occur after patient eligibility has been confirmed by central eligibility review.

[d] If patients have had a TB test and chest x ray within 3 months prior to screening, then these assessments do not need to be repeated during screening. The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

[e] ECGs will be performed after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws.

[f] Injection site reaction assessments to be performed at 2 hours postdose.

[g] Vital signs will be assessed after the patient has been supine and at rest ≥ 5 minutes. Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours postdose, as well as on each of the scheduled outpatient days in the table above (excluding PK-only site visits at Days 7, 187, and 195). When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**

[h] Clinical laboratory assessments will include a fasting glucose and lipid panel, with exception of screening (Visit 1) which will be nonfasting.

[i] When clinically indicated for hemolytic anemia.

[j] Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only assayed (analyzed) if the patient had a positive ADA on Day 90.

[k] nAb is collected for all patients, though will only be analyzed by central lab if patient is positive for ADA at Day 90.

[l] Predose (trough) samples only.

[m] Only CCI collected during safety follow-up visits.

[n] Urine pregnancy test will be collected on WOCBP prior to study drug administration on dosing visits.

[o] Cryptosporidium test is required at screening. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

[p] Postdose samples will be collected at 4, 8, and 24 hours after study drug administration on Days 0, 30, and 180.

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC)

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
GENERAL ASSESSMENTS														
Informed consent	X													
Inclusion/Exclusion criteria	X													
Medical history	X													
Demographics	X													
SLICC Criteria for SLE	X													
Concomitant medication[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[c]		X												
BOS161721 or placebo dosing		X		X	X	X	X	X	X					
SAFETY ASSESSMENTS														
Full physical exam	X	X												
Chest x-ray[d]	X													
C-SSRS	X	X				X			X					
AEs and SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	X	X		X		X								X
Injection site reaction assessment		X[f]		X	X	X	X	X	X	X	X	X	X	X
Targeted physical examination			X	X	X	X	X	X	X			X	X	X
Vital signs (BP, HR, and temperature)[g]	X	X	X	X	X	X	X	X	X			X	X	X
EFFICACY ASSESSMENTS														
BILAG-2004 Index	X	X		X	X	X	X	X	X			X	X	X
SLEDAI-2K	X	X		X	X	X	X	X	X			X	X	X
PGA	X	X		X	X	X	X	X	X			X	X	X
ACR-28 joint count	X	X		X	X	X	X	X	X			X	X	X
CLASI	X	X		X	X	X	X	X	X			X	X	X
CCI		X		X	X	X	X	X	X			X	X	X

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC)

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
SLICC/ACR Damage Index		X							X					
CCI		X		X	X	X	X	X	X			X	X	X
LABORATORY ASSESSMENTS														
CD4+ count	X	X	X	X		X			X					
Clinical laboratory assessments (hematology and clinical chemistry)[h]	X	X		X	X	X	X	X	X			X	X	X
Coomb's test direct[i]	X	X		X	X	X	X	X	X			X	X	X
Total IgG and IgM	X	X	X	X		X			X					
Plasma CCI	X	X		X	X	X	X	X	X			X	X	X
Plasma CCI & CCI		X	X	X		X			X					
Whole blood for leukocyte immunophenotype		X	X	X		X			X					
ADA[j]		X	X	X	X	X			X					X
nAb[k]						X			X					
CCI		X	X			X			X					X
CCI		X												
CCI	X	X		X	X	X	X	X	X			X[l]	X[l]	X[l]
CRP	X					X								X
Serum pregnancy test (women)	X													
FSH (postmenopausal women)	X													
Urine pregnancy test (women)[m]		X		X	X	X	X	X	X					X
TB test (QuantiFERON-TB Gold In-Tube)[d]	X													
Serology (hepatitis B and C, HIV-1/2 combination)	X													

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC)

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
Stool sample[n]	X													
Spot urine for protein/creatinine ratio	X	X		X	X	X	X	X	X			X	X	X
Urinalysis	X	X		X	X	X	X	X	X			X	X	X
PK Labs[o]														
Predose		X		X	X	X	X	X	X					
Predose PK Window		60m		± 3d	± 3d	± 3d	± 3d	± 3d	± 3d					
Postdose			X							X	X	X	X	X
Predose PK Window			± 3d							± 3d	± 3d	± 3d	± 3d	± 3d

Abbreviations: ACR = American College of Rheumatology; ADA= anti-drug antibody; AE = adverse event; CCI [redacted]; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; C = complement; CD4+ = cluster of differentiation 4; CLASI = Cutaneous Lupus Area and Severity Index; CRP = C-reactive protein; C-SSRS = Columbia Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; CCI [redacted]; FSH = follicle stimulating hormone; h = hour; HR = heart rate; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IL-21 = interleukin 21; IV = intravenous; m = minute; nAb = neutralizing antibody; PGA = Physician's Global Assessment; PK = pharmacokinetic; SAE = serious adverse event; SC = subcutaneous; CCI [redacted]; SLEDAI-2K = SLE Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; CCI [redacted]; TB = tuberculosis; TDAR = T-cell dependent antigen response.

[a] Screening assessments will be performed over more than 1 visit.

[b] Concomitant use of oral corticosteroids: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). See Section 4.6.1 for further details.

[c] Randomization should occur after patient eligibility has been confirmed. The actual randomization procedure can be completed on Day -1 after eligibility confirmation or the morning of Day 0 prior to dosing for logistical purposes.

[d] If patients have had a TB test and chest x ray within 3 months prior to screening, then these assessments do not need to be repeated during screening. The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

[e] ECGs will be performed after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws.

[f] Injection site reaction assessments to be performed at 2 hours postdose.

[g] Vital signs will be assessed after the patient has been supine and at rest ≥ 5 minutes. Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours postdose, as well as on each of the scheduled outpatient days in the table above (excluding PK-only site visits at Days 187 and 195). When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC)

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**

[h] Clinical laboratory assessments will include a fasting glucose and lipid panel, with exception of screening (Visit 1) which will be nonfasting.

[i] When clinically indicated for hemolytic anemia.

[j] Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only assayed (analyzed) if the patient had a positive ADA on Day 90.

[k] nAb is collected for all patients, though will only be analyzed by central lab if patient is positive for ADA at Day 90.

[l] Only CCI collected during safety follow-up visits.

[m] Urine pregnancy test will be collected on WOCBP prior to study drug administration on dosing visits.

[n] Cryptosporidium test is required at screening. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

[o] PK samples will only be collected at the investigational sites that will be participating in the PK portion of the study.

3.5 End of Study

End of Study (Individual Patient): A patient is considered at the end of study if he/she has withdrawn, prematurely discontinued, or completed all of the study procedures including the last visit.

End of Study (End of trial): The end of the study is defined as the date of the last visit of the last patient in the study globally, or the date of which the last patient withdraws or discontinues if all prior enrolled patients have already completed/withdrawn.

4 POPULATION

4.1 Participant Recruitment

Advertisements approved by the IRB, and investigator databases, may be used as recruitment procedures for adult men and women with moderately to severely active SLE.

4.2 Number of Patients

Approximately 186 male and female patients are planned for enrollment, but may be adjusted upward according to the dropout (noncompliance) rate, which will be monitored in a blinded fashion in an ongoing basis. Approximately 30 patients will be randomized for the MAD Phase 1b portion, and approximately 156 additional patients will be randomized in the POC Phase 2 portion. Note that approximately 24 dropouts are assumed.

4.3 Patient Screening

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular individual. Patient eligibility will be reviewed and confirmed by the medical monitor or designee prior to randomization. Screening assessments (see the Schedule of Assessments [Section 3.4]) for this study must be performed between Day -28 and Day -1.

4.4 Inclusion Criteria

Patients who meet the following criteria will be considered eligible to participate in this clinical study:

1. Men and women, ages 18 to 70 years, inclusive
2. Patients must be mentally capable of giving consent and there must be evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study
3. Patients must have SLE as defined by meeting 4 of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE (with at least 1 clinical and 1

immunologic criterion or Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies), either sequentially or simultaneously

4. At screening, patients must have at least 1 of the following:
   a. Elevated ANA ≥ 1:80 via immunofluorescent assay at the central laboratory
   b. Positive anti-dsDNA or anti-Smith (Sm) above the normal level as determined by the central laboratory
   c. C3 or C4 levels below normal as determined by central lab
5. At screening, the SLE Disease Activity Index 2000 (SLEDAI-2K) must be ≥ 6, including points from at least 1 of the following clinical components:
   a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis
      i. Excluding parameters which require central laboratory results: hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia
      ii. Points from lupus headache and organic brain syndrome will also be excluded
6. On Day 0, the SLEDAI-2K must be ≥ 6, including points from at least 1 of the following clinical components:
   a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis
      i. Excluding parameters which require central laboratory results: hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia
      ii. Points from lupus headache and organic brain syndrome will also be excluded
7. Patients must have at least 1A or 2Bs from the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer:
   a. BILAG A or B score in the mucocutaneous body system
   b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis defined as follows:
      i. "BILAG A:" Severe Arthritis, (BILAG item number 41), manifested by observed active synovitis in ≥ 2 joints with marked loss of functional range of movements and significant impairment of basic activities of daily living that has been present on several days cumulatively over the past 30 days, including at the time of the screening visit. See APPENDIX 5 for additional detailed specifications.
         - Basic ADLs are defined as the following activities which require assistance or assistive devices, (at least 1 must be present and documented in source):

- Ambulation, toileting, grooming- including bathing and dressing; feeding oneself

ii. "BILAG B:" Moderate Arthritis, Tendonitis or Tenosynovitis, (BILAG item number 42), defined as tendonitis/tenosynovitis, or active synovitis in ≥ 1 joint, (observed or throughout history), with some loss of functional range of movements which lead to some loss of functional range of motion as manifested by effects on instrumental ADLs such as:

- Cooking, driving, using the telephone or computer, shopping, cleaning, etc, and has been present on several days over the last 30 days, and is present at the time of the screening visit

If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in the other body systems for a total of 2 "B" BILAG body system scores

8. Patients must be currently receiving at least 1 of the following:
   a. Administration for a minimum of 12 weeks, and a stable dose for at least 56 days (8 weeks prior to signing consent) of the following permitted steroid-sparing agents:
      i. Azathioprine (AZA), mycophenolate mofetil or mycophenolic acid, chloroquine, hydroxychloroquine, or methotrexate (MTX)
   b. Prednisone (or prednisone-equivalent) cannot exceed 30 mg/day at screening for a patient to be eligible and must be stable at a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization) (see APPENDIX 3)
9. Women of childbearing potential (WOCBP; see Section 4.7 for full information regarding WOCBP, definition of menopause, and contraception):
   a. Must have a negative serum pregnancy test at screening. Urine pregnancy test must be negative prior to first dose
   b. Must not be breastfeeding
   c. Must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS161721 plus 30 days (duration of ovulatory cycle) for a total of 36 weeks after treatment completion
10. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of BOS161721 plus 90 days (duration of sperm turnover) for a total of 44 weeks after treatment completion
11. Patients must demonstrate willingness and ability to comply with the scheduled study visits, treatment plans, laboratory tests, and other procedures

4.5 Exclusion Criteria

Patients presenting with any of the following will not be included in this study:

1. Drug-induced SLE, rather than "idiopathic" SLE
2. Other systemic autoimmune disease (eg, erosive arthritis, rheumatoid arthritis [RA], multiple sclerosis [MS], systemic scleroderma, or vasculitis not related to SLE)
   a. RA-Lupus overlap (Rupus), and secondary Sjögren syndrome are allowed
3. Any major surgery within 6 weeks of study drug administration, (Day 0), or any elective surgery planned during the course of the study
4. Any history or risk for tuberculosis (TB), specifically those with:
   a. Current clinical, radiographic, or laboratory evidence of active TB
   b. History of active TB
   c. Latent TB defined as positive QuantiFERON-TB Gold In-Tube (QFT-G) or other diagnostic test in the absence of clinical manifestations. Latent TB is not excluded if the patient has documented completion of adequate course of prophylactic treatment with regimen recommended by local health authority guideline, or the patient has started treatment with isoniazid, or other regimen recommended by local health authority guidelines for at least 1 month before Day 0 and continues to receive the prophylactic treatment during study until the treatment course is completed.
5. Active or unstable lupus neuropsychiatric manifestations, including but not limited to any condition defined by BILAG A criteria, with the exception of mononeuritis multiplex and polyneuropathy, which are allowed
6. Severe proliferative lupus nephritis, (WHO Class III, IV), which requires or may require induction treatment with cytotoxic agents or high dose CS
7. Concomitant illness that, in the opinion of the investigator, is likely to require additional systemic glucocorticosteroid therapy during the study, (eg, asthma), is exclusionary
   a. However, treatment for asthma with inhalational CS therapy is allowed
8. Use or planned use of concomitant medication outside of standard of baseline treatment for SLE from Day -1 or for any time during the study. (See Section 4.6 for prohibited concomitant medication)
9. Active and clinically significant infection (bacterial, fungal, viral, or other) within 60 days prior to first dose of study drug. Clinically significant is defined as requiring systemic parenteral antibiotics or hospitalization
10. A history of opportunistic infection, or a history of recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years
11. Chronic viral hepatitis including hepatitis B (HBV) and hepatitis C (HCV) unless patient received curative treatment for HCV and has a documented negative viral load, known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness

12. Cryptosporidium in the stool sample at screening
13. White blood cells (WBC) < 1,200/mm^3 (1.2×10^9/L) at screening
14. Absolute neutrophil count (ANC) < 500/mm^3 at screening
15. CD4+ count < 350/μL at screening
16. Platelets < 50,000/mm^3 (50×10^9/L) or < 35,000/ mm^3 (35×10^9/L) if related to SLE, at screening
17. Hemoglobin < 8 g/dL or < 7 g/dL at screening if related to SLE
18. Proteinuria > 3.0 g/day (3000 mg/day) at screening or equivalent level of proteinuria as assessed by protein/creatinine ratio (3 mg/mg or 339 mg/mmol)
19. Serum creatinine > 2.0 mg/dL at screening or creatinine clearance (CrCL) < 40 ml/minute based on Cockcroft-Gault calculation[39]:

    GFR = ([1 for male] or [0.85 for female]) × (140 − Age) × BW / (72 × Creatinine)

20. Serum ALT and/or serum AST > 2 × ULN at screening, unless explicitly related to lupus based on the investigator's judgment
21. Creatinine kinase (CK) > 3.0 × ULN at screening, unless it is related to lupus myositis
22. Direct bilirubin > 1.5 × ULN at screening (unless related to Gilbert's syndrome)
23. Any other laboratory test results that, in the opinion of the Investigator, might place a patient at unacceptable risk for participating in this study
24. History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody (eg, IgG protein) or molecules made of components of monoclonal antibodies
25. History substance and/or alcohol abuse or dependence within the past 1 year, at the investigator's judgment
26. History of cancer within the last 5 years (except for cutaneous basal cell or squamous cell cancer, or cervical cancer in situ resolved by excision)
27. Any other severe acute or chronic medical or psychiatric condition, including recent (within the past year) medical conditions (eg, cardiovascular conditions, respiratory illnesses) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study
28. Investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or patients who are employees of the sponsor or directly involved in the conduct of the trial
29. Currently participating in, or who have participated in other interventional (drug or device) clinical study within 30 days or 5 half-lives of baseline, whichever is longer

30. Recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4 or 5 on the C-SSRS
31. Current or pending incarceration
32. Current or pending compulsory detainment for treatment of either a psychiatric or physical (eg, infectious disease) illness

4.6 Concomitant Medications

Any medicinal product, prescribed or OTC, including herbal and other nontraditional remedies, is considered a concomitant medication. Patients should stay on stable regimen of other concomitant medications for the treatment of SLE (eg, analgesics, NSAIDs, statins, ACE inhibitors/ARBs and other antihypertensive drugs), unless changes in these treatments are clinically indicated. Use of any other drugs for non-SLE conditions, including over-the-counter medications and herbal preparations, should remain stable unless change or addition is clinically necessary. Discussion with the medical monitor prior to initiation of new medication is strongly recommended. Any concomitant therapies must be recorded on the eCRF. Prior and concomitant medication use will be recorded for the 30 days prior to screening until the last follow-up visit. In addition, historical treatment for SLE (including immunosuppressant, anti-malarial, corticosteroid, and/or biologic agent) will be recorded for the 48 weeks prior to screening in the eCRF.

4.6.1 Oral Corticosteroid Dose

Prior to randomization, oral CSs (prednisone or prednisone equivalent), may be used in accordance with the investigator's clinical judgment and best standard of care. See APPENDIX 3 for examples of equivalents.

A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day).

After Day 0 (after initiation of study therapy), no up-titration above 10 mg/day is allowed except for up to 1 CS burst for increased disease activity.

Tapering of steroids during the course of the study will be encouraged and should be evaluated at all visits.

- Once a patient has received the first dose of study drug, prednisone (or prednisone equivalent) may be tapered down at the discretion of the investigator
    - Tapering is allowed after randomization except within 60 days of the primary (Day 210) and secondary (Day 120) endpoint assessments. Between Day 60 and Day 120, and between Day 150 and Day 210, oral CS doses must be held constant.

A maximum of 1 oral CS "burst" for increased SLE disease activity will be allowed during the study between Day 0 and Day 60, according to the following:

- An oral CS "burst" between Day 0 and Day 60; (an increase of ≤ 40 mg/day of prednisone or equivalent), which must be tapered down to a maximum of 10 mg/day within 2 weeks of initiation of the "burst"
    - Alternatively, a single intramuscular (IM) dose of methylprednisolone (40 mg or equivalent) is permitted
    - The course of the oral CS "burst" is not permitted to extend beyond Day 60

Treatment with inhalational CS therapy (eg, for asthma), or by any other route, is allowed. Other concomitant medications for SLE need to be taken at stable doses as per the inclusion criteria (Section 4.4).

4.6.2 Other Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study drug administration and during the study are described below, and washout requirements are provided in APPENDIX 4. Medications taken within 30 days prior to screening must be recorded on the eCRF.

1. Prior exposure to BOS161721
2. Patients who have received treatment with anti-CD20 monoclonal antibodies within 24 weeks of screening; recovery of B cells (CD19+) must be documented (record absolute number of CD19+ B cells)
3. Patients who have received treatment with cyclophosphamide within the 24 weeks prior to screening
4. Patients who have received treatment with cyclosporine (with exception of ophthalmic use), any other calcineurin inhibitor or other immunosuppressive medication not specified in the inclusion criteria within 4 weeks for oral use or 8 weeks for topical use of screening
5. Patients who are currently receiving or are scheduled to receive plasmapheresis or lymphapheresis therapy, or have received such therapy within 24 weeks prior to screening
6. Patients who have received any live vaccines within 30 days of screening. Note: Furthermore, live vaccines should not be used during the course of the study and within the 2 months following last dose. Other inactivated vaccines such as tetanus, etc, may be used according to local guidelines during treatment period
7. Patients who are scheduled or anticipated to have elective surgery during the course of the study
8. Initiation of new immunosuppressant or anti-malarial agent is not permitted. Note: Dose reduction or replacement may be allowed due to intolerability or shortage for patients on a stable dose prior to study initiation

4.7 Women of Childbearing Potential

WOCBP is defined as any woman who has experienced menarche and who has not undergone surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) and is not postmenopausal.

See Section 4.7.2 for detailed information regarding contraceptive requirements for WOCBP.

4.7.1 Determination of Menopause

Menopause is defined as at least 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. Women under the age of 55 years must have a documented serum FSH level > 40 mIU/mL at screening to confirm menopause.

4.7.2 Contraception

WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS161721 plus 30 days (duration of ovulatory cycle) for a total of 36 weeks after treatment completion.

Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS161721 plus 90 days (duration of sperm turnover) for a total of 44 weeks after treatment completion.

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

At a minimum, patients must agree to the use of 1 method of highly effective contraception from the following:

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by patients who are WOCBP or a male patient's WOCBP partner. Women who are partner of men who are patients participating in the study may use hormone-based contraceptives as 1 of the acceptable methods of contraception since they will not be receiving study drug.
- IUDs, such as ParaGard®
- Vasectomy
- Complete abstinence, defined as complete avoidance of heterosexual intercourse, is an acceptable form of contraception. Women who are abstinent while participating in the study must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the patient chooses to forego complete abstinence.

Azoospermic men and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing.

4.8 Deviation from Inclusion/Exclusion Criteria

Deviation from the inclusion or exclusion criteria will not be allowed. If deviation of inclusion/exclusion criteria is discovered after randomization, the investigator should contact the medical monitor for discussion. A decision will be made whether to allow a patient to continue or withdrawal from the study medication.

See Section 6.8 for additional details.

4.8.1 Patient Withdrawal and Replacement

See Section 5.5 for reasons for removal from the trial. Withdrawn patients may be replaced during the MAD part of the study after discussion between the principal investigator or designee and sponsor.

5 STUDY PROCEDURES

Refer to the eCRF completion guidelines for data collection requirements and documentation of study assessments/procedures.

5.1 Screening

Screening will be the same for both the MAD and POC portions of the study.

Screening will take place from Day -28 to Day -1, and assessments may be performed over more than 1 visit. Confirmation that the most current IRB/IEC approved informed consent form (ICF) has been signed must occur before any study-specific screening procedures are performed. Procedures that are part of standard of care are not considered study-specific procedures and may be performed prior to informed consent and used to determine eligibility.

All screened patients will be assigned a unique screening number. The screening number will include a 3-digit site number and a 4-digit sequential number to identify patients from the time of screening. Only eligible patients who are confirmed by central review as meeting the inclusion/exclusion criteria, listed in Section 4.4 and Section 4.5 respectively, will be enrolled in the study. Screened patients who drop out of the clinical study before randomization will be recorded as screen failures. If rescreening occurs, the site will assign a new screening number.

Specific procedures at the screening visit will include:

- Medical history documentation
- Review of inclusion and exclusion criteria
  - Patient medical records must contain documentation of SLE diagnosis
  - C-SSRS
- Concomitant medication documentation
- Demographics
- Full physical examination

- Vital signs
- Chest x-ray (a prior x-ray can be used if taken within 12 weeks of screening date)
- Laboratory evaluations (non-fasting):
  - Hematology and clinical chemistry
  - Serology (Hepatitis B and C; HIV-1/2 combination)
  - TB test
  - CRP
  - Direct Coomb's test (if indicated for hemolytic anemia)
  - CD4+ count, total IgG and IgM levels, plasma CCI , CCI [redacted]
  - Serum pregnancy test (WOCBP)
  - FSH (postmenopausal women)
  - Spot urine for protein/creatinine ratio
  - Urinalysis
  - Stool sample
- 12-lead ECG
- SLE-related indices (BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, Physician's Global Assessment (PGA) of disease activity

Screening procedures are listed in the Schedule of Assessments (Section 3.4), and details are provided in Section 6.

5.1.1 Retesting During Screening Period

A single retesting of laboratory parameters and/or other assessments during the screening period is permitted (in addition to any parameters that require a confirmatory value) only if:

- medically indicated
- there is evidence a laboratory sample was mislabeled, indeterminate, inadequately processed, and/or deteriorated in transit to the central laboratory

Any new result will override the previous result (ie, the most current result prior to randomization) and is the value by which study inclusion/exclusion will be assessed, as it represents the patient's most current clinical state. This will also apply to patients who are being rescreened.

5.2 Enrollment/Randomization and Day 0 Treatment

Randomization should occur after patient eligibility for enrollment has been confirmed by the central eligibility review.

Prior to randomization, the study site should confirm that the patient still meets inclusion/exclusion criteria (especially SLE disease activity and treatment). The site will obtain a randomization number when registering the patient in IWRS. All patients will receive

BOS161721 or placebo according to the kit number assigned by the IWRS randomization scheme.

After randomization, procedures include:

- PROs: CCI
- C-SSRS
- Laboratory evaluations (fasting):
  - Hematology and clinical chemistry
  - Direct Coomb's test (if indicated for hemolytic anemia)
  - CD4+ count, total IgG and IgM levels, plasma CCI, plasma CCI and CCI, whole blood for leukocyte immunophenotype
  - ADA
  - pSTAT3 (predose [trough] samples only in Phase 1b)
  - CCI
  - CCI
  - CCI
  - See Table 1 and Table 2 for details of PK sampling in the MAD and POC portions
  - Urine pregnancy test will be collected on WOCBP prior to study drug administration
  - Spot urine for protein/creatinine ratio
  - Urinalysis
- Concomitant medication documentation
- Documentation of AEs and SAEs (see Section 6.2.2.5 on SAE reporting requirements)
- Full physical examination
- Vital signs (prior to PK blood draw, predose, and at 1 and 2 hours postdose on Day 0)
- 12-lead ECG (prior to PK blood draw)
- SLE-related indices (BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, PGA)
- SLICC/ACR damage index
- Study drug administration:
  - Administration of BOS161721 or placebo will take place on-site, and is discussed in Section 7.3
- Injection site reaction assessment performed at 2 hours postdose

Procedures on Day 0 are listed in the Schedule of Assessments (Section 3.4), and details are provided in Section 6.

All patients who are enrolled, randomized, and receive study drug, or undergo study-specific procedures should reconsent with any updated versions of IRB/IEC approved informed consents during study participation as applicable and per institutional guidelines.

5.3 Treatment Period/Follow-Up Visits

The following procedures will be performed as indicated in the Schedule of Assessments (Table 1 and Table 2). See Schedule of Assessment tables for allowable windows for each visit.

- Targeted physical examination
- Vital signs (prior to PK blood draw)
- Concomitant medication documentation
- Documentation of AEs and SAEs (see Section 6.2.2.5 on SAE reporting requirements)
- PROs: CCI
- Urine pregnancy tests will be collected on WOCBP prior to study drug administration
- Injection site reaction assessments will be performed predose
- Direct Coomb's test (if indicated for hemolytic anemia)
- Spot urine for protein to creatinine ratio
- Urinalysis
- CCI
- Plasma CCI
- PGA, BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, and the CLASI will be completed
- SLICC/ACR Damage Index will be completed at Day 180
- C-SSRS
- ECGs prior to PK blood draw
- See Table 1 and Table 2 for details of PK sampling in the MAD and POC studies, respectively
- Fasting hematology and chemistry assessments
- The CD4+ count and total IgG and IgM levels
- Plasma CCI & CCI, ADA, and whole blood for leukocyte immunophenotype
- pSTAT3 (predose [trough] samples only Phase 1b)
- nAb will be analyzed by central lab if patient is positive for ADA
- CRP
- CCI

5.4 Safety Follow-Up Visits

Safety follow-up visits will take place at Days 210, 240, and 270. These visits will include the following assessments as indicated in the Schedule of Assessments (Table 1 and Table 2):

- PROs: CCI
- Documentation of AEs and SAEs (see Section 6.2.2.5 on SAE reporting requirements)
- Injection site reactions
- Targeted physical examination

- Vital signs (prior to PK blood draw)
- Spot urine for protein/creatinine ratio and urinalysis
- Concomitant medication documentation
- BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, and PGA
- Fasting clinical laboratory assessments (hematology and clinical chemistry)
- Direct Coomb's test (if indicated for hemolytic anemia)
- Plasma CCI
- CCI
- 12-lead ECG (prior to PK blood draw)
- CRP
- ADA
- CCI
- Urine pregnancy test
- See Table 1 and Table 2 for details of PK sampling in the MAD and POC portions, respectively

5.5 Premature Discontinuation

While patients are encouraged to complete all study evaluations, they may withdraw from the study at any time and for any reason. Every effort will be made to determine why any patient withdraws from the study prematurely. If the patient is unreachable by telephone, a registered letter, at the minimum, should be sent to the patient requesting him/her to contact the clinic.

All patients who withdraw from the study with an ongoing AE or SAE must be followed until the end of study or until the event is resolved or deemed stable, respectively.

If a patient withdraws prematurely after dosing, an end of treatment (EOT) visit should be performed (Day 180) and a last follow-up visit 90 days after dosing should be scheduled (Day 270). Safety follow-up visit procedures based on the Schedule of Assessments (see Section 5.4).

Patient participation may be terminated prior to completing the study and the reason recorded as follows:

- AE/SAE
- Protocol deviation
- Lost to follow-up
- Patient withdraws consent at their own request
- Investigator decision
- Decision by sponsor (other than AE/SAE, protocol deviation, or lost to follow-up)

Withdrawn patients may be replaced after discussion between the investigator or designee and sponsor.

6 ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, which may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and wellbeing of the patient. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. All protocol violations are entered directly into the eCRFs.

6.1 Medical History, Demographic and Other Baseline Information

The medical history comprises:

- General medical history
- Documentation of SLE diagnosis
- Historical medication therapy for SLE

The following demographic information will be recorded:

- Age
- Ethnic origin (Hispanic/Latino or not Hispanic/not Latino)
- Race (White, American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black/African American)
- Height (without shoes, in cm)
- Body weight, without shoes (kg)
- Body mass index (BMI [kg/m^2])

Other baseline characteristics will be recorded as follows:

- Concomitant medication documentation (see Section 4.6)
- Status of child bearing potential and contraception

6.2 Safety Assessments

6.2.1 Laboratory Assessments

Laboratory tests will be performed at times defined in the Schedule of Assessments (Section 3.4). Patient eligibility will be determined based on these tests at screening. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

A central laboratory will be used (with the exception of urine pregnancy tests) to ensure accuracy and consistency in test results. Laboratory/analyte results that could unblind the study (ie, biomarker results) will not be reported to investigative sites. Urinalysis will be performed on

midstream, clean catch specimens. Some biomarkers listed above will not be drawn at some sites due to geographical logistical challenges. See the laboratory manual for details.

Endpoint analyses will be based on changes from baseline assessments at Days 120 and 210.

Table 3. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other Safety Tests
Hemoglobin	BUN	pH	Spot urine for protein/creatinine ratio
Hematocrit	Creatinine	Glucose (qual)	FSH[b]
RBC count	Glucose (fasting)	Protein (qual)	Urine pregnancy test[c]
RDW	Calcium	Blood (qual)	QuantiFERON®-TB Gold In-Tube test (QFT-G)[d]
MCV	Sodium	Ketones	
MCH	Potassium	Nitrites	Serology[d] (Hepatitis B and C; HIV-1/2 combination)
MCHC	Chloride	Leukocyte esterase	
Platelet count	Total CO_2 (bicarbonate)	Urobilinogen	Stool sample[e]
WBC count	AST, ALT	Urine bilirubin	Serum pregnancy test
CD4+ count	Total bilirubin	Microscopy[a]	
Total neutrophils (Abs)	Alkaline phosphatase		
	Creatine kinase		
Eosinophils (Abs)	Uric acid		
Monocytes (Abs)	Albumin		
Basophils (Abs)	Total cholesterol (fasting)		
Lymphocytes (Abs)	LDL-C (fasting)		
	HDL-C (fasting)		
	Triglycerides (fasting)		
	Total protein		
	PT/INR		

	Additional Tests[f] (potential Hy's Law)	Immunogenicity, PD and other Biomarker Tests
	AST, ALT (repeat)	ADA
	Total bilirubin (repeat)	nAb[g]
	Albumin (repeat)	pSTAT3 (predose [trough] samples only in Phase 1b)
	Alkaline phosphatase (repeat)	Total IgG & IgM
	Direct bilirubin	Plasma CCI
	Indirect bilirubin	Plasma CCI & CCI
	GGT	Whole blood for leukocyte immunophenotype
	Prothrombin time/international normalized ratio (repeat)	CCI
		CCI
	Creatine kinase (repeat)	Antibodies CCI
		CRP
		Direct Coomb's test[h]

Abbreviations: Abs = absolute; ADA = anti-drug antibody; ALT = alanine aminotransferase; CCI ; CCI ; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C = complement; CD4+ = cluster of differentiation 4; CRP = C-reactive protein; CCI ;; FSH = follicle stimulating hormone;

Table 3. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other Safety Tests

GGT = gamma-glutamyltransferase; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ration; IL-21 = interleukin 21; LDL-C = low-density lipoprotein cholesterol; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = Mean corpuscular volume; nAb = neutralizing antibody; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; PT = prothrombin time; qual = qualitative; RBC = red blood cell; RDW = RBC distribution width; SAE = serious adverse event; SC = subcutaneous; CCI ; TB = tuberculosis.

a. On all urine samples.
b. At screening only, in women who are amenorrheic for at least 12 consecutive months and under 55 years old.
c. For WOCBP.
d. Screening only.
e. At screening, and if a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.
f. Additional testing for potential Hy's Law cases only (See Section 6.2.2.6.3).
g. If patient is positive for ADA.
h. If clinically indicated for hemolytic anemia.

6.2.1.1 Pregnancy testing

For WOCBP, a serum pregnancy test will be performed at screening. Following a negative serum pregnancy result at screening, appropriate contraception must be commenced or continued and a further negative urine pregnancy test results will then be required at the baseline visit before the patient may receive the investigational product. Urine pregnancy tests will also be routinely repeated at study drug administration visits prior to study drug administration, at the last follow up visit day (Day 270) and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive pregnancy test or confirmed pregnancy, the patient will be discontinued from study drug, an EOT visit should be performed (Day 180), and a last follow-up visit 90 days after last dose should be scheduled (Day 270). Safety follow-up visit procedures (see Section 5.4) are specified in the Schedule of Assessments (see Section 3.4).

See Section 6.2.2.7.1 for information on reporting of pregnancies as AEs/SAEs during the study.

6.2.1.2 Tuberculosis Screening

During the screening period, it must be determined and documented that a patient does not have evidence of active or latent or inadequately treated TB per the exclusion criteria (Section 4.5). The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

6.2.1.2.1 Mycobacterium Tuberculosis Testing Using QuantiFERON Test[40]

QuantiFERON®-TB Gold In-Tube (QFT-G) is an in vitro diagnostic test using a peptide cocktail simulating ESAT-6, CFP-10, and TB 7.7 proteins to stimulate cells in heparinized whole blood. Detection of INFγ performed by enzyme-linked immunosorbent assay (ELISA) is used to identify in vitro responses to these peptide antigens that are associated with Mycobacterium

tuberculosis infection. QFT-G is an indirect test for M. tuberculosis infection (including disease) and is intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.

Test results will be reported as positive, negative, or indeterminate. A negative QFT-G test result is required to meet the inclusion criterion. In the case of an indeterminate result, repeat tests should be permitted for the purpose of determining eligibility of patients to enroll in this study. If a repeat test is indeterminate again, the patient is a screen failure. The procedure for using this test and interpreting the results will be described fully in the laboratory manual, which will be provided to investigators.

6.2.2 Adverse Events

6.2.2.1 Definitions

An AE is defined as any untoward medical occurrence experienced by a study patient, whether or not considered drug related by the principal investigator.

AEs are unfavorable changes in a general condition, subjective or objective signs or symptoms, worsening of pre-existing concomitant disease, and clinically significant abnormality in laboratory parameters observed in a patient in the course of a clinical study.

Non-serious SLE manifestations or abnormal laboratory results related to SLE disease activity would not be recorded as AEs unless they meet the definition for SAEs (Section 6.2.2.5).

6.2.2.2 Recording of Adverse Events

AEs should be collected and recorded for each patient from the date of the first dose of study drug until the end of their participation in the study, including the safety follow up period.

AEs may be volunteered spontaneously by the study patient, or discovered by the study staff during physical examinations or by asking an open, nonleading question such as 'How have you been feeling since you were last asked?' All AEs and any required remedial action will be recorded on the Adverse Events eCRF and Safety Adverse Event Form. The details of the AE, date of AE onset, date of AE outcome, and action taken for the AE will be documented together with the principal investigator's assessment of the seriousness of the AE and causal relationship to the study drug and/or the study procedure.

All AEs should be recorded individually, using diagnostic terms where possible. If the diagnosis is not established, individual symptoms may be reported. The AEs will subsequently be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

6.2.2.3 Severity of Adverse Events

Each AE will be assessed by the principal investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03 criteria. [41] When changes in the severity (grade) of an AE occur more frequently than once a day, the maximum severity for the event should be noted for that day. Any change in severity of signs

and symptoms over a number of days will be captured by recording a new AE, with the amended severity grade and the date (and time, if known) of the change.

6.2.2.4 Causality of Adverse Events

The principal investigator will assess the causal relationship between BOS161721 or placebo and the AE. One of the following categories (Table 4) should be selected based on medical judgment, considering the definitions below and all contributing factors.

Table 4. Causality Definitions

Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment (dechallenge[a]) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge[b] procedure if necessary.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (eg, concomitant disease, environmental factors, or other drugs or chemicals).

[a] Dechallenge: Upon discontinuation of a drug suspected of causing an AE, the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation (positive dechallenge), or the symptoms continue despite withdrawal of the drug (negative dechallenge). Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists (for example, as in bone marrow suppression, fixed drug eruptions, or tardive dyskinesia).

[b] Rechallenge: Upon re-administration of a drug suspected of causing an AE in a specific patient in the past, the AE recurs upon exposure (positive rechallenge), or the AE does not recur (negative rechallenge).

An unexpected adverse drug event is any adverse drug event for which the specificity or severity is not consistent with the current IP.

6.2.2.5 Seriousness of Adverse Events

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

- Results in death
- Is life threatening; this means that the patient was at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires hospitalization or prolongation in existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly or birth defect
- Is another important medical event (see below)

Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they

may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in inpatient hospitalization
- Development of drug dependency or drug abuse

Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (eg, elective surgery for a pre-existing condition that has not worsened) need not be considered SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'nonserious' according to the usual criteria.

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are associated with the use of the drug and are serious and unexpected.

6.2.2.6 Adverse Events of Special Interest

AEs of special interest in this study include the following:

1. Anaphylaxis and serious allergic reactions
2. Grades 2 to 5 injection site reaction, including erythema, pain, and induration (See APPENDIX 6)
3. Drug Induced Liver Injury (DILI) assessed following Hy's Law
4. Malignancy
5. Opportunistic infections such as disseminated histoplasmosis, cryptococcosis, and disseminated tuberculosis
6. Cryptosporidiasis

6.2.2.6.1 Anaphylaxis and Serious Allergic Reactions

Anaphylaxis will be defined according to the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria.[42] In the event of anaphylactic reaction or severe/serious hypersensitivity/allergic reaction, the patient must discontinue IP and emergency resuscitation measures implemented. In case of other mild to moderate hypersensitivity reaction, depending on the severity, the investigator may manage in accordance with the standard-of-care.

Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus, or flushing, swollen lips-tongue-uvula) and at least 1 of the following:
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
   a. Systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from the patient's baseline

6.2.2.6.2 Injection Site Reactions

Injection site reactions are to be captured and reported as AEs. These will include Grades 2 to 5 injection site erythema, pain, and induration (see APPENDIX 6), which are also captured as Adverse Events of Special Interest (See Section 6.2.2.6). The investigator should provide a clear description of the observed or reported AE including location and severity. All concomitant treatments used to treat injection site reactions should be recorded and captured in the eCRF, together with the AE of injection site reactions.

6.2.2.6.3 Potential Drug-Induced Liver Injury

Abnormal values in AST and/or ALT levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of DILI, and as potential Hy's Law cases, and should always be considered important medical events. If symptoms compatible with DILI precede knowledge of serum chemical test abnormalities, liver enzyme measurements should be made immediately, regardless of when the next visit or monitoring interval is scheduled. In some cases, symptoms may be an early sign of injury and although typically less sensitive than serum enzyme elevations, they may indicate a need for prompt serum testing. An increase in liver enzymes should be confirmed by a repeated test within 48 to 72 hours following the initial test, prior to reporting of a potential DILI event. Patients will continue to have weekly or biweekly liver enzyme measurements until resolution or levels return to baseline.

All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.2.2.7.2 for reporting details).

Potential DILI is defined as:

1. ALT or AST elevation > 3 × ULN

AND

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

AND

3. No other immediately apparent possible causes of ALT or AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

The patient should return to the investigational site and be evaluated as soon as possible, include laboratory tests, detailed history, and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, CK, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/International Normalized Ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

Study drug discontinuation is considered if there is marked serum AST or ALT elevation or evidence of functional impairment (as indicated by rising bilirubin or INR, which represent substantial liver injury) that is related to study drug. Discontinuation of treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5× ULN for more than 2 weeks

Discontinuation of treatment must occur if:

- ALT or AST >3 × ULN and (total bilirubin > 2 × ULN or INR > 1.5)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

6.2.2.6.4 Malignancy

The identification of a malignancy event will be made by the study site and communicated to the sponsor or designee. AEs should be reported as serious per the criteria in Section 6.2.2.5.

After the first dose of study drug, when there is a decision to biopsy a potentially malignant tumor, lymph node, or other tissue, the investigator and/or consultant(s) should contact the sponsor clinicians or designee to discuss the issue and any decisions as soon as possible.

6.2.2.6.5 Specific Infections

Any diagnosis or suggested diagnosis of opportunistic infections such as disseminated histoplasmosis, cryptococcosis, shingles, disseminated herpes simplex, or disseminated tuberculosis will be recorded as AEs of special interest.

Cryptosporidiosis is also considered an AE of special interest. Patients will be evaluated for cryptosporidium in the stool at screening, and as clinically indicated (eg, watery diarrhea) during the study. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

6.2.2.7 Reporting of Adverse Events

AE reporting will be carried out in accordance with applicable local regulations, including regulatory agency and IRB reporting requirements.

Each AE is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate, and is further outlined in Section 6.2.2.7.2.

6.2.2.7.1 Reporting of Pregnancy

As information is available, a pregnancy diagnosed during the study will be reported within 24 hours to the sponsor via the Pregnancy Notification and Outcome Form, including pregnancy in female patients who received study drug and female partners of male study patients who received study drug. The pregnancy should be followed to term and/or outcome and this outcome should also be reported to the sponsor via the Pregnancy Notification and Outcome Form. Pregnancy itself is not regarded as an AE or SAE unless there is complication.

In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an AE or SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the neonatal death as related or possibly related to exposure to investigational product.

6.2.2.7.2 Reporting of Serious Adverse Events

The principal investigator is responsible for providing notification to the sponsor of any SAE via the Safety Adverse Event Form, whether deemed study drug related or not, that a patient experiences during their participation in this study within 24 hours of becoming aware of the event.

If an SAE is fatal or life threatening, notification to the sponsor must be made aware immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding cases. In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

The principal investigator will review each SAE and evaluate the intensity and the causal relationship of the event to the study drug. All SAEs will be recorded from the time of first dose of study drug through the safety follow-up period (up to Day 270). SAEs occurring after the final follow-up visit and coming to the attention of the principal investigator must be reported only if there is (in the opinion of the principal investigator) reasonable causal relationship with the study drug.

As a minimum requirement, the initial notification should provide the following information:

- Study number
- Patient number
- Details of the SAE (verbatim details are sufficient for immediate notification)
- Criterion for classification as 'serious'
- Causality assessment (which may be updated in a follow-up report when sufficient information is available to make this classification)

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (eg, hospital reports, consultant reports, autopsy reports, etc), with the study patient's personal identifiers removed. All relevant information obtained by the principal investigator through review of these documents will be recorded and submitted to the sponsor within 24 hours of receipt of the information. If a new Safety Adverse Event Form is submitted, then the principal investigator must sign and date the form. The sponsor may also request additional information on the SAE, or clarification of omitted or discrepant information from the initial notification, which the principal investigator or an authorized delegate should submit to the sponsor within 24 hours of the request as possible.

6.2.2.7.3 Reporting of Adverse Events of Special Interest

AEs of special interest will be reported to safety immediately or within 24 hours of the site becoming aware of the event and recorded as such on the Adverse Events eCRF and Safety Adverse Event Form.

Potential DILI will be reported based on specifications mentioned in Section 6.2.2.6.3.

Each AE of special interest is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate, and is further outlined in Section 6.2.2.7.2.

6.2.2.8 Follow Up of Adverse Events

All AEs will be followed up through the safety follow-up visits. All SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the event has resolved, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the principal investigator and medical monitor, until there is a satisfactory explanation for the changes observed, or until the patient is lost to follow-up.

See Section 6.2.2.7.1 for details related to follow-up of pregnancy. See Section 6.2.2.6.3 for details related to follow-up of potential DILI. See Section 6.2.2.6.4 for details related to follow-up of malignancy.

6.2.3 Vital Signs

Vital signs (blood pressure, heart rate, and body temperature) will be assessed as specified in the Schedule of Assessments (Section 3.4). Vital signs will be assessed on Day 0 at predose and at Day 0, 1 and 2 hours postdose, as well as on each of the scheduled visit days during the study (excluding PK-only site visits). Supine BP and heart rate recordings will be made after the patient has been recumbent and at rest ≥ 5 minutes. When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

6.2.4 12-Lead Electrocardiograms

ECG will be assessed as specified in the Schedule of Assessments (Section 3.4). ECG recording will initiate after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws, though timing will be such that PK draws are collected on their scheduled times where possible.

The ECG will include all 12 standard leads and a Lead II rhythm strip on the bottom of the tracing. The ECG will be recorded at a paper speed of 25 mm/second. The following ECG parameters will be collected: PR interval, QRS interval, RR interval, QT interval, and QT interval corrected for heart rate using Fridericia's formula (QTcF).

All ECGs must be evaluated by a qualified physician or qualified designee for the presence of abnormalities and will be captured electronically and retained for future evaluation if required, up to the time of the clinical study report (CSR) completion.

6.2.5 Physical Examinations

The full physical examination will be completed at screening and Day 0. It includes an assessment of general appearance and evaluation of head, eyes, ears, nose, mouth, throat, neck,

thyroid, lymph nodes, and extremities, and dermatologic, respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurologic, and psychiatric systems.

The targeted (limited) physical examination will be completed at all other visits as indicated in the Schedule of Assessments (Section 3.4). It includes evaluation of patient complaints and SLE disease-related issues, and will exclude the genitourinary system.

6.2.6 C-SSRS

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed by Columbia University researchers for the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment. It is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening.[43]

The C-SSRS evaluation will be performed as specified in the Schedule of Assessments (Section 3.4). Patients with recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4, or 5 is exclusionary at screening will be excluded from the study. Patients with recent or active suicidal ideation or behavior at subsequent study visits will have responses to the C-SSRS reviewed in detail to assess patient risk, and appropriate consultative mental health services will be provided.

6.2.7 Injection Site Reactions

Patients will be monitored for local injection site reactions as specified in the Schedule of Assessments (Section 3.4). Local injection site reactions will be assessed at 2 hours postdose at baseline, and predose for each injection after baseline. Injection site reactions should be managed according to the standard of care. Injection site reactions, Grades 2 to 5, are to be reported as AEs of special interest (see Section 6.2.2.7.3).

6.2.8 Immunogenicity

The serum samples to measure the presence of ADA will be collected as specified in the Schedule of Assessments (Section 3.4). Blood samples (4 mL) to provide approximately 1.5 mL of plasma for anti BOS161721 antibody analysis will be collected into appropriately labeled tubes containing K_2EDTA. The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods. Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only analyzed by a central lab if the patient had a positive ADA on Day 90.

After the first dose, if a patient tests positive in the validated confirmatory ADA assay, a sample from this patient will be further analyzed in the neutralizing antibody (nAb) assay by a central lab.

6.3 Efficacy Assessments

All efficacy assessments will be performed at times defined in the Schedule of Assessments (Section 3.4).

6.3.1 SLEDAI-2K

The SLEDAI-2K is a validated instrument that measures disease activity in SLE patients at the time of the visit and in the previous 30 days. It is a global index and includes 24 clinical and laboratory variables that are weighted by the type of manifestation, but not by severity. The total score falls between 0 and 105, with higher scores representing increased disease activity. The SLEDAI-2K has been shown to be a valid and reliable disease activity measure in multiple patient groups. A SLEDAI -2K of 6 or more generally represents moderately to severely active disease.[44]

6.3.2 BILAG 2004

The BILAG-2004 index is an organ-specific 97-question assessment based on the principle of the doctor's intent to treat. Only clinical features attributable to SLE disease activity are to be recorded and based on the patient's condition in the last 4 weeks compared with the previous 4 weeks. It will be scored as not present (0), improved (1), the same (2), worse (3), or new (4). Disease activity is graded separately for 9 body systems to 5 different grades (A to E) as follows: A ("Active") is very active disease, B ("Beware") is moderate activity, C ("Contentment") is mild stable disease, D ("Discount") is inactive now but previously active, and E ("Excluded") indicates the organ was never involved.[44] A shift from BILAG-2004 Grade A or B to a lower grade indicates a clinically relevant change in disease activity as the BILAG-2004 grades mirror the decision points for treatment interventions.

Only investigators that complete BILAG-2004 training will be allowed to perform the BILAG-2004 assessments. Preferably, the same investigator should evaluate the patient at each BILAG-2004 assessment from screening to study completion. The investigator must maintain documentation with descriptive details supporting the BILAG-2004 scoring (eg, chart, worksheet, clinic notes, and labs) at each visit.

See APPENDIX 5 for detailed specifications.

6.3.3 PGA of Disease Activity

The PGA is used to assess investigator's general impression on the patient's overall status of SLE disease activity via visual analogue scale (100 mm) with 0 being "very good, asymptomatic and no limitation of normal activities" with 100 mm being "most severe possible disease ever seen in all SLE patients". PGA worsening is defined as an increase of $\geq$ 30 mm from baseline.

When scoring the PGA, the assessor should always look back at the score from the previous visit.

6.3.4 Composite Endpoints: SRI-4, SRI-5, SRI-6, and BICLA Response

6.3.4.1 SRI-4 Response

The SRI-4 is a composite index of SLE disease improvement that consists of scores derived from the SLEDAI-2K and the BILAG 2004 Index. Response based on the SRI-4 is defined by:

1) ≥ 4-point reduction in SLEDAI-2K global score, 2) no new severe disease activity (BILAG A organ score) or more than 1 new moderate organ score (BILAG B), and 3) no deterioration from baseline in the PGA by ≥ 30 mm. The SRI-4 response in patients with moderate to severe SLE is associated with broad improvements in clinical and patient-reported outcomes.[45]

6.3.4.2 SRI-5 and SRI-6 Response

Like the SRI-4, the SRI-5 and SRI-6 are composite indices of SLE disease improvement that consists of scores derived from the SLEDAI-2K and the BILAG 2004 Index. However, the SRI-5 and SRI-6 are computed with a minimal five-point or six-point improvement in SLEDAI-2K being required, respectively.[46]

6.3.4.3 BICLA Response

The BICLA is a responder index developed to measure response to therapy, and it includes scores from the BILAG, SLEDAI-2K, and PGA. BICLA response is defined as 1) at least 1 gradation of improvement in baseline BILAG 2004 scores in all body systems with moderate disease activity at entry (eg, all B [moderate disease] scores falling to C [mild], or D [no activity]); 2) no new BILAG A or more than 1 new BILAG B scores; 3) no worsening of total SLEDAI-2K score from baseline; 4) ≤ 10% deterioration in PGA score and 5) no treatment failure.[44] It is driven primarily by the BILAG, and has been used in Phase 2 and 3 mAb studies.[47]

For the endpoints of BICLA response at Days 210, 240, and 270, patient scores will be completed and response determined.

6.3.5 CLASI Response

The CLASI is a comprehensive tool for assessment of disease activity and damage in cutaneous lupus, shown to be valid, reliable, and sensitive to changes in disease activity.[48] Response is defined as 50% improvement from baseline in "A" or "B" scores. This assessment will be applied to all patients as all are required to have cutaneous disease activity.

For the secondary efficacy endpoint of CLASI response at Day 210, patient scores on MAD and POC studies will be compared with baseline for 50% improvement.

6.3.6 ACR-28 Joint Count

The ACR-28 joint count will evaluate the number of tender and swollen joints in the shoulder, elbow, wrist, hand, knee joints. Joints of the feet are excluded.

6.4 Other Variables

6.4.1 SLICC/ACR Damage Index

The SLICC/ACR damage index is a validated instrument to assess damage, defined as irreversible impairment, continuously persistent for 6 months (ascertained by clinical assessment), occurring since the onset of lupus, and it is based on a weighted scoring system. This index records damage occurring in patients with SLE regardless of cause, with demonstrated content, face, criterion, and discriminant validity.[49] It will be performed on Days 0 and 180.

6.4.2 PROs

Patients should be encouraged to complete the PROs at the clinic at the beginning of the study visit prior to any clinical assessments. A member of the staff should be available if a patient requires further instruction and to review the PRO questionnaires for completeness prior to leaving the clinic. The PROs include the CCI and the CCI and will be assessed as specified in the Schedule of Assessments (Section 3.4).

CCI [50]

CCI .

6.5 Pharmacokinetic Assessments

During the MAD Phase 1b (all sites) and POC Phase 2 (select sites only) parts of the study, blood samples for PK analysis of BOS161721 or placebo concentration will be collected according to Table 1 and Table 2.

Plasma concentrations of BOS161721 will be measured using a validated immunoassay. The PK parameters will be calculated from the plasma concentration actual time profiles.

6.6 Pharmacodynamic Assessments

Blood samples for PD parameters (plasma) will be collected at times indicated in the Schedule of Assessments (Section 3.4) for each of the following parameters:

- pSTAT3 (predose [trough] samples only Phase 1b)
- Antibodies: CCI
- Plasma complement (CCI)
- Plasma CCI and CCI
- Whole blood for leukocyte immunophenotype

6.7 Pharmacokinetic/Pharmacodynamic Relationship

Evidence of any PK/PD relationships will be evaluated between BOS161721 plasma concentrations and the available PD endpoints and biomarkers.

6.8 Protocol Deviations

Protocol deviations will be documented during the study.

7 STUDY DRUG MANAGEMENT

7.1 Description

7.1.1 Formulation

CCI [redacted]

CCI [redacted]

Additional information regarding dose preparation will be provided in a separate Pharmacy Manual.

7.1.2 Storage

All supplies of BOS161721 or placebo must be stored in accordance with the manufacturer's instructions. BOS161721 or placebo will be stored in a securely locked area, accessible to authorized persons only, until needed for dosing.

Information regarding storage and dose preparation will be provided in a separate Pharmacy Manual.

7.2 Packaging and Shipment

Investigational medicinal products will be supplied by Boston Pharmaceuticals, Inc. Investigational medicinal products will be packaged and labeled according to applicable local and regulatory requirements.

7.3 Dose and Administration

Details of dosing are provided in Section 3.1.

Each unit dose will be prepared by a qualified staff member. The vials of investigational product (IP) will appear identical and will have a "blinded" label on the vials that will state CCI [redacted] mg or placebo. When the site goes into the IWRS to request the patient kit(s), the IWRS will assign the

appropriate number of kits (regardless of assignment to placebo or active treatment) per the dose (ie, CCI [redacted]). If a patient is randomized to the placebo arm, they will receive the matching number of kits.

The designated staff member (or designee under the direction of the designated staff member) will dispense BOS161721 or placebo for each patient according to the protocol, randomization list, and Pharmacy Manual, if applicable.

After receiving sponsor approval in writing, the investigational site is responsible for returning all unused or partially used BOS161721 or placebo to the sponsor or designated third party or for preparing BOS161721 or placebo for destruction via incineration.

Further details are found in a separate Pharmacy Manual.

7.4 Accountability

The Principal Investigator or designee is responsible for maintaining accurate accountability records of BOS161721 or placebo throughout the clinical study. The drug accountability log includes information such as, randomization number, amount dispensed and amount returned to the pharmacy (if any). Products returned to the pharmacy will be stored under the same conditions as products not yet dispensed. The returned products should be marked as 'returned' and kept separate from the products not yet dispensed.

All dispensing and accountability records will be available for sponsor review after database lock procedures are completed. During safety monitoring, the drug accountability log will be reconciled with the products stored in the pharmacy.

7.5 Prohibited Concomitant Therapy

Prohibited concomitant medications are discussed in Section 4.6 and APPENDIX 4 and will be listed as protocol violations if taken when not permitted.

7.6 Compliance

Dosing will be performed by trained, qualified personnel designated by the principal investigator. The date and time of dosing will be documented on each dosing day. Comments will be recorded if there are any deviations from the planned dosing procedures.

8 STATISTICS

The following analyses are planned:

- An IA will be performed during the last cohort of the MAD portion to determine dose selection for the POC part of the study.
- The final analysis will be performed when all patients have completed the POC safety follow-up or withdrawn from the study.
- Safety analyses will be performed for DMC reviews throughout the study to evaluate dose escalation decisions and accumulating safety data. The frequency and details of the

content and format of the safety review meetings will be described in the SAP and/or DMC charter.

All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9 or higher.

The following standards will be applied for the analysis unless otherwise specified. Data will be summarized descriptively by treatment and overall for each study portion. For the MAD part of the study, BOS161721 will be summarized overall and by each dose level, and placebo patients from each cohort will be combined. Select parameters may be summarized using patients from both study parts. Statistical testing will be performed on data from the Phase 2 portion only.

Continuous data will be summarized using number, mean, standard deviation (SD), 25th and 75th percentiles, minimum, median, and maximum. Categorical data will be summarized by treatment group using frequency tables (number and percentage). Time to event data will be summarized using counts, medians, 25th and 75th percentiles, and standard error. All data will be listed for all patients.

Statistical inference will be based on a 2-tailed test with an overall 0.10 level of significance, unless stated otherwise.

The effects of noncompliance, background therapy use, treatment discontinuations, premature withdrawal from study and covariates will be assessed to determine the impact on the general applicability of results from this study. Exploratory analyses of the data will be conducted as deemed appropriate. Any deviations from the planned analyses will be described and justified in the final integrated CSR.

Protocol deviations and prohibited medications that define medication failures will be fully assigned and documented before database lock and unblinding.

Further details of the analysis, including the handling of missing data, transformations and other data handling procedures will be provided in the SAP.

8.1 Sample Size

Sample size in the Phase 1b part of the study is based on operational consideration.

The sample size in the Phase 2 portion is based on the primary endpoint, SRI-4 Response at Day 210. Approximately 156 additional patients will be randomized in a 2:1 ratio to BOS161721 versus placebo to achieve 132 evaluable patients in the FAS. This assumes 24 patients will drop prior to having received treatment and an evaluable post-baseline efficacy measure. Enrollment and randomization will be monitored in a blinded fashion and increased if needed to ensure at least 132 patients are randomized into the FAS.

A total of 132 patients randomized provides more than 80% power to detect a treatment difference of 25% in SRI-4 response rates at Day 210, based on a targeted 2-sided significance level of 10% and using a 2-sided Pearson's chi-squared test. This assumes of a response rate of 65% for BOS161721 and 40% for placebo, where missing data at Day 210 is carried forward

from most recent non-missing result and patients are treated as a non-responder if a prohibited medication defined as a medication failure occurs.

8.2 Statistical Methods

8.2.1 Analysis Populations

The primary efficacy analysis will be based on the FAS, defined as all patients who receive at least 1 dose of study treatment and at have least 1 evaluable post-baseline efficacy evaluation. FAS analyses will be conducted on the basis of the randomized treatment.

A per protocol (PP) analysis set may be defined to exclude major protocol violations from the efficacy analysis. The PP Population will include all patients from the FAS except those with major violations to the protocol deemed to impact the analysis of the primary endpoint. These violations will be identified based on blinded data prior to study unblinding. PP analyses will be conducted on the basis of the randomized treatment.

Safety analyses will be based on the safety analysis set (SS), defined as all patients who receive at least 1 dose of study treatment. Safety analyses will be conducted on the basis of actual treatment received.

Pharmacokinetic analysis will be conducted on the PK analysis set, defined as the FAS with sufficient concentration data for the calculation of PK parameters.

8.2.2 Demographics and Baseline Characteristics

Baseline and patient characteristics will be summarized using all randomized patients.

8.2.3 Primary Efficacy Endpoint(s)

The proportion of patients who achieve a SRI-4 response at Day 210 will be assessed via Pearson's chi-squared analysis. The primary efficacy endpoint will be analyzed using the FAS and if needed repeated in the PP analysis set. Missing values will be addressed by employing a last observation carried forward (LOCF) analysis. Other imputation methods may be employed as a sensitivity analysis and will be described in the SAP. Additional analyses exploring impact of baseline factors such as baseline disease severity, race, and other characteristics may be performed.

Patients that received prohibited medications or unallowable CS usage as described in Section 4.6 will be considered "medication failures" and will be treated as non-responders for the primary efficacy analysis. Patients that received an allowable CS burst but having missing data at Day 210 will considered a medication failure and will be treated as non-responders for the primary efficacy analysis. The determination of medication failures will be reviewed using blinded data and finalized prior to unblinding.

The superiority of BOS161721 relative to placebo will be evaluated. If the proportion of SRI-4 responders for the selected POC dose in BOS161721 arm is higher than that of the placebo arm, then BOS161721 will be considered superior to placebo if the 2-sided p-value is less than 0.10.

Secondary and exploratory endpoints for this POC portion will be evaluated based on the same statistical hypothesis.

8.2.4 Secondary Efficacy Endpoint(s)

Binary efficacy endpoints will be assessed via Pearson's chi-squared analysis. Continuous efficacy endpoints will be assessed via analysis of variance (ANOVA) or analysis of covariance (ANCOVA) and treatment will be compared using the F-test. Repeated measures mixed models may be performed to evaluate data collected at each visit and overall. Time-to-event endpoints will be assessed via Kaplan-Meier methodology and treatment will be compared using the log-rank test. The secondary efficacy endpoints will be analyzed on the FAS and if needed repeated in the PP analysis set. Details including handling of missing data and "medication failures" will be available in the SAP.

8.2.5 Analysis of Safety

8.2.5.1 Safety Analysis

Safety analyses will be performed on the SS. AE data will be coded to system organ class and preferred term using MedDRA. The number and percentage of patients experiencing any treatment-emergent AE, overall, and by system organ class and preferred term, will be tabulated. Treatment-emergent AEs will also be summarized by severity and relationship.

Concomitant medications will be coded using the WHO Drug dictionary. Observed values and changes from baseline in vital signs, ECG readings, and hematology and clinical chemistry parameters will be summarized at each individual visit.

8.2.6 Pharmacokinetic and Pharmacodynamic Data

8.2.6.1 Analysis of Pharmacokinetic Data

PK parameters will be calculated from concentration data collected during the MAD Phase 1b portion of the study using non-compartmental analysis and include the following:

- C_{max}, T_{max}, AUC, $t_{½}$, CL, V_d

The PK parameter data will be listed and summarized descriptively in tabular format.

If data permit, the following analyses will be performed for plasma BOS161721 concentration data:

- A listing of all plasma BOS161721 concentrations by patient at actual times post dose;
- A descriptive summary of plasma BOS161721 concentrations. Summary statistics of geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum will be tabulated by study days with PK assessments.

8.2.6.2 Analysis of Pharmacodynamic Data

The PD parameter data will be listed and summarized descriptively in tabular format.

Exploratory analyses examining the relationship between PD parameters and PK concentration and PK parameters will be performed.

8.2.6.3 Population Pharmacokinetic Analysis or PK/PD Modeling

Plots of individual patient values for each relevant PD parameter on Y-axis and each relevant PK parameter on X-axis will be examined for relationship. If relationships are revealed by these diagnostic plots, PK and PD data from this study may be analyzed using modeling approaches to describe the relationship and may also be pooled with data from other studies to investigate any association between BOS161721 exposure and biomarkers or significant safety endpoints.

8.3 Interim Analysis and Power

One IA is planned for this study and will be conducted at the time of the POC decision for dose selection.

Since there is no IA during the POC part of the study, there is no impact on the type 1 error.

9 ETHICS AND RESPONSIBILITIES

9.1 Good Clinical Practice

The procedures set out in this protocol are designed to ensure that the sponsor and the principal investigator abide by the principles of the International Council for Harmonisation (ICH) guidelines on GCP and the Declaration of Helsinki (Version 2013). The clinical study also will be carried out in the keeping with national and local legal requirements (in accordance with US IND regulations [21 CFR 56]).

9.2 DMC

This study will use an external DMC. The DMC is an independent committee established to provide oversight of safety considerations in study and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of enrolled patients and those yet to be recruited to the trial as well as for the continuing validity and scientific merit of the study results. The DMC is charged with assessing such actions in light of an acceptable benefit/risk profile for BOS161721. The recommendations made by the DMC (ie, dose escalation, etc.) will be forwarded to the sponsor for final decision. The sponsor will forward such decisions, which may include summaries of safety data which are not endpoints, to regulatory authorities, as appropriate.

The sponsor will appoint a DMC for the periodic review of available study data. The DMC is an independent group of experts that advises the sponsor and the study investigators. The members of the DMC serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DMC are to (1) periodically review and evaluate the

accumulated study data for participant safety, study conduct, and progress, (2) make recommendations to the sponsor concerning the continuation, modification, or termination of the study and (3) suggest dose for POC portion of the study as described in Section 3.1.1.3.

The DMC considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. The DMC is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking (unblinding), and voting procedures prior to initiating any data review. The DMC is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

The DMC will have access to unblinded treatment information during the clinical trial. Details regarding management and process of this committee are found in the DMC Charter.

The DMC may recommend termination of BOS161721 treatment arm or the entire BOS161721 MAD/POC trial for any safety concern that is felt to outweigh potential benefits. The recommendation must be supported by the sponsor as indicated in the DMC Charter.

9.3 Institutional Review Board/Independent Ethics Committee

Independent Ethics Committees (IEC)/Institutional Review Boards (IRB) must meet the guidelines set out by the U.S. Food and Drug Administration (FDA) and conform to local laws and customs where appropriate. Written IRB/IEC approval for the protocol and the signed ICF must be obtained and transmitted to Boston Pharmaceuticals or representative before the study can be initiated. The IRB/IEC must be informed of and approve all protocol amendments. The investigator will ensure that this study is conducted in full conformance with all applicable local and regional laws and regulations. The complete text of the World Medical Association Declaration of Helsinki is given in APPENDIX 2.

9.4 Informed Consent

Before each patient undergoes any protocol required assessments or procedure, the written informed consent will be obtained according to the regulatory and legal requirements of the participating country. As part of this procedure, the principal investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study patient should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. The principal investigator or designee will provide the sponsor with a copy of the IRB-approved ICF prior to the start of the study.

The informed consent document must be signed and dated; 1 copy will be handed to the patient and the principal investigator will retain a copy as part of the clinical study records. The principal investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

If the informed consent document is revised, it must be reviewed and approved by the responsible IRB/IEC. Patients currently enrolled may need to sign this revision (based on IRB/IEC requirements) and all future patients enrolled in the clinical study will be required to sign this revised ICF.

9.5 Records Management

The principal investigator will ensure the accuracy, completeness, and timeliness of the data reported to the sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The principal investigator or designee will cooperate with the sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The principal investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each patient receiving BOS161721 or placebo.

The principal investigator will allow sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB to have direct access to all documents pertaining to the study.

Electronic case report forms are required and should be completed for each randomized patient. It is the principal investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported on the patients' eCRF. Electronic case report forms should be completed in a timely fashion to support the study timelines. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status. The principal investigator or designated representative should complete and the principal investigator should verify the source documents as the information is collected. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The principal investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes.

9.6 Source Documentation

The documents that will form the source data for the clinical study (eg, patient charts, laboratory reports) must be defined and documented in the in-house study master file prior to the start of the study. Data on the eCRFs which will be checked against source data during monitoring visits

must also be defined and documented in the in-house study master file including the percentage of each of the source data to be verified and the percentage of patients' eCRFs to be monitored.

9.7 Study Files and Record Retention

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of BOS161721. However, these documents should be retained for a longer period if required by the applicable legal requirements.

10 AUDITING AND MONITORING

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and on-site visits. The study will be routinely monitored to ensure compliance with the study protocol and the overall quality of data collected. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor may periodically request review of the investigator study file to assure the completeness of documentation in all respects of clinical study conduct. The study monitor will verify that each patient has proper consent documentation from the patient and/or patient's authorized representative for study procedures and for the release of medical records to the sponsor, FDA, other regulatory authorities, and the IRB. The study monitor will also verify that assent was obtained for patients not capable of providing informed consent or that documentation is provided by the investigator explaining why the patient was unable to provide assent. The investigator or appointed delegate will receive the study monitor during these on-site visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies. On completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

Throughout the course of the study, the medical monitor will determine eligibility of all screened patients, will address any medical issues that might arise, clarify medical questions, review patient safety data (eg, AE/SAE, laboratory, and ECG), and partner with the study team in the overall study management. The study medical monitoring plan will document additional details of the study medical oversight and monitoring.

11 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by Boston Pharmaceuticals. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before

implementing the changes. Boston Pharmaceuticals will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, and/or Boston Pharmaceuticals, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the patient and/or has an impact on the patient's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for patients enrolled in the study before continued participation.

12 STUDY REPORT AND PUBLICATIONS

Boston Pharmaceuticals is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

By signing the protocol, the principal investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the competent authorities will be notified of the principal investigator's name, address, qualifications, and extent of involvement.

The principal investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted and obtained approval from the sponsor in advance.

13 STUDY DISCONTINUATION

Both Boston Pharmaceuticals and the principal investigator reserve the right to terminate the study at the investigator's site at any time. Should this be necessary, Boston Pharmaceuticals or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the principal investigator will inform the IRB/IEC of the same. In terminating the study Boston Pharmaceuticals and the principal investigator will assure that adequate consideration is given to the protection of the patients' interests.

14 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Boston Pharmaceuticals, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial or to comply with regulatory requirements. However, authorized regulatory officials, IRB/IEC personnel, Boston Pharmaceuticals, and its authorized representatives are allowed full access to the records.

Identification of patients and eCRFs shall be by initials, birthdate, or patient number. Documents that identify the patient (eg, the signed informed consent document) must be maintained in confidence by the principal investigator. If required, the patient's full name may be made known to an authorized regulatory agency or other authorized official.

15 REFERENCES

1 Urowitz MB, Gladman DD. How to improve morbidity and mortality in systemic lupus erythematosus. Rheumatology 2000;39:238-44.

2 Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Morbidity and Mortality in Systemic Lupus Erythematosus During a 10-Year Period. Medicine 2003;82(5):299-308.

3 Pons-Estel GJ, Alarcón GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. Semin Arthritis Rheum. 2010;39(4):257. Epub 2009 Jan 10.

4 Kanta H, Mohan C. Three Checkpoints in lupus development: central tolerance in adaptive immunity, peripheral amplification by innate immunity, and end-organ inflammation. Genes and Immunity 2009;10:390-6.

5 Dall'Aqua WF, Kiener PA, Wu H. Properties of Human IgG1s Engineered for Enhanced Binding to the Neonatal Fc Receptor (FcRn). J Biol Chem. 2006 Aug 18, 281(33):23514-24.

6 Spolski R, Leonard WJ. The Yin and Yang of interleukin-21 in allergy, autoimmunity and cancer. Curr Opin Immunol. 2008a;20:295-301.

7 Asao H, Okuyama C, Kumaki S, Ishii N, Tsuchiya S, Foster D, et al. Cutting edge: the common gamma-chain is an indispensable subunit of the IL-21 receptor complex. J Immunol. 2001;167:1-5.

8 Habib T, Senadheera S, Weinberg K, Kaushansky K. The common gamma chain (gamma c) is a required signaling component of the IL-21 receptor and supports IL-21-induced cell proliferation via JAK3. Biochemistry. 2002;41:8725-31.

9 Spolski R, Leonard WJ. Interleukin-21: basic biology and implications for cancer and autoimmunity. Annu Rev Immunol. 2008b;26:57-79.

10 Puga I, Cols M, Barra CM, He B, Cassis L, Gentile M, et al. B-cell-helper neutrophils stimulate the diversification and production of immunoglobulin in the marginal zone of the spleen. Nat Immunol. 2011;13(2):170-80.

11 Costanzo A, Chimenti MS, Botti E, Caruso R, Sarra M, Monteleone G. IL-21 in the pathogenesis and treatment of skin diseases. J Dermatol Sci. 2010;60(2):61-6.

12 Avery DT, Bryant VL, Ma CS, de Waal Malefy R, Tangye SG. IL-21-induced isotype switching to IgG and IgA by human naive B cells is differentially regulated by IL-4. J Immunol. 2008;181:1767-79.

13 Rasmussen TK, Andersen T, Bak, RO, Yiu G, Sorensen CM, Stengaard-Pedersen K, et al. Overexpression of microRNA-155 increases IL-21 mediated STAT3 signaling and IL-21 production in systemic lupus erythematosus. Arthritis Research & Therapy 2015;17(154)

14 Ettinger R, Kuchen S, Lipsky PE. The role of IL-21 in regulating B-cell function in health and disease. Immunol Rev. 2008;223:60-86.

15 Caprioli F, Sarra M, Caruso R, Stolfi C, Fina D, Sica G, et al. Autocrine regulation of IL-21 production in human T lymphocytes. J Immunol. 2008;180(3):1800-7.

16 Yang L, Anderson DE, Baecher-Allan C, Hastings WD, Bettelli E, Oukka M, et al. IL-21 and TGF-beta are required for differentiation of human T(H)17 cells. Nature. 2008;454(7202):350-2.

17 Tangye SG, Ma CS, Brink R, Deenick EK. The good, the bad and the ugly - TFH cells in human health and disease. Nat Rev Immunol. 2013;13(6):412-26.

18 Fantini MC, Rizzo A, Fina D, Caruso R, Becker C, Neurath MF, et al. IL-21 regulates experimental colitis by modulating the balance between Treg and Th17 cells. Eur J Immunol. 2007;37(11):3155-63.

19 Peluso I, Fantini MC, Fina D, Caruso R, Boirivant M, MacDonald TT, et al. IL-21 counteracts the regulatory T-cell-mediated suppression of human CD4+ T lymphocytes. J Immunol. 2007;178(2):732-9.

20 Hippen KL, Bucher C, Schirm DK, Bearl AM, Brender T, Mink KA, et al. Blocking IL-21 signaling ameliorates xenogeneic GVHD induced by human lymphocytes. Blood. 2012;119(2):619-28.

21 Davis ID, Skrumsager BK, Cebon J, Nicholaou T, Barlow JW, Moller NP, et al. An open-label, two-arm, phase I trial of recombinant human interleukin-21 in patients with metastatic melanoma. Clin Cancer Res. 2007;13:3630-6.

22 Frederiksen KS, Lundsgaard D, Freeman JA, Hughes SD, Holm TL, Skrumsager BK, et al. IL-21 induces in vivo immune activation of NK cells and CD8(+) T-cells in patients with metastatic melanoma and renal cell carcinoma. Cancer Immunol Immunother. 2008;57(10):1439-49.

23 Karrich JJ, Jachimowski LC, Nagasawa M, Kamp A, Balzarolo M, Wolkers MC, et al. IL-21- stimulated human plasmacytoid dendritic cells secrete granzyme B, which impairs their capacity to induce T-cell proliferation. Blood. 2013;121(16):3103-11.

24 Lindner S, Dahlke K, Sontheimer K, Hagn M, Kaltenmeier C, Barth TF, et al. Interleukin-21-induced granzyme B-expressing B-cells infiltrate tumors and regulate T-cells. Cancer Res. 2013;73(8):2468-79.

25 Monteleone G, Caruso R, Fina D, Peluso I, Gioia V, Stolfi C, et al. Control of matrix metalloproteinase production in human intestinal fibroblasts by interleukin 21. Gut. 2006;55(12):1774-80.

26 Nakou M, Papadimitraki ED, Fanouriakis A, Bertsias GK, Choulaki C, Goulidaki N, et al. Interleukin-21 is increased in active systemic lupus erythematosus patients and contributes to the generation of plasma B-cells. Clin Exp Rheumatol. 2013;31(2):172-9.

27 Li Q, Liu Z, Dang E, Jin L, He Z, Yang L, et al. Follicular helper T-cells (Tfh) and IL-21 involvement in the pathogenesis of bullous pemphigoid. PLoS One. 2013;8(7):e68145.

28 Liu R, Wu Q, Su D, Che N, Chen H, Geng L, et al. A regulatory effect of IL-21 on T follicular helper-like cell and B-cell in rheumatoid arthritis. Arthritis Res Ther. 2012;14(6):R255.

29 Kang KY, Kim HO, Kwok SK, Ju JH, Park KS, Sun DI, et al. Impact of interleukin-21 in the pathogenesis of primary Sjögren's syndrome: increased serum levels of interleukin-21 and its expression in the labial salivary glands. Arthritis Res Ther. 2011;13(5):R179.

30 Terrier B, Geri G, Chaara W, Allenbach Y, Rosenzwajg M, Costedoat-Chalumeau N, et al. Interleukin-21 modulates Th1 and Th17 responses in gianT-cell arteritis. Arthritis Rheum. 2012a;64(6):2001-11.

31 Terrier B, Costedoat-Chalumeau N, Garrido M, Geri G, Rosenzwajg M, Musset L, et al. Interleukin 21 correlates with T-cell and B-cell subset alterations in systemic lupus erythematosus. J Rheumatol. 2012b;39(9):1819-28.

32 International Conference on Harmonisation. Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6 (R1). 2011.

33 Wang W, Wang EQ, Balthasar JP. Monoclonal Antibody Pharmacokinetics and Pharmacodynamics. Clin Pharm & Ther 2008; 84(5):548-58.

34 Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. Journal of Allergy and Clinical Immunology 2006;117:391–7.

35 Elsaesser H, Sauer K, Brooks DG. IL-21 is required to control chronic viral infection. Science. 2009;324(5934):1569-72

36 Kotlarz D, Zietara N, Uzel G, Weidemann T, Braun CJ, Diestelhorst J, et al. Loss-of-function mutations in the IL-21 receptor gene cause a primary immunodeficiency syndrome. J Exp Med. 2013;210(3):433-43.

37 Hunter PR, Nichols G. Epidemiology and clinical features of Cryptosporidium infection in immunocompromised patients. Clinical microbiology reviews. 2002;15(1):145-54.

38 Desjardins M, Mazer BD. B-cell memory and primary immune deficiencies: interleukin-21 related defects. Curr Opin Allergy Clin Immunol. 2013;13(6):639-45.

39 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.

40 Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, US: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a4.htm.

41 NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, available at https://evs.nci.nih.gov/ftp1/CTCAE/About.html.

42 Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. Journal of Allergy and Clinical Immunology 2006;117:391–7.

43 Posner K, Melvin G a, Stanley B, Oquendo M a, Gould M. Factors in the assessment of suicidality in youth. *CNS Spectr*. 2007;12(2):156-162.

44 Castrejon I, Tani C, Jolly M, Huang A, Mosca M. Indices to assess patients with systemic lupus erythematosus in clinical trials, long-term observational studies, and clinical care. Clin Exp Rheumatol 2014; 32(85):S85-95.

45 Furie R, Wang L, Drappa J, Illei G. Systemic Lupus Erythematosus (SLE) Responder Index [SRI(4)] Response Is Associated with Global Benefit in Patients with Moderate to Severe SLE [abstract]. *Arthritis Rheumatol.* 2016; 68 (suppl 10).

46 Thanou A, Chakravarty E, James JA, Merrill JT. Which outcome measures in SLE clinical trials best reflect medical judgment? Lupus Science & Medicine 2014;1:e000005. doi:10.1136/lupus-2013-000005.

47 Wallace DJ, Kalunian K, Petri MA, Strand V, Houssiau FA, Pike M,*et al.* Efficacy and safety of epratuzumab in patients with moderate/severe active systemic lupus erythematosus: results from EMBLEM, a phase IIb, randomised, double-blind, placebo-controlled, multicentre study. *Ann Rheum Dis* 2014;73:183-90.

48 Albrecht J, Taylor L, Berlin JA, Dulay S, Ang G, Fakharzadeh S. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): An Outcome Instrument for Cutaneous Lupus Erythematosus. J Invest Derm. 2005;125(5):889-94.

49 Stoll T, Seifert B, Isenberg DA. SLICC/ACR Damage Index is Valid, and Renal and Pulmonary Organ Scores are Predictors of Sever Outcome in Patients with Systemic Lupus Erythematosus. Br J Rheumatol. 1996;35:248-54.

50 CCI [redacted].

16 APPENDICES

APPENDIX 1 NAMES OF STUDY PERSONNEL

Sponsor:	Boston Pharmaceuticals 55 Cambridge Parkway Suite 400 Cambridge, MA 02142, USA
Medical Monitor:	PPD
	PPD
	PPD
Clinical Research Organizations:	PPD
	PPD
	PPD
Bioanalytical Laboratory:	PPD
Central Laboratory:	PPD

APPENDIX 2 DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles
For
Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subject."

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic, and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility, and quality.

In current medical practice and in medical research, most prophylactic, diagnostic, and therapeutic procedures involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Research investigators should be aware of the ethical, legal, and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal, or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any SAEs. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a subject of the research, even though the subject has given consent.

Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the

subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

The subjects must be volunteers and informed participants in the research project.

The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the subject's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining

informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic, or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the subjects who are research subjects.

The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists.

At the conclusion of the study, every subject entered into the study should be assured of access to the best-proven prophylactic, diagnostic, and therapeutic methods identified by the study.

The physician should fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study must never interfere with the subject-physician relationship.

In the treatment of a subject, where proven prophylactic, diagnostic, and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the subject, must be free to use unproven or new prophylactic, diagnostic, and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health, or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

APPENDIX 3 COMMONLY USED CORTICOSTEROID EQUIVALENTS

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

APPENDIX 4 MEDICATION WASHOUT PERIODS

WASHOUT TIMES OF MEDICATIONS BASED ON 5 HALF-LIVES

Medication	**Discontinuing Prior to Signing Consent**
Abatacept (CTLA4Ig)	24 weeks
Alefacept	12 weeks
AMG 623 (blisibimod)	24 weeks
Anifrolumab	12 weeks
Atacicept (TACI-Ig)	12 weeks
Belimumab	24 weeks
Cyclophosphamide	24 weeks
Cyclosporine (except for CSA eye drops)	4 weeks for oral and 8 weeks for topical
Danazol	4 weeks
Dapsone	4 weeks
Eculizumab	12 weeks
Efalizumab	12 weeks
Epratuzumab	24 weeks
Intravenous globulin	4 weeks
Leflunomide	8 weeks (4 weeks for washout with cholestyramine)
Lenalidomide with cholestiramine	8 weeks
Lupuzor	12 weeks
Memantine	4 weeks
Natalizumab	24 weeks
Ocrelizumab	48 weeks (or 24 weeks with recovery of B cell)
Pimecrolimus	4 weeks
Plasmapheresis	24 weeks
Retinoids (oral or topical)	4 weeks
Rituximab	48 weeks (or 24 weeks with recovery of B cell)
Sirolimus	4 weeks
Tacrolimus	4 weeks
Thalidomide	8 weeks
Tocilizumab	12 weeks

APPENDIX 5 BILAG-2004 (STUDY-SPECIFIC MODIFIED CRITERIA)

CCI

APPENDIX 6 INJECTION SITE REACTION GRADING SCALE

Adverse event Injection site reaction	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection	Tenderness with or without associated symptoms (eg, warmth, erythema, itching)	Pain; Lipodystrophy; Edema; phlebitis	Ulceration or necrosis; Severe tissue damage; Operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	-
Rash maculopapular/Erythema /Induration Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally, and associated with pruritus.	Macules/papules covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness) Erythema covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness)	Macules/papules covering 10% - 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL; Erythema 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering > 30% BSA with or without associated symptoms; limiting self-care ADL Erythema covering > 30% BSA with or without associated symptoms; limiting self-careADL	-	-

ADL = active daily living

APPENDIX 7 PROTOCOL SUMMARY OF CHANGES

The protocol summary of changes was moved to the end of the protocol for easier readability.

Significant changes are described in the table below. Changed text is displayed for the first major occurrence only. Deleted text is presented in strikethrough format, and added text is presented in bold format.

Section	Description of Changes	Rationale
Global	Replace: Protocol Date and Version: 21 March 2018; V3.0 With: Protocol Date and Version: **27 July** 2018; V**4**.0	Administrative
Global	Change: Changed Version number from V3.0 (Amendment 2) to V**4**.0 (Amendment **3**) and Version date from 21 March 2018 to **27 July 2018**.	Administrative
Global	Made administrative and editorial (formatting, typographical, and grammatical) updates.	Administrative
Global	Replaced subjects with **patients**.	Corrected wording used to refer to those participating in study with SLE.
Global	All references directly or contextually to MAD/POC "phase" or "study" have been replaced with "MAD **portion/part/part of the study)**" or "POC **portion/part/part of the study**".	Clarifies that MAD and POC are 2 portions of this 1 study and not 2 separate studies.
Global	When referring to the DMC and Boston Pharmaceuticals conducting a data review to determine POC dose, all instances of the phrase "suggest which dose should" have been replaced with "**determine** which dose **will**".	Protocol clarification.
Title Page	Replace: Boston Pharmaceuticals, Inc. 55 Cambridge Parkway, Suite 401 Cambridge, MA 02142	Administrative
Appendix 1		

Section	Description of Changes	Rationale
	United States of America (USA) With: Boston Pharmaceuticals, Inc. 55 Cambridge Parkway, Suite 40**0** Cambridge, MA 02142 United States of America (USA)	
CLINICAL PROTOCOL APPROVAL FORM	Add: Name and Title PPD **, MD, PhD** **Chief Medical Officer** **Boston Pharmaceuticals** PPD , MD**, FACR** Vice President, Clinical Development Boston Pharmaceuticals	Administrative
CONFIDENTIALITY AND INVESTIGATOR STATEMENT	Replace: I have read the protocol (V3.0 [Amendment 2], dated 21 March 2018), including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. With: I have read the protocol (Version **4**.0, dated **27 July** 2018), including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described.	Administrative
PROTOCOL SUMMARY, Background and Rationale	Replace: The no observed adverse effect levels (NOAELs) in Cynomolgus monkeys were determined to be 100 mg/kg IV and 50 mg/kg SC, the highest doses tested. No SC animals had injection reactions. With: The no observed adverse effect level (NOAEL) in Cynomolgus monkeys w**as** determined to be 100 mg/kg **(**SC **and** IV**)**, the highest dose tested. **There were no** injection **site** reactions **in animals dosed subcutaneously**.	Updated based on new data describing NOAEL based on 6-month study data.

Section	Description of Changes	Rationale
PROTOCOL SUMMARY, Background and Rationale Section 1.2.2.3, Clinical Studies	Delete: Overall, there were no clinically significant safety or tolerability findings from this study~~, following an interim cut and review of the data at Day 90 postdose~~.	Removed since this date has been superseded.
PROTOCOL SUMMARY, Objectives and Endpoints, MAD Phase 1b, Safety Endpoints PROTOCOL SUMMARY, Objectives and Endpoints, POC Phase 2, Safety Endpoints Section 2.1, Phase 1b Multiple Ascending Dose, Safety Endpoints Section 2.2, Phase 2 Proof of Concept, Safety Endpoints	Delete: • ~~Concomitant medication usage~~	Removed as not a safety endpoint.
PROTOCOL SUMMARY, Objectives and Endpoints, MAD Phase 1b, Efficacy Endpoints Section 2.1, Phase 1b Multiple Ascending Dose, Efficacy Endpoints	Replace: • CCI [redacted]	Statistical clarification.

Section	Description of Changes	Rationale
	- CCI  With: • CCI 	
PROTOCOL SUMMARY, Objectives and Endpoints, POC Phase 2, Secondary Efficacy Endpoints Section 2.2, Phase 2 Proof of Concept, Secondary Efficacy Endpoints	Add: • The proportion of **patients** with: - SRI-4 response at each visit - SRI-5 and SRI-6 response **at each visit** (Section 6.3.4.2) - a sustained reduction of oral corticosteroid (CS) (≤ 10 mg/day and ≤ Day 0 dose) between Day 120 and Day 210 - new BILAG A flare or > 1 BILAG B flares relative to baseline through Day 210 - PGA worsening - a BICLA response - a CLASI response - medication failures • Results and changes from baseline in: - CLASI - swollen and tender joints ACR-28	Statistical clarification.

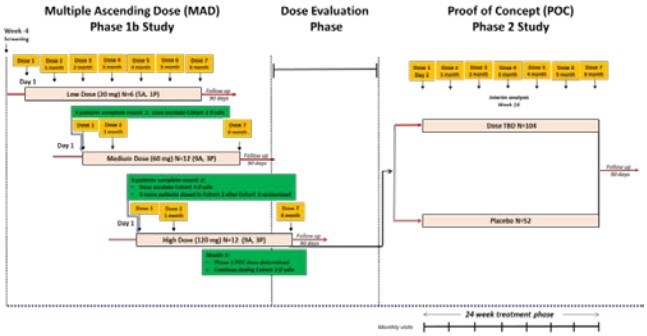
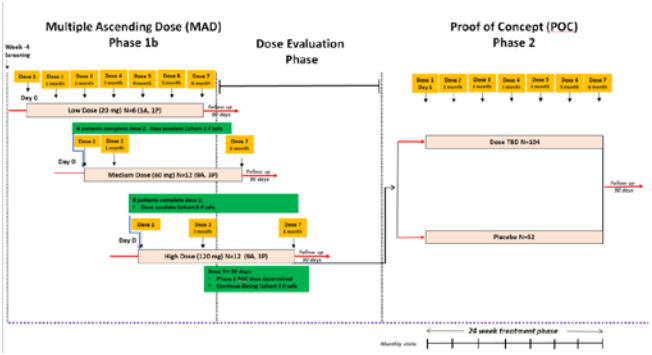
Section	Description of Changes	Rationale
	- SLEDAI-2K - SLICC/ACR damage index • Time to medication failure • Duration of **longest** SRI-4 response • Time to first SRI-4 response • Time to BILAG A flare or > 1 BILAG B flare compared to baseline through Day 210	
PROTOCOL SUMMARY, Study Design Section 1.2.4, Risk-Benefit Assessment	Replace: Two weeks after the last patient in Cohort 3 receives the second dose, the DMC and Boston Pharmaceuticals will conduct a data review to suggest which dose should be carried forward into the POC Phase 2 study. With: **Thirty days** after the last patient in Cohort 3 receives the **third** dose, the DMC and Boston Pharmaceuticals will conduct a data review to **determine** which dose **will** be carried forward into the POC **part of the** study.	To include more data from the 120 mg cohort in data review to determine POC dose.
PROTOCOL SUMMARY, Study Design Section 3.1, Study Design	Add: After successfully completing a screening phase, **eligible** patients will be randomized to a specified dose of BOS161721 or placebo.	Protocol clarification.
PROTOCOL SUMMARY, Inclusion Criteria Section 4.4, Inclusion Criteria	Add: 4 At screening, patients must have at least 1 of the following: a. Elevated ANA ≥ 1:80 via immunofluorescent assay at the central laboratory b. Positive anti-dsDNA or anti-Smith (Sm) above the normal level as determined by the central laboratory c. C3 or C4 **levels** below normal as determined by the central lab	Protocol clarification.
PROTOCOL SUMMARY, Exclusion Criteria Section 4.5, Exclusion Criteria	Add: 9 Active and clinically significant infection (bacterial, fungal, viral, or other) within 60 days prior to first dose of study drug. Clinically significant is defined as requiring systemic **parenteral** antibiotics or hospitalization 11 Chronic viral hepatitis including hepatitis B (HBV) and hepatitis C (HCV) **unless patient received curative treatment for HCV and has a documented negative viral load**, known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness	Protocol clarification.

Section	Description of Changes	Rationale
PROTOCOL SUMMARY, Exclusion Criteria Section 4.5, Exclusion Criteria	Replace: 15 CD4+ count < 500/µL at screening With: 15 CD4+ count < **35**0/µL at screening	DMC recommendation: The cut off for CD4+ T cells of 500 absolute count/µL was based on normal circulating levels in healthy individuals. The current trial is enrolling Systemic Lupus Erythematosus patients that, due to the disease, are known to have lymphopenia and specifically CD4+ lymphopenia with values typically below 500 cells/µL. According to the "WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children", CD4+ count < 350 cell/µL in adults is classified as significant immunodeficiency, thus the proposed cutoff threshold for exclusion criteria will be < 350 CD4+ cells/ µL.
PROTOCOL SUMMARY, Exclusion Criteria Section 4.5, Exclusion Criteria	Delete: 17 Hemoglobin < 8 g/dL or < 7 g/dL at screening if ~~due to anemia~~ related to SLE	Text removed as lab values would already qualify as anemic.
PROTOCOL SUMMARY, Statistical Considerations	Replace: Two analyses are planned: 1) an interim analysis to select the Phase 2 dose based on Phase 1 data, and 2) a final analysis at study completion. Additionally, DMC safety analyses will be performed after each Phase 1 cohort and throughout Phase 2 to monitor patient safety. Unless stated otherwise, statistical testing will only be performed on the Phase 2 data and will be done using 2-sided overall alpha of 0.10. With: Two analyses are planned: 1) an interim analysis to select the **POC** dose based on the **MAD** data, and 2) a final analysis at study completion. Additionally, DMC safety analyses will be performed **for** each **MAD** cohort and throughout **the POC** to monitor patient safety **as described in the DMC charter**. Unless stated otherwise, statistical testing will only be performed on the **POC** data and will be done using 2-sided overall alpha of 0.10.	Protocol clarification to confirm DMC will meet after each cohort is enrolled and not after each cohort is complete. Minor text changes and additions to provide further clarity to Phase 1 and 2 being MAD and POC.
Section 1.2.2, BOS161721 Development	Add: Boston Pharmaceuticals is developing BOS161721 for the treatment of SLE. BOS161721 is a humanized immunoglobulin G1 (IgG1) mAb **with extended half-life** directed against human IL-21.	Protocol clarification.

Section	Description of Changes	Rationale
Section 1.2.2,2 Preclinical Studies	Replace: The NOAELs were determined to be 100 mg/kg IV and 50 mg/kg SC, the highest doses tested. With: The NOAEL w**as** determined to be 100 mg/kg **(**SC and IV**)**, the highest dose tested.	Updated based on new data describing NOAEL based on 6-month study data.
Section 1.2.2,2 Preclinical Studies	Add: **An additional GLP, repeat-dose toxicity study was conducted in Cynomolgus monkeys (4 males and 4 females per dose group) following every 2 weeks (Q2W) administration by SC (10, 30, and 100 mg/kg) injection for a total of 14 doses.** CCI [redacted] **There were no BOS161721-related effects on survival, clinical signs, male body weights, ophthalmologic parameters, electrocardiogram (ECG) findings, clinical pathology, macroscopic observations, organ weights, or microscopic observations.** CCI [redacted] **The 100 mg/kg/dose was the NOAEL and** CCI [redacted]	Data from a 6 month GLP Toxicology study conducted in Cynomolgus monkeys was not available at the time the original protocol was written.
Section 1.2.3, Study Dose Selection	Add: Doses have been selected for the multiple ascending dose (MAD) Phase 1**b portion** based on a 90-day safety, tolerability, PK, and PD data review from the Phase 1 SAD study (BOS161721-01); the SDMT reviewed the blinded safety data from subjects for each dose cohort (8 cohorts, evaluating 1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg), along with the accumulated safety and available PK/PD data from all subjects in the previous dose cohorts, to make a decision on whether to proceed to the next higher dose level, repeat a dose level, or stop dose escalation.	Protocol clarification.

Section	Description of Changes	Rationale
Section 1.2.5, Potential Risks	Delete: ADAs could result in immune complex disease (with manifestations such as arthralgias, serum-sickness, and vasculitis), ~~autoimmunity,~~ or altered BOS161721 levels or activity.	Protocol clarification.
Section 1.2.5.2, Injection Site Reactions	Replace: In a repeat-dose GLP toxicology study in Cynomolgus monkeys, BOS161721 was administered every 2 weeks by IV or SC (50 mg/kg) for 3 months (a total of 7 doses); no SC animals had injection reactions. With: In a repeat-dose GLP toxicology study in Cynomolgus monkeys, BOS161721 was administered every 2 weeks by IV or SC for 3 months (a total of 7 doses). **There were no injection site reactions in animals dosed subcutaneously. Further, there were no reports of injection site reactions in the 26-week GLP toxicology study in Cynomolgus monkeys.**	Data was not available at the time the original protocol was written.
Section 1.2.5.4, Infections	Replace: Since the risk of opportunistic cryptosporidium infection increases with low levels of CD4+ T-cells,[37] patients with a CD4+ count < 500 cell/mm^3 were excluded from the Phase 1 SAD study (BOS161721-01), and will be excluded from the proposed MAD/POC studies. With: Since the risk of opportunistic cryptosporidium infection increases with low levels of CD4+ T-cells,[37] patients with a CD4+ count < 500 cell/mm^3 were excluded from the Phase 1 SAD study (BOS161721-01), and **CD4 + < 350 cells/mm^3** will be excluded from the MAD/POC **parts of the study**.	DMC recommendation: The cut off for CD4+ T cells of 500 absolute count/µL was based on normal circulating levels in healthy individuals. The current trial is enrolling Systemic Lupus Erythematosus patients that, due to the disease, are known to have lymphopenia and specifically CD4+ lymphopenia with values typically below 500 cells/µL. According to the "WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children", CD4+ count < 350 cell/µL in adults is classified as significant immunodeficiency, thus the proposed cutoff threshold for exclusion criteria will be < 350 CD4+ cells/µL.

Section	Description of Changes	Rationale
Section 1.2.5.6, Hepatic Function Abnormality	Replace: However, as a precaution, patients with a history of abnormal alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), or bilirubin at screening (ALT/AST > 2 × upper limit of normal [ULN]; total bilirubin > 1.5 × [ULN] and judged by the investigator to be clinically significant) were excluded from the Phase 1 SAD study (BOS161721-01), and will be excluded from the MAD study. With: However, as a precaution, patients with a history of abnormal alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), or bilirubin at screening (ALT/AST > 2 × upper limit of normal [ULN]; total bilirubin > 1.5 × [ULN] and judged by the investigator to be clinically significant) were excluded from the Phase 1 SAD study (BOS161721-01), and will be excluded from **this trial**.	Protocol clarification - MAD and POC have the same entrance criteria.
Section 3.1, Study Design	Replace: The scope of responsibility includes, but is not limited to, review and confirmation of "A" and "B" BILAG system organ disease, confirmation of clinical components of the SLEDAI-2K score at screening and during the study, and cross-validation of the instruments used in this study to assess the disease being studied. With: The scope of responsibility includes, but is not limited to, review and confirmation of "A" and "B" BILAG system organ disease, confirmation of clinical components of the SLEDAI-2K score at screening and during the study, and cross-validation of the instruments used in this study to assess the disease **activity**.	Protocol clarification.
Section 3.1.1, Multiple Ascending Dose Phase 1b Study	Add: All doses selected for the MAD **part of the** study are projected not to exceed the mean exposure of that achieved in the SAD study.	Protocol clarification.
Section 3.1.1.3, DMC Recommendations	Replace: The DMC will be reviewing all relevant data from Cohorts 1, 2, and 3 that is available at the time the last patient in Cohort 3 completes the Day 44 visit (2 weeks after dose 2). With: The DMC will be reviewing all relevant data from Cohorts 1, 2, and 3 that is available **30 days after the last patient from Cohort 3 receives the third dose**.	To include more data from the 120 mg cohort in data review to determine the POC dose.

Section	Description of Changes	Rationale
Section 3.1.2.1, BOS161721 Dose	Delete: The optimal dose ~~evaluation~~ is chosen based on MAD Phase 1b safety, tolerability, immunogenicity, and PK and PD data.	Protocol clarification.
Section 3.2, Randomization and blinding, Table footnote	Replace: *Additional patients may be enrolled to confirm sufficient numbers of patients are in the full analysis set (FAS). With: *Additional patients may be enrolled to **ensure** sufficient numbers of patients are in the full analysis set (FAS).	Protocol clarification.
Section 3.2, Randomization and blinding	Add: Similarly, patients in the Phase 1**b** MAD will be assigned to the cohort which is active.	Protocol clarification.
Section 3.3, Study Schematic	Replace: Figure 2. Study Diagram for MAD Phase 1b and POC Phase 2 Studies  With: Figure 2. Study Diagram for MAD Phase 1b and POC Phase 2  	Protocol clarification.

Section	Description of Changes	Rationale
Section 3.4, Schedule of Assessments, Table 1, Safety Follow-Up column	Add:	Protocol clarification. Urine pregnancy test added at day 270 to ensure patient is not pregnant at end of 90 day follow-up due to 41 day half-life of study drug.
Section 3.4, Schedule of Assessments, Table 1, PK Labs Windows	Add:	Adding PK windows for added flexibility.
Section 3.4, Schedule of Assessments, Table 1 footnotes Section 3.4, Schedule of Assessments, Table 2 footnotes	Add: [j] Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only assayed **(analyzed)** if the patient had a positive ADA on Day 90.	Protocol clarification.
Section 3.4, Schedule of Assessments, Table 1 footnotes	Replace: [k] nAb is assessed if patient is positive for ADA.	Protocol clarification.
Section 3.4, Schedule of Assessments, Table 2 footnotes	With: [k] nAb is **collected for all** patient**s, though will only be analyzed by central lab if patient** is positive for ADA **at Day 90**.	
Section 3.4, Schedule of Assessments, Table 1 footnotes	Add: [m] Only CCI collected during safety follow-up visits.	Protocol clarification.

	Safety Follow-Up		
Days	210 (± 3)	240 (± 3)	270 (± 3)
Visit Number	11	12	13
Urine pregnancy test (women)[n]			**X**

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	-28 to -1	0	7 (± 1)	15 (± 3)	30 (± 3)	44 (± 3)	60 (± 3)	90 (± 3)	120 (± 3)	150 (± 3)	180 (± 3)	187 (± 3)	195 (± 3)	210 (± 3)	240 (± 3)	270 (± 3)
Visit number	1	2	--	3	4	5	6	7	8	9	10	--	--	11	12	13
PK Labs																
Predose		X			X		X	X	X	X	X					
Predose PK Window		60m			± 3d		± 3d	± 3d	± 3d	± 3d	± 3d					
Postdose		X[p]	X	X	X[p]						X[p]	X	X	X	X	X
Postdose PK Window		4h ± 30m 8h ± 45m 24h ± 60m	± 1d	± 3d	4h ± 30m 8h ± 45m 24h ± 60m						4h ± 30m 8h ± 45m 24h ± 60m	± 3d	± 3d	± 3d	± 3d	± 3d

Section	Description of Changes	Rationale
Section 3.4, Schedule of Assessments, Table 2 Safety Follow-Up column	Add: 		Safety Follow-Up		
---	---	---	---
Days	210 (± 3)	240 (± 3)	270 (± 3)
Visit Number	10	11	12
Urine pregnancy test (women)[m]			**X**		Protocol clarification - urine pregnancy test added at day 270 to ensure patient is not pregnant at end of 90 day follow-up due to 41 day half-life of study drug.
Section 3.4, Schedule of Assessments, Table 2, PK Labs Window	Add: 		Screen[a]	Enroll	Treatment Period Follow-up								Safety Follow-Up		
---	---	---	---	---	---	---	---	---	---	---	---	---	---
Days	-28 to -1	0	15 (± 3)	30 (± 3)	60 (± 3)	90 (± 3)	120 (± 3)	150 (± 3)	180 (± 3)	187 (± 3)	195 (± 3)	210 (± 3)	240 (± 3)	270 (± 3)
Visit Number	1	2	3	4	5	6	7	8	9	--	--	10	11	12
PK Labs[s]														
Predose		X		X	X	X	X	X	X					
Predose PK Window		60m		± 3d	± 3d	± 3d	± 3d	± 3d	± 3d					
Postdose			X							X	X	X	X	X
Predose PK Window			± 3d							± 3d	± 3d	± 3d	± 3d	± 3d		Adding PK windows for added flexibility.
Section 3.4, Schedule of Assessments, Table 2 footnotes	Add: [l] Only CCI collected during safety follow-up visits.	Protocol clarification.
Section 3.5, End of Study	Add: **3.5 End of Study** **End of Study (Individual Patient): A patient is considered at the end of study if he/she has withdrawn, prematurely discontinued, or completed all of the study procedures including the last visit.** **End of Study (End of trial): The end of the study is defined as the date of the last visit of the last patient in the study globally, or the date of which the last patient withdraws or discontinues if all prior enrolled patients have already completed/withdrawn.**	Added end of study definitions in alignment with recent agency protocol authoring guidance.
Section 4.6.2, Other Prohibited and/or Restricted Treatments	Replace: 2 Patients who have received treatment with anti-CD20 monoclonal antibodies within 6 months of screening; recovery of B cells (CD19+) must be documented (record absolute number of CD19+ B cells) 3 Patients who have received treatment with cyclophosphamide within the 1 year prior to screening 4 Patients who have received treatment with cyclosporine (with exception of ophthalmic use), any other calcineurin inhibitor or other immunosuppressive medication not specified in the inclusion criteria (oral or topical) within 3 months of screening 5 Patients who are currently receiving or are scheduled to receive	Protocol clarification to align with appendices, align with other windows in protocol, and further clarification in #4 for sites to differentiate between oral and topical washout.

Section	Description of Changes	Rationale
	plasmapheresis or lymphapheresis therapy, or have received such therapy within 8 weeks prior to screening With: 2 Patients who have received treatment with anti-CD20 monoclonal antibodies within **24 weeks** of screening; recovery of B cells (CD19+) must be documented (record absolute number of CD19+ B cells) 3 Patients who have received treatment with cyclophosphamide within the **24 weeks** prior to screening 4 Patients who have received treatment with cyclosporine (with exception of ophthalmic use), any other calcineurin inhibitor or other immunosuppressive medication not specified in the inclusion criteria **within 4 weeks for** oral **use** or **8 weeks for** topical **use** of screening 5 Patients who are currently receiving or are scheduled to receive plasmapheresis or lymphapheresis therapy, or have received such therapy within **24** weeks prior to screening	
Section 5.1, Screening	Add: • Chest x-ray **(a prior x-ray can be used if taken within 12 weeks of screening date)**	Protocol clarification.
Section 5.2, Enrollment/ Randomization and Day 0 Treatment	Replace: The study site will obtain a randomization number when registering the patient in IWRS. With: **Prior to randomization, the study site should confirm that the patient still meets inclusion/exclusion criteria (especially SLE disease activity and treatment).** The site will obtain a randomization number when registering the patient in IWRS.	Added text to ensure eligibility prior to randomization
Section 5.3, Treatment Period/Follow-Up Visits	Replace: • CRP and nAb will be assessed if patient is positive for ADA With: • nAb will be **analyzed by central lab** if patient is positive for ADA • CRP	Protocol clarification.

Section	Description of Changes	Rationale
Section 5.4, Safety Follow-Up Visits	Add: • **Urine pregnancy test**	Urine pregnancy test added at day 270 to ensure patient is not pregnant at end of 90 day follow up due to 41 day half-life of study drug.
Section 6.2.1, Laboratory Assessments	Delete: A central laboratory will be used (with the exception of urine pregnancy tests ~~and stool analysis~~) to ensure accuracy and consistency in test results. ~~The central laboratory will transmit all results for protocol tests, scheduled and unscheduled, to the clinical data base.~~	Central data is not being transmitted into the clinical database.
Section 6.2.1, Laboratory Assessments, Table 3, Other Safety Tests column	Add: Other Safety Tests Spot urine for protein/creatinine ratio FSH[b] Urine pregnancy test[c] QuantiFERON®-TB Gold In-Tube test (QFT-G)[d] Serology[d] (Hepatitis B and C; HIV-1/2 combination) Stool sample[e] **Serum pregnancy test**	Protocol clarification to align with Schedule of Assessments.
Section 6.2.1, Laboratory Assessments, Table 3, Additional Tests column	Add: Additional Tests[f] (potential Hy's Law) AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin GGT **Prothrombin time/international normalized ratio (repeat)** **Creatine kinase (repeat)**	Protocol clarification to align with Schedule of Assessments.
Section 6.2.1.1, Pregnancy Testing	Add: Urine pregnancy tests will also be routinely repeated at study drug administration visits prior to study drug administration, **at the last follow up visit day (Day 270)** and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected.	Urine pregnancy test added at day 270 to ensure patient is not pregnant at end of 90 day follow up due to 41 day half-life of study drug.

Section	Description of Changes	Rationale
Section 6.2.2.2, Recording of Adverse Events	Delete: The details of the AE, date of AE onset ~~(and time, if known)~~, date of AE outcome ~~(and time, if known)~~, and action taken for the AE will be documented together with the principal investigator's assessment of the seriousness of the AE and causal relationship to the study drug and/or the study procedure.	Exact time of adverse event is not needed for this study. If serious adverse event, time of onset will be provided in narrative.
Section 6.2.2.6.2, Injection Site Reactions	Add: These will include Grades 2 to 5 injection site erythema, pain, and induration (see APPENDIX 6)**, which are also captured as Adverse Events of Special Interest (See Section 6.2.2.6)**.	Protocol clarification.
Section 6.2.3, Vital Signs	Add: Vital signs will be assessed on Day 0 at predose and at **Day 0,** 1 and 2 hours postdose, as well as on each of the scheduled visit days during the study (excluding PK-only site visits).	Protocol clarification.
Section 6.2.8, Immunogenicity	Replace: Subsequent ADA samples will be collected from all patients but only assayed if the patient had a positive ADA on Day 90. After the first dose, if a patient tests positive in the validated confirmatory ADA assay, the sample from this patient will be further analyzed in the neutralizing antibody (nAb) assay. With: Subsequent ADA samples will be collected from all patients but only **analyzed by a central lab** if the patient had a positive ADA on Day 90. After the first dose, if a patient tests positive in the validated confirmatory ADA assay, **a** sample from this patient will be further analyzed in the neutralizing antibody (nAb) assay **by a central lab**.	Protocol clarification.
Section 6.3.3, PGA of Disease Activity	Add: **PGA worsening is defined as an increase of > 30 mm from baseline.**	Added definition of worsening PGA.
Section 6.3.4.1, SRI-4 Response	Replace: no deterioration from baseline in the PGA by ≥ 0.3 points With: no deterioration from baseline in the PGA by ≥ **30 mm**	Unit was incorrectly presented in previous protocol version.

Section	Description of Changes	Rationale
Section 6.3.4.2, SRI-5 and SRI-6 Response	Replace: However, the SRI-5 and SRI-6 are computed with a minimal three-point or five-point improvement in SLEDAI-2K being required, respectively. With: However, the SRI-5 and SRI-6 are computed with a minimal **five**-point or **six**-point improvement in SLEDAI-2K being required, respectively.	Units incorrectly presented in previous protocol version.
Section 6.4.2, PROs	Add: CCI [redacted]	Protocol clarification.
Section 8, Statistics	Add: • The final analysis will be performed when all patients have completed the **POC** safety follow-up or withdrawn from the study.	Protocol clarification.
Section 8, Statistics	Replace: Select parameters will be summarized using patients from both study phases. With: Select parameters **may** be summarized using patients from both study **parts**.	If an interpolated dose is selected for POC, dose levels may not be combined.
Section 8.2.3, Primary Efficacy Endpoint(s)	Delete: If the proportion of SRI-4 responders for the selected POC dose in BOS161721 arm is higher than that of the placebo arm, then BOS161721 will be considered superior to placebo if the 2-sided p-value is less than ~~or equal to~~ 0.10.	Statistical inference will be based on a 2-tailed test with an overall 0.10 level of significance.
Appendix 1	Replace: PPD [redacted] PPD [redacted] With: PPD [redacted]	Administrative

Section	Description of Changes	Rationale
	PPD	
	PPD	
	PPD	
Appendix 4	Add:	Protocol clarification.

Cyclosporine (except for CSA eye drops)	4 weeks **for oral and 8 weeks for topical**

A RANDOMIZED DOUBLE-BLIND PHASE 1b/2 COMBINED STAGGERED MULTIPLE DOSE ESCALATION STUDY OF BOS161721 IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS ON A BACKGROUND OF LIMITED STANDARD OF CARE

SPONSOR	Boston Pharmaceuticals, Inc. 55 Cambridge Parkway, Suite 401 Cambridge, MA 02142 United States of America (USA)
INVESTIGATIONAL COMPOUND:	BOS161721
PROTOCOL NUMBER:	BOS161721-02
PHASE	Phase 1b/2
INVESTIGATIONAL NEW DRUG (IND) NUMBER:	131796
ORIGINAL PROTOCOL DATE:	06 October 2017
VERSION NUMBER:	V3.0 (Amendment 2)
VERSION DATE:	21 March 2018

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care

Study No: BOS161721-02
Original Protocol Date: 06 October 2017
Protocol Version No: v2.0 (Amendment 1)
Protocol Version Date: 14 November 2017
Protocol Version No: v3.0 (Amendment 2)
Protocol Version Date: 21 March 2018

This study protocol was subject to critical review and has been approved by sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (APPENDIX 2), and principles of Good Clinical Practices (GCP) as described in 21 Code of Federal Regulations (CFR) parts 50, 54, 56 and 312 and according to applicable local requirements.

The investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

I agree with these statements and indicate my approval by signature for this protocol:

Name and Title	Signature and Date
PPD , MD Vice President, Clinical Development Boston Pharmaceuticals	PPD
PPD Clinical Operations Lead Boston Pharmaceuticals	PPD
PPD , MD, PhD Vice President, Clinical Development and Safety Officer Boston Pharmaceuticals	PPD

BOS161721-02

A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to BOS161721 are the confidential and proprietary information of Boston Pharmaceuticals, Inc., and except as may be required by federal, state, or local laws or regulation, may not be disclosed to others without prior written permission of Boston Pharmaceuticals, Inc.

I have read the protocol (V3.0 [Amendment 2], dated 21 March 2018), including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Council for Harmonisation (ICH) guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Boston Pharmaceuticals, Inc., or specified designees. I will discuss the material with them to ensure that they are fully informed about BOS161721 and the study.

_____ _____

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

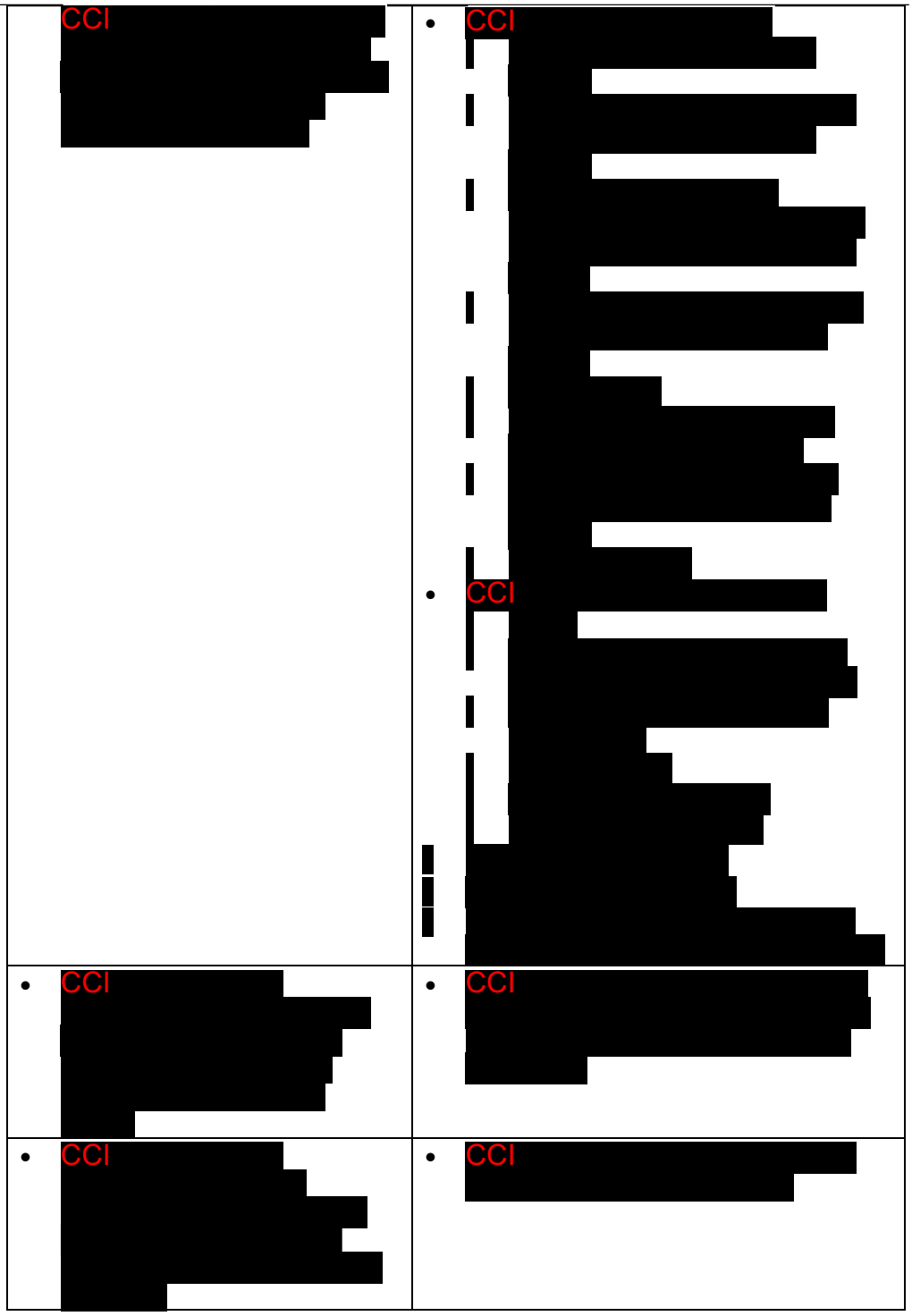
PROTOCOL SUMMARY

Title:	A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care
Indication	Adults with moderately to severely active SLE
Background and Rationale	SLE is a chronic systemic autoimmune disease with considerable heterogeneity in clinical manifestations and disease course. There is evidence that B- and T-cells are critical to the development of the disease, and that T-cell-derived cytokines such as interleukin-21 (IL-21) are involved in the SLE-associated inflammatory pathological response. BOS161721 is a humanized immunoglobulin G1 (IgG1) triple mutation monoclonal antibody (mAb) intended to have an extended terminal elimination half-life ($t_{1/2}$) that selectively binds to and neutralizes IL-21, which acts on multiple cell types that drive inflammation and autoimmunity. In vivo, BOS161721 inhibits T-cell dependent antigen responses of B-cells and is being developed as a potential treatment for adults with moderately to severely active SLE. Nonclinical studies have evaluated the toxicity, pharmacodynamics (PD), toxicokinetics (TK), pharmacokinetics (PK), and immunogenicity of BOS161721 administered intravenously (IV) and subcutaneously (SC). The no observed adverse effect levels (NOAELs) in Cynomolgus monkeys were determined to be 100 mg/kg IV and 50 mg/kg SC, the highest doses tested. No SC animals had injection reactions. In a Phase 1 single ascending dose (SAD) study, BOS161721 was administered IV and SC to healthy male and female adult subjects. This double-blind, placebo-controlled study evaluated 8 ascending dose levels (1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg) for safety, tolerability, PK, PD and immunogenicity. Overall, there were no clinically significant safety or tolerability findings from this study, following an interim cut and review of the data at Day 90 postdose. Results from the Phase 1 SAD study informed the dose regimens used for the multiple ascending doses (MAD) Phase 1b study in this trial. The MAD study will involve 3 cohorts. The Phase 2 portion will be a proof of concept (POC) study, where dose selection will be based on the data monitoring committee (DMC) and sponsor's assessment of safety, tolerability, immunogenicity, and PK and PD data from the MAD study of 30 patients treated with BOS161721/placebo. The purpose of the study is to establish safe and effective dosages for adult patients with moderately to severely active SLE.

Objectives and Endpoints:

MAD Phase 1b Study

OBJECTIVES	ENDPOINTS
Primary	
• To assess safety, tolerability, and immunogenicity of repeat doses of BOS161721 (20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment, in order to estimate the optimal dose.	Safety Endpoints • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • Columbia Suicide severity Rating Scale (C-SSRS) • 12-lead electrocardiograms (ECGs) parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from baseline • Physical examinations changes from baseline • Anti-drug antibodies (ADAs) • Study drug exposure/compliance • Concomitant medication usage
Secondary	
• To characterize the PK of BOS161721 and select the optimal dose of BOS161721 based on safety, PK, and PD effects in patients with mild to moderate SLE.	Pharmacokinetic Endpoints • BOS161721 concentration by visit and time point • Maximum observed concentration (C_{max}), first time to maximum concentration (T_{max}), area under the concentration-time curve (AUC), $t_{½}$, systematic clearance (C_L), volume of distribution (V_d) Pharmacodynamic Endpoints • Results and changes (or shifts) from baseline to each visit in phosphorylated signal transducer and activator of transcription 3 (pSTAT3), C3 and C4 levels, and leukocyte immunophenotype • Results and changes (or shifts) from baseline in anti-double-stranded DNA (dsDNA), antinuclear antibodies (ANA), anti-Sjögren syndrome A and B (SSA, SSB), Smith (Sm), and antiphospholipid (APL) autoantibodies at each visit • Results and changes (or shifts) from baseline in abrogation of IL-21 gene signature at each indicated visit
Exploratory	
• CCI	CCI



POC Phase 2 Study

OBJECTIVES	ENDPOINTS
Primary	

• To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on the SLE Responder Index 4 (SRI-4)	Primary Efficacy Endpoint • The proportion of subjects with a SRI-4 response at Day 210 (see Section 6.3.4.1)
Secondary	
• To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on clinical indicators of SLE activity, in adult patients with moderately to severely active SLE on limited background standard of care treatment	Secondary Efficacy Endpoints • The proportion of subjects with: - SRI-4 response at each visit - SRI-5 and SRI-6 response (Section 6.3.4.2) - a sustained reduction of oral corticosteroid (CS) (≤ 10 mg/day and ≤ Day 0 dose) between Day 120 and Day 210 - new BILAG A flare or > 1 BILAG B flares relative to baseline through Day 210 - PGA worsening - a BICLA response - a CLASI response - medication failures • Results and changes from baseline in: - CLASI - swollen and tender joints ACR-28 - SLEDAI-2K - SLICC/ACR damage index - Time to medication failure • Duration of SRI-4 response • Time to first SRI-4 response • Time to BILAG A flare or > 1 BILAG B flare compared to baseline through Day 210
Safety	

• To assess safety and tolerability of repeat doses of BOS161721 (20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment	Safety Endpoints • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • C-SSRS • 12-lead ECGs parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from baseline • Physical examinations changes from baseline • ADAs • Study drug exposure/compliance Concomitant medication usage
Exploratory	
• CCI	CCI
• CCI	• CCI
• CCI	• CCI

Study Design: This is a Phase 1b/2 combined, randomized, multicenter, double-blind, placebo-controlled trial to study the clinical efficacy, safety, and PK of multiple SC doses of BOS161721 in adult patients with moderately to severely active SLE. After successfully completing a screening phase, patients will be randomized to a specified dose of BOS161721 or placebo. The dosing schedule will be monthly. The trial will consist of 2 double-blinded studies: MAD Phase 1b and POC Phase 2. Patients may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90,

120, 150, and 180, followed by safety follow-up visits at Days 210, 240, and 270.

The MAD Phase 1b study phase will consist of 3 cohorts, with Cohort 1 containing 6 patients, where 5 of these patients will receive BOS161721 (active), and 1 will receive placebo. Cohorts 2 and 3 will each contain 12 patients, including 9 active and 3 placebo patients. Dose selection for each cohort is based on 90-day safety, tolerability, PK, and PD data review from the Phase 1 SAD study (BOS161721-01) in healthy subjects. Each of the 3 doses (20, 60, and 120 mg) selected for the MAD study are projected not to exceed the mean exposure of that achieved in the SAD study following the single 240 mg SC dose. Each patient may receive a total of 7 SC monthly doses on Days 0, 30, 60, 90, 120, 150, and 180.

The MAD study design is staggered, where after the 6 patients in Cohort 1 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 2 begins dosing (after a DMC evaluates the safety and tolerability data from Cohort 1). Similarly, after 8 of the 12 patients in Cohort 2 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 3 begins dosing after DMC evaluation of the safety and tolerability data from Cohort 2 and Cohort 1. Two weeks after the last patient in Cohort 3 receives the second dose, the DMC and Boston Pharmaceuticals will conduct a data review to suggest which dose should be carried forward into the POC Phase 2 study. This dose will not exceed doses tested during the MAD study.

For the POC study, approximately 156 additional patients will be randomized to active or placebo groups in a 2:1 ratio. As in the MAD study, each patient in the POC study may receive a total of 7 SC monthly doses on Days 0, 30, 60, 90, 120, 150, and 180.

A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). One oral CS “burst” for increased SLE disease activity may occur during the study between Day 0 and Day 60. Tapering of steroids during the course of the study will be encouraged and should be evaluated at all visits. Tapering may occur after randomization except within 60 days of the primary (Day 210) and secondary (Day 120) endpoint assessments. Between Day 60 and Day 120, and between Day 150 and Day 210, oral CS doses must be held constant.

DMC safety reviews will be conducted periodically throughout the study as described in the DMC charter.

Main Criteria for Inclusion

Inclusion Criteria:

and Exclusion

1. Men and women, ages 18 to 70 years, inclusive

2. Patients must be mentally capable of giving consent and there must be evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study

3. Patients must have SLE as defined by meeting 4 of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE (with at least 1 clinical and 1 immunologic criterion OR Lupus nephritis as the sole clinical criterion in the presence of antinuclear antibodies [ANA] or anti- double-stranded deoxyribonucleic acid [dsDNA] antibodies), either sequentially or simultaneously

4. At screening, patients must have at least 1 of the following:

    a. Elevated ANA ≥ 1:80 via immunofluorescent assay at the central laboratory

    b. Positive anti-dsDNA or anti-Smith (Sm) above the normal level as determined by the central laboratory

    c. C3 or C4 below normal as determined by the central lab

5. At screening, the SLEDAI-2K must be ≥ 6, including points from at least 1 of the following clinical components:

    a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis

        i. Excluding parameters which require central laboratory results: (hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia)

        ii. Points from lupus headache and organic brain syndrome will also be excluded

6. On Day 0, the SLEDAI-2K must be ≥ 6, including points from at least 1 of the following clinical components:

    a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis

        i. Excluding parameters which require central laboratory results: hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia

        ii. Points from lupus headache and organic brain syndrome will also

be excluded

7. Patients must have at least 1A or 2Bs from the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer:

    a. BILAG A or B score in the mucocutaneous body system

    b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis as defined in the protocol Section 4.4

    If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in the other body systems for a total of 2 "B" BILAG body system scores

8. Patients must be currently receiving at least 1 of the following:

    a. Administration for a minimum of 12 weeks, and a stable dose for at least 56 days (8 weeks prior to signing consent) of the following permitted steroid-sparing agents:

        i. Azathioprine (AZA), mycophenolate mofetil or mycophenolic acid, chloroquine, hydroxychloroquine, or methotrexate (MTX)

    b. Prednisone (or prednisone-equivalent) cannot exceed 30 mg/day at screening for a patient to be eligible and must be stable at a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization)

9. Women of childbearing potential (WOCBP; see Section 4.7 for full information regarding WOCBP, definition of menopause, and contraception):

    a. Must have a negative serum pregnancy test at screening. Urine pregnancy test must be negative prior to first dose

    b. Must not be breastfeeding

    c. Must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS161721 plus 30 days (duration of ovulatory cycle) for a total of 36 weeks after treatment completion

10. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of BOS161721 plus 90 days (duration of

sperm turnover) for a total of 44 weeks after treatment completion

11. Patients must demonstrate willingness and ability to comply with the scheduled study visits, treatment plans, laboratory tests, and other procedures

Exclusion Criteria

Patients presenting with any of the following will not be included in this study:

1. Drug-induced SLE, rather than "idiopathic" SLE
2. Other systemic autoimmune disease (eg, erosive arthritis, rheumatoid arthritis [RA], multiple sclerosis [MS], systemic scleroderma, or vasculitis not related to SLE)
    a. RA-Lupus overlap (Rupus), and secondary Sjögren syndrome are allowed
3. Any major surgery within 6 weeks of study drug administration, (Day 0), or any elective surgery planned during the course of the study
4. Any history or risk for tuberculosis (TB), specifically those with:
    a. Current clinical, radiographic, or laboratory evidence of active TB
    b. History of active TB
    c. Latent TB defined as positive QuantiFERON-TB Gold In-Tube (QFT-G) or other diagnostic test in the absence of clinical manifestations. Latent TB is not excluded if the patient has documented completion of adequate course of prophylactic treatment with regimen recommended by local health authority guideline, or the patient has started treatment with isoniazid, or other regimen recommended by local health authority guidelines for at least 1 month before Day 0 and continues to receive the prophylactic treatment during study until the treatment course is completed
5. Active or unstable lupus neuropsychiatric manifestations, including but not limited to any condition defined by BILAG A criteria, with the exception of mononeuritis multiplex and polyneuropathy, which are allowed
6. Severe proliferative lupus nephritis, (WHO Class III, IV), which requires or may require induction treatment with cytotoxic agents or high dose CS
7. Concomitant illness that, in the opinion of the investigator, is likely to require additional systemic glucocorticosteroid therapy during the study, (eg, asthma), is exclusionary
    a. However, treatment for asthma with inhalational CS therapy is allowed

8. Use or planned use of concomitant medication outside of standard of baseline treatment for SLE from Day -1 or for any time during the study
9. Active and clinically significant infection (bacterial, fungal, viral, or other) within 60 days prior to first dose of study drug. Clinically significant is defined as requiring systemic antibiotics or hospitalization
10. A history of opportunistic infection, or a history of recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years
11. Chronic viral hepatitis including hepatitis B (HBV) and hepatitis C (HCV), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness
12. Cryptosporidium in the stool sample at screening
13. White blood cells (WBC) < 1,200/mm^3 (1.2×10^9/L) at screening
14. Absolute neutrophil count (ANC) < 500/mm^3 at screening
15. CD4+ count < 500/µL at screening
16. Platelets < 50,000/mm^3 (50×10^9/L) or < 35,000/ mm^3 (35×10^9/L) if related to SLE, at screening
17. Hemoglobin < 8 g/dL or < 7 g/dL at screening if due to anemia related to SLE
18. Proteinuria > 3.0 g/day (3000 mg/day) at screening or equivalent level of proteinuria as assessed by protein/creatinine ratio (3 mg/mg or 339 mg/mmol)
19. Serum creatinine > 2.0 mg/dL at screening or creatinine clearance (CrCL) < 40 ml/minute based on Cockcroft-Gault calculation
20. Serum alanine aminotransferase (ALT) and/or serum aspartate aminotransferase (AST) > 2 × the upper limit of normal (ULN) at screening, unless explicitly related to lupus based on the investigator's judgment
21. Creatinine kinase (CK) > 3.0 × ULN at screening unless related to lupus myositis
22. Direct bilirubin > 1.5 × ULN at screening (unless related to Gilbert's syndrome)
23. Any other laboratory test results that, in the opinion of the Investigator, might place a patient at unacceptable risk for participating in this study
24. History of allergic or anaphylactic reaction to any therapeutic or diagnostic mAb (eg, IgG protein) or molecules made of components of mAbs
25. History substance and/or alcohol abuse, or dependence within the past 1 year, at the investigator's judgment

26. History of cancer within the last 5 years (except for cutaneous basal cell or squamous cell cancer, or cervical cancer in situ resolved by excision
27. Any other severe acute or chronic medical or psychiatric condition, including recent (within the past year) medical conditions (eg, cardiovascular conditions, respiratory illnesses) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study
28. Investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or patients who are employees of the sponsor or directly involved in the conduct of the trial
29. Currently participating in, or who have participated in other interventional (drug or device) clinical study within 30 days or 5 half-lives of baseline, whichever is longer
30. Recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4, or 5 on the C-SSRS
31. Current or pending incarceration
32. Current or pending compulsory detainment for treatment of either a psychiatric or physical (eg, infectious disease) illness

Statistical Considerations

Below is a summary of the statistical methods. Further details can be found in Section 8.

Two analyses are planned: 1) an interim analysis to select the Phase 2 dose based on Phase 1 data, and 2) a final analysis at study completion. Additionally, DMC safety analyses will be performed after each Phase 1 cohort and throughout Phase 2 to monitor patient safety.

Unless stated otherwise, statistical testing will only be performed on the Phase 2 data and will be done using 2-sided overall alpha of 0.10. Data will be summarized descriptively by treatment and overall for each study phase. For the MAD phase, BOS161721 will be summarized overall and by each dose level and placebo patients from each cohort will be combined.

The descriptive summaries for the categorical data will include number and percentage. The descriptive summaries for the continuous data will include number, mean, median, standard deviations (SD), 25th and 75th percentiles, minimum, median, and maximum. Counts, medians, 25th and 75th percentiles, and standard error will be presented for time-to-event data.

All safety analyses will be performed using the safety analysis set (SS), defined as all patients who receive at least 1 dose of study treatment. All efficacy analyses will be performed using the full analysis set (FAS), defined

as all patients who receive at least 1 dose of study treatment and have at least 1 evaluable post-baseline efficacy evaluation. Select efficacy analyses may also be performed on the per protocol (PP) set.

Binary efficacy endpoints, including the primary efficacy endpoint, will be assessed via Pearson's chi-squared analysis.

Continuous efficacy endpoints will be assessed via analysis of variance (ANOVA) or analysis of covariance (ANCOVA) when applicable, adjusting for the baseline value. Repeated measures mixed models may be performed to evaluate data collected at each visit and overall. Time-to-event endpoints will be assessed via Kaplan-Meier methodology and treatment will be compared using the log-rank test.

Adverse event data will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients experiencing any treatment-emergent AE, overall, and by system organ class and preferred term will be tabulated. Treatment-emergent AEs will also be summarized by severity and relationship.

Concomitant medications will be summarized, based on coded terms, using frequency and percentage of patients. Observed values and changes from baseline in vital signs, ECG readings, and hematology and clinical chemistry parameters, will be summarized at each individual visit.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADA	anti-drug antibody
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANC	absolute neutrophil count
ANOVA	analysis of variance
ANCOVA	analysis of covariance
APL	antiphospholipid
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AZA	azathioprine
BICLA	BILAG-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BP	blood pressure
BUN	blood urea nitrogen
BW	body weight
C	complement
CS	corticosteroids
C-SSRS	Columbia Suicide Severity Rating Scale
CD	cluster of differentiation
CK	creatine kinase
C_L	systematic clearance
CLASI	Cutaneous Lupus Erythematosus Area and Severity Index
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CS	corticosteroids
CSR	clinical study report
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
dsDNA	double-stranded deoxyribonucleic acid
ECG	electrocardiogram
EOT	end of treatment
eCRF	electronic case report form
F	female
CCI	[redacted]
FAS	full analysis set

Fc	fragment crystallizable
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
eGFR	estimated glomerular filtration rate
GLP	Good Laboratory Practice
GWAS	genome-wide association studies
γc	gamma chain
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCl	hydrochloride
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IL	interleukin
IL-21R	interleukin 21 receptor
IM	intramuscular
INFγ	interferon gamma
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
IVRS	interactive voice response system
JAK	Janus kinase
kg	kilogram
KLH	keyhole limpet hemocyanin
LOCF	last observation carried forward
M	male
mAb	monoclonal antibody
MAD	multiple ascending dose
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary of Regulatory Activities
MS	multiple sclerosis
MTX	methotrexate

NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIAID/FAAN	National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network
NK	natural killer
NOAEL	no observed adverse event level
NO	nitric oxide
OTC	over-the-counter
PD	pharmacodynamics
PEF	peak expiratory flow
PGA	Physician's Global Assessment
PK	pharmacokinetics
POC	proof of concept
PP	per protocol
PR	(interval) from onset of the p-wave to the end of the r-wave
pSS	primary Sjögren's syndrome
pSTAT3	phosphorylated signal transducer and activator of transcription 3
PT	preferred term
QRS	(interval) from the onset of the q-wave to the end of the s-wave
QT	(interval) from onset of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
QFT-G	QuantiFERON-TB Gold In-Tube
RA	rheumatoid arthritis
RR	(interval) from the onset of the r-wave to the onset of the next consecutive r-wave
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SDMT	safety data monitoring board
CCI	[redacted]
SLE	systemic lupus erythematosus
SLEDAI-2K	SLE Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
Sm	Smith
SOC	system organ class
SRI-4	SLE Responder Index 4
SRI-5	SLE Responder Index 5
SRI-6	SLE Responder Index 6
SS	safety analysis set
SSA	Sjögren syndrome-A (Ro)
SSB	Sjögren syndrome-B (La)

STAT3	signal transducer and activator of transcription 3
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
TB	tuberculosis
TDAR	T-cell dependent antibody response
Tfh	T-follicular helper
Th	T-helper
TK	toxicokinetics
T_{max}	first time to maximum concentration
Treg	regulatory T-cell
TT	tetanus toxoid
ULN	upper limit of normal
US	United States
Vd	volume of distribution
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
YTE	triple mutation

1. INTRODUCTION AND RATIONALE

1.1 Indication

BOS161721 is a humanized monoclonal antibody (mAb), which binds to and inhibits interleukin-21 (IL-21) bioactivity, and is being developed for the treatment of moderately to severely active systemic lupus erythematosus (SLE) in adults.

1.2 Background and Rationale

1.2.1 Overview of the Disease State

SLE is a chronic inflammatory autoimmune disease that has variable manifestations in multiple organ systems and follows a relapsing and remitting course. The disease process includes abnormal immune responses mediated by tissue-binding autoantibodies and immune complex deposition, giving rise to tissue damage often resulting in end organ disease and even mortality. Survival of SLE has improved due to earlier detection, improved overall medical care, and standardized SLE treatment with corticosteroids (CS), immunosuppressants, and cytotoxic agents.[1] However, some of the morbidity in patients with SLE is related to its treatment. Comparison of early and late outcomes in patients with SLE demonstrate that death in early disease is most commonly due to infections and active SLE causing multi-system organ damage, while thromboses were the most common cause of death during later disease.[2]

The reported prevalence of SLE in the United States (US) is 20 to 70 cases per 100,000 people.[3] More than 90% of cases of SLE occur in women, frequently starting at childbearing age. Women of color are disproportionately affected by SLE. This suggests multiple genetic and environmental factors are at play. Accordingly, a multifactorial view of the immunopathogenesis of SLE suggests more than 1 area of interest, including breach in central tolerance in the adaptive arm of the immune system, peripheral amplification of the autoimmune response by the innate immune system, and local processes in the target organ that facilitate end-organ disease.[4]

1.2.2 BOS161721 Development

Boston Pharmaceuticals is developing BOS161721 for the treatment of SLE. BOS161721 is a humanized immunoglobulin G1 (IgG1) mAb directed against human IL-21.

Murine mAb 19E3, the progenitor of BOS161721, was generated using mouse hybridoma technology. 19E3 has subpicomolar (pM) affinity to human IL-21 and was selected for its potent neutralization of IL-21 bioactivity. BOS161721 was generated by the humanization of mAb 19E3 where its complementarity-determining regions were grafted onto a human IgG1 kappa backbone. The fragment crystallizable (Fc) portion of BOS161721 contains a YTE (M252Y/S254T/T256E triple mutation) in the constant domain of the IgG1 heavy chain that was introduced into the parental molecule, 19E3, intended to prolong the in vivo terminal elimination half-life ($t_{1/2}$) of the mAb.[5] Thus, BOS161721 retains sub-pM binding to IL-21 and prevents IL-21 from binding to the IL-21 receptor (IL-21R), inhibiting IL-21 bioactivity.

BOS161721 binds to human IL-21 and Cynomolgus monkey IL-21, which are highly homologous, and neutralizes the bioactivity of both. BOS161721 is specific for IL-21 as it does not bind to or inhibit the other gamma-chain (γc) family of cytokines, and acts to specifically neutralize the IL-21 pathway. In *in vitro* studies, BOS161721 inhibited downstream IL-21-induced signaling, IL-21-induced plasma cell differentiation, and IL-21-induced natural killer (NK) cell activation. In *in vivo* studies, BOS161721 significantly inhibited the T-cell dependent antibody response (TDAR) to immunization with a protein antigen as well as B-cell expansion following a second protein antigen immunization in Cynomolgus monkeys.

1.2.2.1 Interleukin-21

IL-21 is an inflammatory cytokine, which belongs to a family of cytokines that also includes IL-2, IL-4, IL-7, IL-9, and IL-15, all of which bind to private receptors in complex with the common cytokine receptor γc.[6] Most cytokines in this family are critically important for both the maintenance and function of T-cell and B-cell responses. IL-21 signals through a receptor complex consisting of its own private receptor, the IL-21R and γc.[6,7] Engagement of the IL-21R/γc complex leads to the activation of several signaling pathways, including the Janus kinase/signal transducer and activator of transcription, mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase pathways.[8] IL-21 is produced mainly by T-cells and NK T-cells, but neutrophils have also been reported to produce IL-21.[9,10] The IL-21R is expressed on a broad array of cell types, including B-cells, T-cells, NK-cells, macrophages and dendritic cells, as well as other hematopoietic and nonhematopoietic cells such as fibroblasts, keratinocytes, and intestinal epithelial cells.[9,11] Activation of signal transducer and activator of transcription 3 (STAT3) via phosphorylation is critical in regulating human B-cell responses to IL-21[12]; phosphorylated STAT3 (pSTAT3) forms a homodimer, which translocates to the nucleus where it initiates transcription of the IL-21 gene, forming an autocrine loop for IL-21 production via STAT3 phosphorylation.[13] In addition, IL-21 has been shown to upregulate expression of its own receptor[14] and induces an autocrine feedback loop.[15]

IL-21 modulates various aspects of immune function. It promotes cluster of differentiation 4 (CD4+) T-cell differentiation and promotes the generation of T-helper (Th)17[16] and T-follicular helper (Tfh) cells.[15,17] In mice, IL-21 has been shown to regulate the balance between Th17 and regulatory T-cell (Treg), in that it increases Th17, while inhibiting Treg differentiation.[18] Less is understood with regards to human Tregs, although IL-21 has been reported to counteract Treg suppression of human effector T-cells[19] and blockade of IL-21 promotes Treg generation in a murine model of graft versus host disease induced by human T-cells.[20] IL-21 upregulates CD8+ T-cell and NK-cell expansion and cytolytic activity by increasing granzyme B and perforin.[21,22] IL-21 also has been reported to increase granzyme B in plasmacytoid dendritic cells and B-cells resulting in inhibition of T-cell responses.[23,24] IL-21 also has a variety of effects on nonhematopoietic cells, such as stromal cells and induces inflammation through matrix metalloproteinase release by gut intestinal fibroblasts.[25]

One principal non-redundant role of IL-21 is the promotion of B-cell activation, differentiation, or death during humoral immune responses.[14] Furthermore, increased IL-21 production is characteristic of several autoimmune diseases and is likely to contribute to autoantibody production as well as pathologic features of autoimmune disease.[26] The critical role of IL-21 in promoting humoral and other immune responses makes it an important focus of potential

therapeutic interventions in conditions characterized by overproduction of pathogenic autoantibodies. IL-21 production by Tfh cells in humans is believed to play a major role in driving the autoantibody production through its role in plasma cell differentiation. Importantly, Tfh cell populations are expanded in patients with autoimmune diseases such as lupus, bullous pemphigoid, rheumatoid arthritis (RA) and primary Sjögren's syndrome (pSS) and have been reported to correlate with IL-21 levels, autoantibodies, and disease severity.[26,27,28,29] Furthermore, loss of number and functionality of Tregs has been associated with autoimmune diseases such as SLE and giant cell arteritis, which IL-21 is expected to modulate.[30,31] Thus, neutralization of IL-21 in settings of autoimmunity is expected to impact several cell populations believed to be involved in the pathogenesis of autoimmune disorders including SLE.

BOS161721 selectively binds IL-21 with high affinity to neutralize IL-21, and due to its pleiotropic nature, neutralization of IL-21 is expected to impact several cell populations believed to be involved in the pathogenesis of SLE. Importantly, patients with SLE have elevated IL-21 plasma levels that correlate with the severity of the disease. Recently, genome-wide association studies (GWAS) have provided convincing evidence that the chromosomal 4q 27 region harbors the IL-21 genes and is associated with chronic inflammatory disorders, including SLE.[29]

1.2.2.2 Preclinical Studies

The pharmacokinetics (PK) of BOS161721 were characterized following single-dose intravenous (IV) administration of BOS161721 (0.01 to 30 mg/kg) in male Cynomolgus monkeys or repeat, every 2 weeks IV administration (15 to 100 mg/kg) and subcutaneous (SC) administration (50 mg/kg) in male and female Cynomolgus monkeys. Systemic exposure was approximately dose-proportional within the tested dose range. SC bioavailability was determined to be 64.3%. CCI [redacted]

Two single-dose (IV) non-good laboratory practice (GLP) studies conducted in Cynomolgus monkeys evaluated the toxicity, pharmacodynamics (PD), toxicokinetics (TK), and immunogenicity of BOS161721. Following a single IV administration (slow bolus), there were no BOS161721-related adverse changes, resulting in a no-observed-adverse-effect-level (NOAEL) value of 30 mg/kg, the highest dose tested among 2 studies. CCI [redacted]

In a repeat-dose GLP toxicology study in Cynomolgus monkeys, BOS161721 was administered every 2 weeks by IV or SC (50 mg/kg) administration for 3 months (a total of 7 doses). CCI [redacted]

CCI [redacted] The NOAELs were determined to be 100 mg/kg IV and 50 mg/kg SC, the highest doses tested.

1.2.2.3 Clinical Studies

BOS161721-01 was a double-blind, Phase 1, single ascending dose (SAD) study to assess the safety, PK, and PD of BOS161721 in healthy subjects. The primary objective of the study was to characterize the safety and tolerability of IV and SC SADs of BOS161721 in an otherwise healthy subject population without concomitant illnesses, immune abnormalities, or concomitant medications. Secondary objectives included characterization of the PK and immunogenicity of BOS161721, and exploratory objectives included the evaluation of the effect of BOS161721 on TDAR to keyhole limpet hemocyanin (KLH) (primary and secondary immunizations) in healthy subjects, the effects of BOS161721 on plasma levels of IL-21 (free and bound), and the evaluation of the effect of BOS161721 on IL-21 gene expression (via gene signature) in blood. This study consisted of 8 cohorts. Subjects were randomized in a 3:1 ratio (BOS161721: placebo) and received either a single dose of BOS161721 (1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg) or placebo, with safety follow-up. For the first cohort, after the first 2 subjects were dosed (1 active and 1 placebo), there was a minimum gap of 48 hours before the remaining subjects from that cohort were dosed, to allow for an initial review of any emerging safety and tolerability data. For all cohorts, escalation to the next dose was not sooner than 8 days after all the subjects in the prior cohort had been dosed and were based on a review of at least 7 days of safety and tolerability data by the Safety Data Monitoring Team (SDMT).

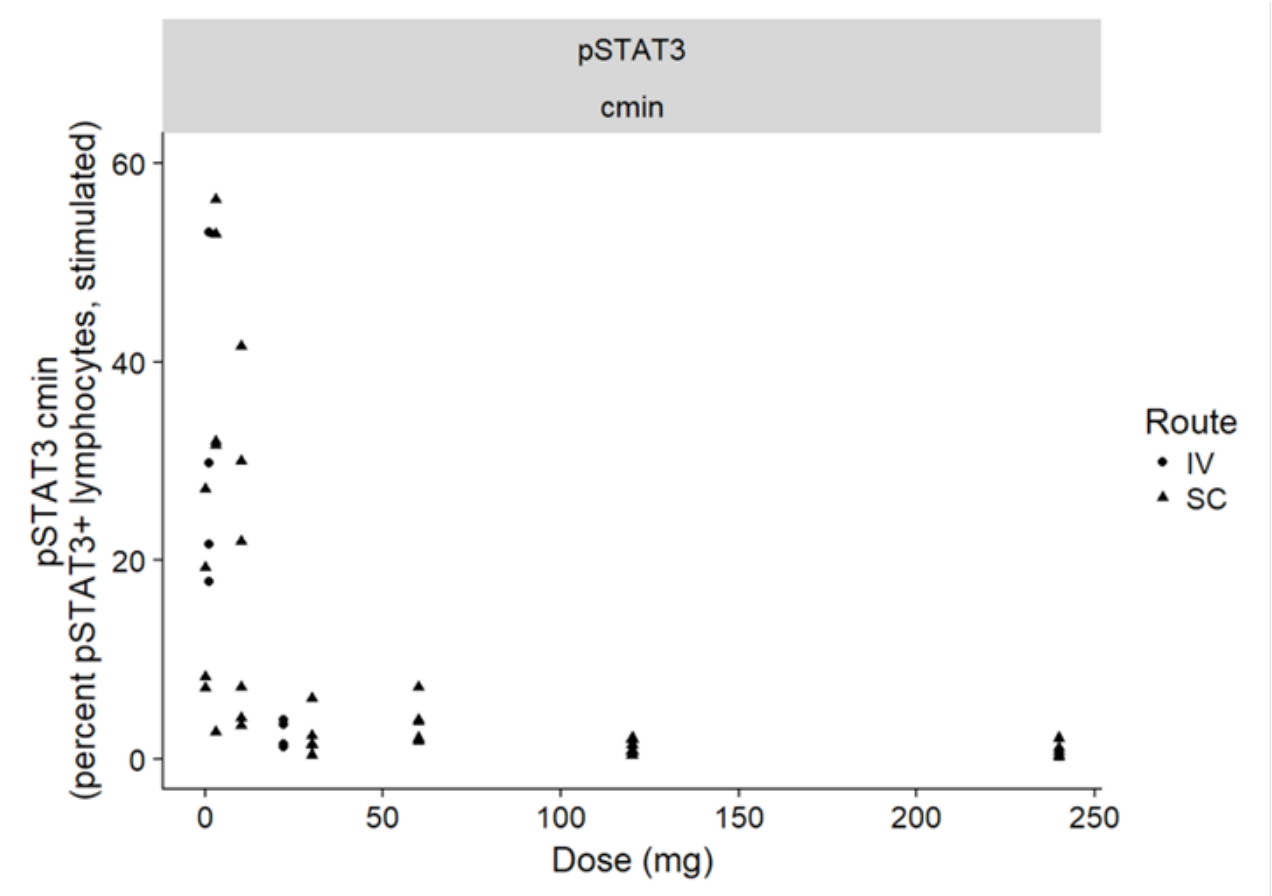
Blood samples were collected at every in-house study visit for BOS161721 concentration determinations. Blood samples were also collected for determination of IL-21 plasma levels (free and total). Safety was assessed based on the occurrence of treatment-emergent AEs, hepatic function abnormality, and acute and delayed hypersensitivity reactions. Other safety variables included electrocardiograms (ECGs), vital signs (blood pressure [BP], heart rate, and temperature), safety laboratory assessments, blood sampling for ADAs, total IgG and immunoglobulin M (IgM) levels, CD4+ count, and full and targeted physical examinations. Overall, there were no clinically significant findings from this study, following an interim cut and review of the data at Day 90 postdose. Adverse events reported as related to the study drug, particularly infections, were expected for the compound, and there were no clinically relevant changes in laboratory and ECG results or vital signs. There was 1 serious adverse event (SAE; death due to pulmonary embolism) that occurred 127 days after a single administration of 240 mg SC dose of BOS161721. The causality of this single SAE was not attributed to study drug and further information can be found in the Investigator's Brochure. PK data from the SAD study demonstrates BOS161721 has an extended $t_{1/2}$ (provisional single dose data indicates this to be approximately 42-46 days) which supports evaluation of monthly dosing.

1.2.3 Study Dose Selection

Doses have been selected for the multiple ascending dose (MAD) Phase 1 study based on a 90-day safety, tolerability, PK, and PD data review from the Phase 1 SAD study (BOS161721-01); the SDMT reviewed the blinded safety data from subjects for each dose cohort (8 cohorts, evaluating 1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg), along with the accumulated safety and available PK/PD data from all subjects in the previous dose cohorts, to make a decision on whether to proceed to the next higher dose level, repeat a dose level, or stop dose escalation. Overall, there were no clinically significant safety or tolerability findings from this study.

Based on the Day-90 interim cut of the PK and biomarker data in the BOS161721-01 study, the recommended doses for evaluation in the MAD phase of this study are 20, 60, and 120 mg SC monthly. This dose recommendation is supported by evidence of linear PK with BOS161721 resulting in a median first time to maximum concentration (T_{max}) of 6 days and an apparent terminal half-life of 44 days. Furthermore, pSTAT3 suppression, a marker of IL-21 target engagement, follows a similar time course of the mAb levels, with maximal and sustained suppression apparent with doses greater than 30 mg SC (Figure 1).

Figure 1. Individual pSTAT3 C_{min} Levels Versus Dose



IV = intravenous, pSTAT3 = phosphorylated signal transducer and activator of transcription 3; SC = subcutaneous

All doses selected for the MAD study are projected not to exceed the mean exposure of that achieved following the highest single dose of 240 mg SC administered in the Phase 1 SAD study. Cohort 1 will include randomized treatment to the 20 mg dose. Based on the staggered study design, the data monitoring committee (DMC) will perform a scheduled review of safety data and sequentially consider dose escalation for Cohorts 2 and 3. In addition, the DMC and Boston Pharmaceuticals will conduct a data review to suggest which dose should be carried forward into the proof of concept (POC) Phase 2 study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2 and 3 from the MAD study (see Section 3.1.1.1).

1.2.4 Risk-Benefit Assessment

The available preclinical data on BOS161721, the findings in clinical study BOS161721-01, and existing clinical information on IL-21 inhibitors suggest that the present clinical study has an acceptable risk-benefit ratio. In this study, the risk-benefit assessment of BOS161721 in adult patients with moderately to severely active SLE will be ongoing, with step-wise evaluations during the staggered MAD study. The DMC used in this study is charged with assessing such actions in light of an acceptable benefit-risk profile for BOS161721 as an anti-IL-21 mAb. Formal DMC monitoring meetings will occur as described in the DMC Charter. Two weeks after Cohort 1 has received a second dose of study drug, the DMC will evaluate the safety and tolerability data from Cohort 1 to determine the recommended dose for Cohort 2. Two weeks after 8 patients in Cohort 2 receive a second dose, the DMC will determine if dose escalation to Cohort 3 can proceed. Two weeks after the last patient in Cohort 3 receives the second dose, the DMC and Boston Pharmaceuticals will conduct a data review to suggest which dose should be carried forward into the POC Phase 2 study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2 and 3 during the MAD study. Thereafter, DMC safety reviews will be conducted periodically throughout the study as described in the DMC charter. With the agreement of the DMC and sponsor, this schedule may be modified depending on the rate of patient accrual. Additional details can be found in the DMC Charter.

The benefit of participation for all patients in this study is close monitoring of their medical condition and safety of their treatment. Those randomized to the active treatment arm may potentially experience improvement in their SLE disease. Those randomized to the placebo (in combination with standard of care) arm are not expected to obtain any additional benefit, beyond those of their background treatment, though close monitoring of their medical condition and safety may itself be associated with improving their SLE.

1.2.5 Potential Risks

Potential risks based on the mechanism of action of BOS161721 include infections, risks associated with the administration of any foreign protein or biologic agent, including injection site reaction, anaphylaxis, serious allergic reaction, and development of ADAs. ADAs could result in immune complex disease (with manifestations such as arthralgias, serum-sickness, and vasculitis), autoimmunity, or altered BOS161721 levels or activity. Further details can be found

in the current Investigator's Brochure (IB) for BOS161721, which contains comprehensive toxicology, preclinical and clinical information on BOS161721.

Two investigational drug products are considered to be in the same pharmacological class as BOS161721 based on interruption of signaling through the IL-21 signaling pathway. No potential risk generalizable across the class has been observed with these investigational products. Based on the clinical Phase 1 SAD study (BOS161721-01), AEs reported as related to the study drug, particularly infections (flu-like symptoms, etc), were expected for the compound, and there were no clinically relevant changes in laboratory and ECG results or vital signs.

The majority of IgG elimination occurs via intracellular catabolism, following fluid-phase or receptor-mediated endocytosis. This type of endocytosis and elimination is a form of target-mediated disposition where the interaction of the drug and its pharmacological target (eg, a target receptor) serves as a significant contributor to the kinetics of antibody distribution and elimination. Renal elimination, which is a primary pathway of clearance of small-molecule drugs, is relatively unimportant for IgG, as its large size prevents efficient filtration through the glomerulus. Secretion into the bile is an important pathway of elimination of IgA antibodies, but this route is not a significant contributor to the elimination of IgG antibodies. Thus, risk to renal and hepatic systems due to metabolism of BOS161721 is low.[33]

1.2.5.1 Anaphylaxis and Serious Allergic Reactions

As with the administration of any foreign protein and/or other biological agents, acute hypersensitivity reactions, including acute anaphylactic/hypersensitivity, severe allergic, and anaphylactoid reactions may follow infusion of mAbs and can be caused by various mechanisms. These acute hypersensitivity reactions may be severe and result in death.

Anaphylaxis will be defined according to the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria,[34] and are discussed in Section 6.2.2.6.1.

Based on the limited Phase 1 SAD study (BOS161721-01), anaphylaxis and serious allergic reactions in subjects who received BOS161721 was not observed.

Patients with a known history of allergy or severe hypersensitivity reaction to any component of BOS161721 formulation or patients with a history of anaphylaxis to any other biological therapy such as mAbs will be excluded from studies with BOS161721. In addition, appropriate drugs and medical equipment to treat acute hypotensive, bronchoconstrictive, or anaphylactic reactions will be immediately available at the unit and study personnel will be trained to recognize and treat these reactions.

1.2.5.2 Injection Site Reactions

In a repeat-dose GLP toxicology study in Cynomolgus monkeys, BOS161721 was administered every 2 weeks by IV or SC (50 mg/kg) for 3 months (a total of 7 doses); no SC animals had injection reactions.

Based on the Phase 1 SAD study (BOS161721-01), incidence of injection site reactions in subjects who received BOS161721 was similar to placebo.

Patients will be monitored for local injection site reactions in this study. See Section 6.2.7.

1.2.5.3 Immune Complex Disease

The potential risk of immune complex disease for BOS161721 is theoretical, based on the known risks associated with mAbs. The administration of a mAb can result in the formation of ADAs. Administration of the mAb in the presence of ADA may result in the formation of circulating antibody-antigen complexes potentially resulting in altered BOS161721 levels or activity or deposition of the complexes in microvasculature. Complement is frequently involved in the latter setting, and the breakdown products of complement attract polymorphonuclear leukocytes to the site of deposition where they can provoke local tissue damage through specific or nonspecific release of enzymes. Two of the more common end-organ targets are the blood vessels (vasculitis) and kidney (nephritis). These clinical manifestations represent immune complex disease or Type III hypersensitivity. Although BOS161721 is a humanized mAb, ADAs may develop; however, the likelihood of occurrence of immune complex disease with BOS161721 is low. The findings of immune complex disease are typically reversible when mAb administration stops and the antibody-antigen complexes are cleared from the body.

Based on the limited Phase 1 SAD study (BOS161721-01), immune complex disease in subjects who received BOS161721 was not observed.

1.2.5.4 Infections

BOS161721 is expected to diminish the activity of T-cell, B-cell and NK-cell lines. Like other medications modulating immune response, BOS161721 may increase the potential risk for infection, including serious infections. IL-21 produced by CD4+ Th cells is required to sustain the anti-viral function of CD8+ T-cells against chronic viral infections. Nonclinical evidence suggests that the risk of chronic viral infection recurrence or increased severity may occur with IL-21 inhibition.[35]

These conditions will be fully characterized with clinical descriptions and routine laboratory and/or specialty testing and treated where indicated with appropriate local standard of care.

Patients with a history of opportunistic infection, including recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years, or any other underlying pathology predisposing to serious infection, are excluded from studies with BOS161721 (for further details please refer to the current IB for BOS161721).

Patients will be assessed for hepatitis B, and C, and HIV-1/2 combination, at screening.

Cryptosporidium Infection

Cryptosporidium infection was noted in patients with an IL-21 receptor loss-of-function gene mutation and similar findings of cryptosporidium infection have been observed in immunosuppressed liver transplant and human immunodeficiency virus patients.[36,37] Since

BOS161721 is expected to diminish the immunosurveillance activity of T-cell, B-cell, and NK-cell lines, a similar risk is biologically plausible with prolonged exposure to BOS161721.

Since the risk of opportunistic cryptosporidium infection increases with low levels of CD4+ T-cells,[37] patients with a CD4+ count < 500 cell/mm^3 were excluded from the Phase 1 SAD study (BOS161721-01), and will be excluded from the proposed MAD/POC studies. Patients exposed to investigational product who develop diarrhea during the course of the study should immediately undergo an assessment for opportunistic infection including stool for ova and parasites and stool examination for cryptosporidium. Positive cryptosporidium in stool sample at screening is an exclusion. Treatment by the investigator where indicated should be guided by findings and be consistent with local standard of care.

Based on the limited Phase 1 SAD study (BOS161721-01), infections in subjects who received BOS161721 was not observed.

1.2.5.5 Malignancy

The stimulatory effect of IL-21 on NK cells and CD8+ T-cells suggests the cytokine may have anti-tumor activity. Nonclinical studies have demonstrated significant anti-tumor effects of IL-21 in a number of tumor models. IL-21 therapy of human metastatic melanoma and renal cell carcinoma has demonstrated POC with significant increases in levels of perforin, granzyme B, and interferon gamma (IFNγ) expression in CD8+ T-cells and NK T-cells. Clinical response has been limited in these generally unmanageable diseases.

The impact of treatment with anti-IL-21 therapy on the development or growth of malignancies is not known; however, as with other immunomodulatory biologic agents, treatment with BOS161721 may result in an increase in the risk of malignancies. NK cell suppression by IL-21 neutralization may represent a biological mechanism for a potential risk for malignancy. Patients with a history or current diagnosis of cancer within the past 5 years, with the exception of non-melanoma skin cancer or cervical cancer in situ treated with apparent success with curative therapy, are excluded from the study.

Based on the limited Phase 1 SAD study (BOS161721-01), malignancy in subjects who received BOS161721 was not observed.

1.2.5.6 Hepatic Function Abnormality

There is no substantial evidence suggesting BOS161721 is associated with liver function abnormality. However, as a precaution, patients with a history of abnormal alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), or bilirubin at screening (ALT/AST > 2 × upper limit of normal [ULN]; total bilirubin > 1.5 × [ULN] and judged by the investigator to be clinically significant) were excluded from the Phase 1 SAD study (BOS161721-01), and will be excluded from the MAD study. Patients with a positive hepatitis B or C test or a history of alcohol dependence will also be excluded.

Based on the limited Phase 1 SAD study (BOS161721-01), hepatic function abnormality in subjects who received BOS161721 was not observed.

1.2.5.7 Failure of Vaccination

IL-21 is a key cytokine in development of B-cells into immunoglobulin-secreting plasma cells. Abnormal signaling through the IL-21R/Janus Kinase (JAK)3/signal transducer and activator of transcription (STAT3) pathway leads to defective humoral immune responses to both T-dependent and T-independent antigens and impairs the establishment of long-lasting B-cell memory. Abnormal signaling through the pathway has been related to decreased specific antibody responses following vaccination, and to increased susceptibility to encapsulated bacterial infections.[38]

The effect of BOS161721 was evaluated in in vivo single dose studies in Cynomolgus monkey in which the animals received vaccination to T-cell dependent KLH antigen to stimulate a TDAR. These in vivo studies demonstrated that BOS161721 significantly inhibited B-cell proliferation and IgG antibody responses to the KLH protein antigen; however, it is worth noting that BOS161721 administration did not produce any remarkable changes in anti-KLH antibody data for IgM, IgG1, IgG3, and IgG4 or anti-tetanus toxoid (TT) antibody data for IgM, IgG, IgG1, or IgE during the dosing phase in the same study.

1.2.5.8 Potential for Drug-Drug Interactions

Drug-drug interactions were not evaluated in the Phase 1 SAD study (BOS161721-01), which included only healthy adult subjects. Use of prescription medications (with the exceptions of oral contraceptives), and over-the-counter (OTC) treatments including herbal supplements such as St John's Wort (except multivitamins), in the 2 weeks prior to screening was prohibited in the SAD study.

See Section 4.5 for other specific exclusion criteria which support lowered risk of interactions, and Section 4.6.1 for corticosteroid (CS) dosing. In addition, Section 1.2.5.6 describes considerations for hepatic function for this study.

1.2.5.9 Potential Risk to Fetal Development

No data on preclinical reproductive toxicity are available at the time of this study.

2 STUDY OBJECTIVES AND ENDPOINTS

This trial has separate objectives and endpoints for the MAD Phase 1b and POC Phase 2 studies. The primary, secondary, and exploratory objectives for each phase, as applicable, are described below with their corresponding endpoints.

2.1 Phase 1b Multiple Ascending Dose

OBJECTIVES	ENDPOINTS
Primary	
• To assess safety, tolerability, and immunogenicity of repeat doses of BOS161721 (20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment, in order to estimate the optimal dose.	Safety Endpoints • Incidence and severity of AEs and SAEs, related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • Columbia Suicide severity Rating Scale (C-SSRS) • 12-lead ECGs parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from baseline • Physical examinations changes from baseline • ADAs • Study drug exposure/compliance • Concomitant medication usage
Secondary	
• To characterize the PK of BOS161721 and select the optimal dose of BOS161721 based on safety, PK, and PD effects in patients with mild to moderate SLE.	Pharmacokinetic Endpoints • BOS161721 concentration by visit and time point • Maximum observed concentration (C_{max}), T_{max}, area under the concentration-time curve (AUC), terminal elimination half-life ($t_{½}$), systematic clearance (C_L), volume of distribution (V_d) Pharmacodynamic Endpoints • Results and changes (or shifts) from baseline to each visit in phosphorylated signal transducer and activator of transcription 3 (pSTAT3), C3 and C4 levels, and leukocyte immunophenotype • Results and changes (or shifts) from baseline in anti-double-stranded DNA (dsDNA), antinuclear antibodies (ANA), anti-Sjögren syndrome A and B (SSA, SSB), Smith (Sm), and antiphospholipid (APL) autoantibodies at each visit • Results and changes (or shifts) from baseline in abrogation of IL-21 gene signature at each indicated visit

Exploratory	
• CCI [redacted]	CCI [redacted] • CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

2.2 Phase 2 Proof of Concept

OBJECTIVES	ENDPOINTS
Primary	
• To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on the SRI-4	Primary Efficacy Endpoint • The proportion of subjects with a SRI-4 response at Day 210 (see Section 6.3.4.1)
Secondary	
To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on clinical indicators of SLE activity, in adult	Secondary Efficacy Endpoints • The proportion of subjects with: - SRI-4 response at each visit

patients with moderately to severely active SLE on limited background standard of care treatment	- SRI-5 and SRI-6 response (Section 6.3.4.2) - a sustained reduction of oral corticosteroid (CS) (≤ 10 mg/day and ≤ Day 0 dose) between Day 120 and Day 210 - new BILAG A flare or > 1 BILAG B flares relative to baseline through Day 210 - PGA worsening - a BICLA response - a CLASI response - medication failures • Results and changes from baseline in: - CLASI - swollen and tender joints ACR-28 - SLEDAI-2K - SLICC/ACR damage index - Time to medication failure • Duration of SRI-4 response • Time to first SRI-4 response • Time to BILAG A flare or > 1 BILAG B flare compared to baseline through Day 210
Safety	
• To assess safety and tolerability of repeat doses of BOS161721 (20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment	Safety Endpoints • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness • Injection site reactions • C-SSRS • 12-lead ECGs parameter results at each visit and change from baseline • Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and change from baseline • Clinical laboratory results and change from baseline • Physical examinations changes from baseline • ADAs • Study drug exposure/compliance • Concomitant medication usage
Exploratory	
• CCI [redacted]	CCI [redacted]

	CCI
• CCI	• CCI
• CCI	• CCI

3 STUDY PLAN

3.1 Study Design

This is a Phase 1b/2 combined, randomized, multicenter, double-blind, placebo-controlled trial to study the clinical efficacy, safety, and PK of SC doses of BOS161721 in adult patients with moderately to severely active SLE. After successfully completing a screening phase, patients will be randomized to a specified dose of BOS161721 or placebo. The dosing schedule will be monthly.

The trial will consist of 2 double-blinded studies: MAD Phase 1b and POC Phase 2. Patients may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180, followed by safety follow-up visits at Days 210, 240, and 270.

SLE disease activity assessment data will be centrally reviewed by medical monitor and sponsor to ensure the scores are clinically meaningful and compliant with specific definition. The scope of responsibility includes, but is not limited to, review and confirmation of "A" and "B" BILAG system organ disease, confirmation of clinical components of the SLEDAI-2K score at screening and during the study, and cross-validation of the instruments used in this study to assess the disease being studied. Further details on the content and methods of data reports by the medical monitor and sponsor will be outlined in the Medical Data Review Plan along with the processes and procedures that will be followed.

3.1.1 Multiple Ascending Dose Phase 1b Study

The MAD study will consist of 3 cohorts:

- Cohort 1 (20 mg SC) will include 6 patients
  - 5 patients will receive BOS161721 (active group) and 1 patient will receive placebo (placebo group)
- Cohorts 2 (60 mg SC) and 3 (120 mg SC) will include 12 patients each
  - 9 patients in the active group and 3 in the placebo group

Doses selected for each of the 3 cohorts is based on a 90-day safety, tolerability, PK and PD data review from the Phase 1 SAD study (BOS161721-01) in healthy subjects. All doses selected for

the MAD study are projected not to exceed the mean exposure of that achieved in the SAD study.

3.1.1.1 Dose Escalation for the MAD Study

The MAD study design is staggered, where after the 6 patients in Cohort 1 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 2 begins dosing (after DMC evaluation of the safety and tolerability data from Cohort 1). Similarly, after 8 of the 12 patients in Cohort 2 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 3 begins dosing after DMC evaluation of the safety and tolerability data from Cohorts 1 and 2. Each cohort will continue at their assigned dose level through their respective 6-month treatment periods (See Study Schematic, Section 3.1). If patients discontinue the study in a cohort prior to adequate safety follow-up, he/she may be replaced.

Criteria for dose escalation are further described in the DMC Charter. See Section 3.1.1.2 for additional details about DLTs.

3.1.1.2 Dose Limiting Toxicity (DLT)

Severity of adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. For the purpose of dose escalation, any of the following AEs occurring after study drug administration, which are attributable to the study drug, will be considered DLTs:

Hematologic:

- Grade 4 neutropenia
- Grade 3 neutropenic infection
- Grade 3 thrombocytopenia with bleeding
- Grade 4 thrombocytopenia

Non-Hematologic:

- Grade 3 or above toxicities, persisting after optimal treatment with standard medical therapy (eg, anti-emetics, anti-diarrheals)
- Drug-induced liver injury ([DILI], Hy's Law), as defined in Section 6.2.2.6.3

Investigators should always manage their patients according to their medical judgment which may include interruption of study drug based on the particular clinical circumstances.

3.1.1.3 DMC Recommendations

During scheduled meetings, the DMC will review relevant study data for safety or benefit-risk concern. During the MAD study, the DMC may provide the following recommendations to the sponsor:

- Expanding a cohort at a specific dosing level, or repeating a lower dose in a subsequent cohort
- Continuing a dose level for a given cohort
- Escalating a dose level for a subsequent cohort
- Termination of current or previous cohort(s)

Further dosing in a given cohort will be halted if 2 or more DLTs are identified intra- and inter-patients dosed. For the POC study, the DMC and Boston Pharmaceuticals will conduct a data review to suggest which dose should be carried forward into the POC Phase 2 study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2, and 3; this dose will not exceed doses tested during the MAD study. The DMC will be reviewing all relevant data from Cohorts 1, 2, and 3 that is available at the time the last patient in Cohort 3 completes the Day 44 visit (2 weeks after dose 2). Details are provided in the DMC Charter.

3.1.2 POC Phase 2 Study

3.1.2.1 BOS161721 Dose

The optimal dose evaluation is chosen based on MAD Phase 1b safety, tolerability, immunogenicity, and PK and PD data. The dose will be communicated by a letter to site investigators participating in the POC Phase 2 study, and to the IRB/IEC.

3.1.2.2 POC Study Design

For the POC study, approximately 156 additional patients will be randomized to active or placebo groups in a 2:1 ratio.

As in the MAD study, each patient in the POC study may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180. Assessments will be completed according to the Schedule of Assessments (Section 3.4). Dose selection will be based on the DMC and sponsor's assessment of safety, tolerability, immunogenicity, and PK and PD data from the MAD study of 30 patients treated with BOS161721/placebo.

DMC safety reviews will be conducted periodically throughout the study as described in the DMC charter.

3.2 Randomization and Blinding

This is a randomized, double-blind study.

Patients meeting all inclusion and exclusion criteria will be centrally randomized to either placebo or BOS161721 using an IWRS according to a randomization list generated by an independent, non-study statistician. Randomization will be performed separately for each study phase and separately for each cohort in the Phase 1b and 2 portions as follows:

Phase/Cohort	Number of Patients	Randomization Ratio BOS161721:Placebo
Phase 1b/Cohort 1	6	5:1
Phase 1b/Cohort 2	12	3:1
Phase 1b/Cohort 3	12	3:1
Phase 2	156*	2:1

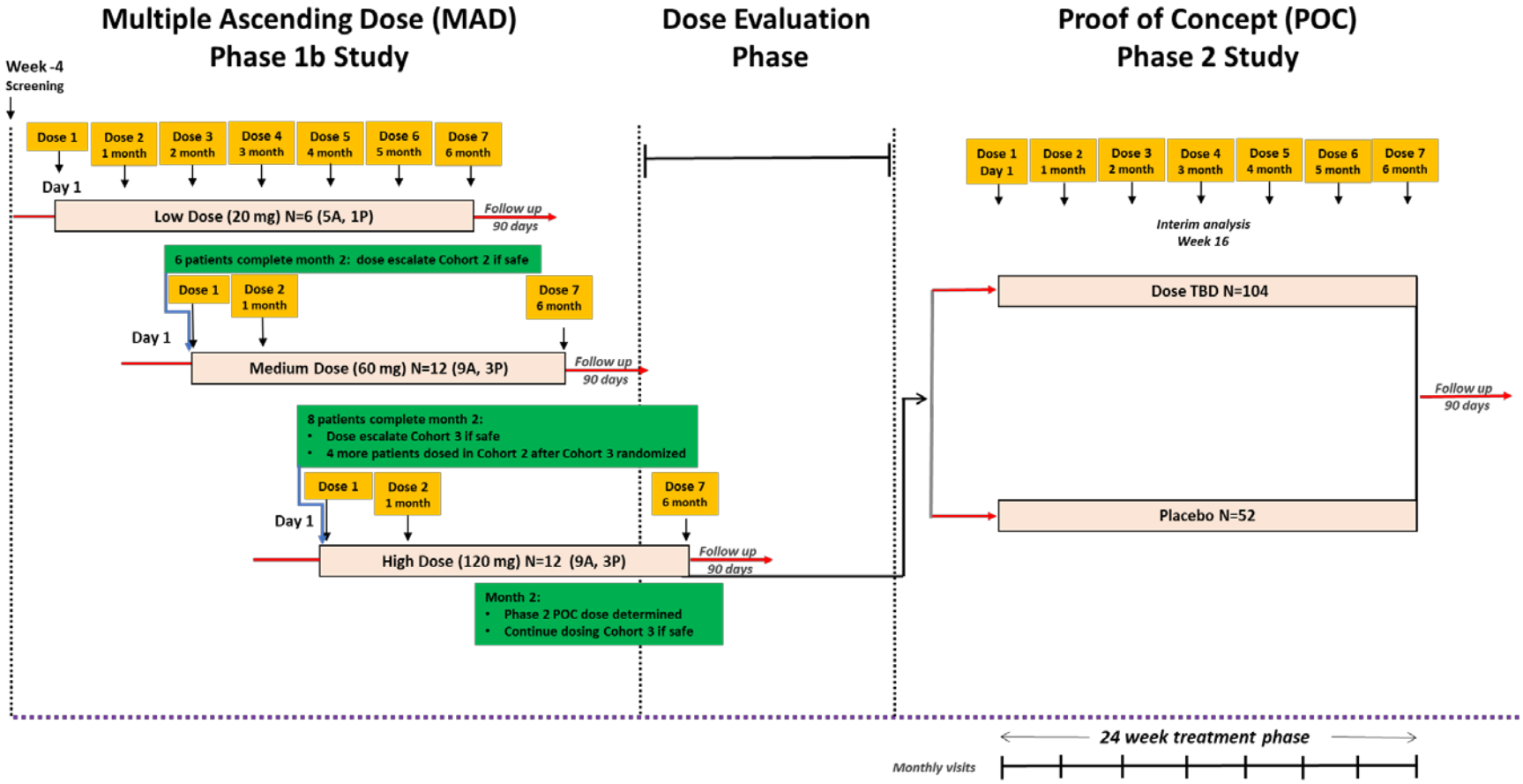
*Additional patients may be enrolled to confirm sufficient numbers of patients are in the full analysis set (FAS).

Eligible patients will be assigned to the study phase which is active at time of enrollment. Similarly, patients in the Phase 1 MAD will be assigned to the cohort which is active. Each patient will be assigned a unique randomization number which will not be reused.

All patients, investigators, and study team participants will be blinded to treatment assignment. An independent biostatistician not otherwise involved on the study will be unblinded and prepare materials for the interim analysis (IA) and the DMC safety reviews. The DMC will review unblinded data during safety reviews and the IA. A limited team at Boston Pharmaceuticals will review unblinded results from the Phase 1b MAD portion during the IA to determine the dose that will be used for the Phase 2 POC portion of the study. Details regarding maintenance of the blinding and content of data reviews will be described in the DMC charter or related study documentation.

3.3 Study Schematic

Figure 2. Study Diagram for MAD Phase 1b and POC Phase 2 Studies



A = active drug (BOS161721); P = placebo

3.4 Schedule of Assessments

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
GENERAL ASSESSMENTS																
Informed consent	X															
Inclusion/Exclusion criteria	X															
Medical history	X															
Demographics	X															
SLICC Criteria for SLE	X															
Concomitant medication[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[c]		X														
BOS161721 or placebo dosing		X			X		X	X	X	X	X					
SAFETY ASSESSMENTS																
Full physical exam	X	X														
Chest x-ray[d]	X															
C-SSRS	X	X						X			X					
AEs and SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	X	X			X			X								X
Injection site reaction assessment		X[f]	X		X		X	X	X	X	X	X	X	X	X	X
Targeted physical examination				X	X	X	X	X	X	X	X			X	X	X
Vital signs (BP, HR, and temperature)[g]	X	X		X	X	X	X	X	X	X	X			X	X	X
EFFICACY ASSESSMENTS																
BILAG-2004 Index	X	X			X		X	X	X	X	X			X	X	X

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
SLEDAI-2K	X	X			X		X	X	X	X	X			X	X	X
PGA of disease activity	X	X			X		X	X	X	X	X			X	X	X
ACR-28 joint count	X	X			X		X	X	X	X	X			X	X	X
CLASI	X	X			X		X	X	X	X	X			X	X	X
CCI		X			X		X	X	X	X	X			X	X	X
SLICC/ACR Damage Index		X									X					
CCI		X			X		X	X	X	X	X			X	X	X
LABORATORY ASSESSMENTS																
CD4+ count	X	X		X	X	X		X			X					
Clinical laboratory assessments (hematology and clinical chemistry)[h]	X	X			X	X	X	X	X	X	X			X	X	X
Coomb's test direct[i]	X	X			X		X	X	X	X	X			X	X	X
Total IgG and IgM	X	X		X	X	X		X			X					
Plasma CCI	X	X			X		X	X	X	X	X			X	X	X
Plasma CCI & CCI		X		X	X		X	X			X					
Whole blood for leukocyte immunophenotype		X		X	X		X	X			X					
ADA[j]		X		X	X		X	X			X					X
nAb[k]								X			X					
pSTAT3[l]		X			X	X	X	X								
CCI		X		X				X			X					X
CCI		X														

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
CCI [redacted]	X	X			X		X	X	X	X	X			X[m]	X[m]	X[m]
CRP	X							X								X
Serum pregnancy test (women)	X															
FSH (postmenopausal women)	X															
Urine pregnancy test (women)[n]		X			X		X	X	X	X	X					
TB test (QuantiFERON-TB Gold In-Tube)[d]	X															
Serology (hepatitis B and C, HIV-1/2 combination)	X															
Stool sample[o]	X															
Spot urine for protein/creatinine ratio	X	X			X		X	X	X	X	X			X	X	X
Urinalysis	X	X			X		X	X	X	X	X			X	X	X
PK Labs																
Predose		X			X		X	X	X	X	X					
Postdose		X[q]	X	X	X[q]						X[q]	X	X	X	X	X

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	-28 to -1	0	7 (± 1)	15 (± 3)	30 (± 3)	44 (± 3)	60 (± 3)	90 (± 3)	120 (± 3)	150 (± 3)	180 (± 3)	187 (± 3)	195 (± 3)	210 (± 3)	240 (± 3)	270 (± 3)
Visit Number	1	2	--	3	4	5	6	7	8	9	10	--	--	11	12	13

Abbreviations: ACR = American College of Rheumatology; ADA= anti-drug antibody; AE = adverse event; CCI [redacted]; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; C = complement; CD4+ = cluster of differentiation 4; CLASI = Cutaneous Lupus Area and Severity Index; CRP = C-reactive protein; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; CCI [redacted]; FSH = follicle stimulating hormone; HR = heart rate; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IL-21 = interleukin 21; IV = intravenous; nAb = neutralizing antibody; PGA = Physician's Global Assessment; PK = pharmacokinetic; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; SAE = serious adverse event; SC = subcutaneous; CCI [redacted]; SLEDAI-2K = SLE Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; CCI [redacted]; TB = tuberculosis; TDAR = T-cell dependent antigen response.

[a] Screening assessments will be performed over more than 1 visit.

[b] Concomitant use of oral corticosteroids: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). See Section 4.6.1 for further details.

[c] Randomization should occur after patient eligibility has been confirmed by central eligibility review.

[d] If patients have had a TB test and chest x ray within 3 months prior to screening, then these assessments do not need to be repeated during screening. The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

[e] ECGs will be performed after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws.

[f] Injection site reaction assessments to be performed at 2 hours postdose.

[g] Vital signs will be assessed after the patient has been supine and at rest ≥ 5 minutes. Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours postdose, as well as on each of the scheduled outpatient days in the table above (excluding PK-only site visits at Days 7, 187, and 195). When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

[h] Clinical laboratory assessments will include a fasting glucose and lipid panel, with exception of screening (Visit 1) which will be nonfasting.

[i] When clinically indicated for hemolytic anemia.

[j] Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only assayed if the patient had a positive ADA on Day 90.

[k] nAb is assessed if patient is positive for ADA.

[l] Predose (trough) samples only.

[m] Only dsDNA collected during safety follow-up visits.

[n] Urine pregnancy test will be collected on WOCBP prior to study drug administration on dosing visits.

[o] Cryptosporidium test is required at screening. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

[p] Postdose samples will be collected at 4, 8, and 24 hours after study drug administration on Days 0, 30, and 180.

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC) Study

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
GENERAL ASSESSMENTS														
Informed consent	X													
Inclusion/Exclusion criteria	X													
Medical history	X													
Demographics	X													
SLICC Criteria for SLE	X													
Concomitant medication[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[c]		X												
BOS161721 or placebo dosing		X		X	X	X	X	X	X					
SAFETY ASSESSMENTS														
Full physical exam	X	X												
Chest x-ray[d]	X													
C-SSRS	X	X				X			X					
AEs and SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	X	X		X		X								X
Injection site reaction assessment		X[f]		X	X	X	X	X	X	X	X	X	X	X
Targeted physical examination			X	X	X	X	X	X	X			X	X	X
Vital signs (BP, HR, and temperature)[g]	X	X	X	X	X	X	X	X	X			X	X	X
EFFICACY ASSESSMENTS														
BILAG-2004 Index	X	X		X	X	X	X	X	X			X	X	X
SLEDAI-2K	X	X		X	X	X	X	X	X			X	X	X
PGA	X	X		X	X	X	X	X	X			X	X	X
ACR-28 joint count	X	X		X	X	X	X	X	X			X	X	X
CLASI	X	X		X	X	X	X	X	X			X	X	X
CCI		X		X	X	X	X	X	X			X	X	X

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC) Study

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
SLICC/ACR Damage Index		X							X					
CCI		X		X	X	X	X	X	X			X	X	X
LABORATORY ASSESSMENTS														
CD4+ count	X	X	X	X		X			X					
Clinical laboratory assessments (hematology and clinical chemistry)[h]	X	X		X	X	X	X	X	X			X	X	X
Coomb's test direct[i]	X	X		X	X	X	X	X	X			X	X	X
Total IgG and IgM	X	X	X	X		X			X					
Plasma CCI	X	X		X	X	X	X	X	X			X	X	X
Plasma CCI & CCI		X	X	X		X			X					
Whole blood for leukocyte immunophenotype		X	X	X		X			X					
ADA[j]		X	X	X	X	X			X					X
nAb[k]						X			X					
CCI		X	X			X			X					X
CCI		X												
CCI	X	X		X	X	X	X	X	X			X[l]	X[l]	X[l]
CRP	X					X								X
Serum pregnancy test (women)	X													
FSH (postmenopausal women)	X													
Urine pregnancy test (women)[m]		X		X	X	X	X	X	X					
TB test (QuantiFERON-TB Gold In-Tube)[d]	X													
Serology (hepatitis B and C, HIV-1/2 combination)	X													
Stool sample[n]	X													

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC) Study

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
Spot urine for protein/creatinine ratio	X	X		X	X	X	X	X	X			X	X	X
Urinalysis	X	X		X	X	X	X	X	X			X	X	X
PK Labs[o]														
Predose		X		X	X	X	X	X	X					
Postdose			X							X	X	X	X	X

Abbreviations: ACR = American College of Rheumatology; ADA= anti-drug antibody; AE = adverse event; CCI [redacted]; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; C = complement; CD4+ = cluster of differentiation 4; CLASI = Cutaneous Lupus Area and Severity Index; CRP = C-reactive protein; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; CCI [redacted]; FSH = follicle stimulating hormone; HR = heart rate; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IL-21 = interleukin 21; IV = intravenous; nAb = neutralizing antibody; PGA = Physician's Global Assessment; PK = pharmacokinetic; SAE = serious adverse event; SC = subcutaneous; CCI [redacted]; SLEDAI-2K = SLE Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; CCI [redacted]; TB = tuberculosis; TDAR = T-cell dependent antigen response.

[a] Screening assessments will be performed over more than 1 visit.

[b] Concomitant use of oral corticosteroids: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). See Section 4.6.1 for further details.

[c] Randomization should occur after patient eligibility has been confirmed. The actual randomization procedure can be completed on Day -1 after eligibility confirmation or the morning of Day 0 prior to dosing for logistical purposes.

[d] If patients have had a TB test and chest x ray within 3 months prior to screening, then these assessments do not need to be repeated during screening. The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

[e] ECGs will be performed after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws.

[f] Injection site reaction assessments to be performed at 2 hours postdose.

[g] Vital signs will be assessed after the patient has been supine and at rest ≥ 5 minutes. Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours postdose, as well as on each of the scheduled outpatient days in the table above (excluding PK-only site visits at Days 187 and 195). When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

[h] Clinical laboratory assessments will include a fasting glucose and lipid panel, with exception of screening (Visit 1) which will be nonfasting.

[i] When clinically indicated for hemolytic anemia.

[j] Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only assayed if the patient had a positive ADA on Day 90.

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC) Study

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**

[k] nAb is assessed if patient is positive for ADA.

[l] Only CCI collected during safety follow-up visits.

[m] Urine pregnancy test will be collected on WOCBP prior to study drug administration on dosing visits.

[n] Cryptosporidium test is required at screening. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

[o] PK samples will only be collected at the investigational sites that will be participating in the PK portion of the study.

4 POPULATION

4.1 Participant Recruitment

Advertisements approved by the IRB, and investigator databases, may be used as recruitment procedures for adult men and women with moderately to severely active SLE.

4.2 Number of Patients

Approximately 186 male and female patients are planned for enrollment, but may be adjusted upward according to the dropout (noncompliance) rate, which will be monitored in a blinded fashion in an ongoing basis. Approximately 30 patients will be randomized for the MAD Phase 1b study, and approximately 156 additional patients will be randomized in the POC Phase 2 study. Note that approximately 24 dropouts are assumed.

4.3 Patient Screening

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular individual. Patient eligibility will be reviewed and confirmed by the medical monitor or designee prior to randomization. Screening assessments (see the Schedule of Assessments [Section 3.4]) for this study must be performed between Day -28 and Day -1.

4.4 Inclusion Criteria

Patients who meet the following criteria will be considered eligible to participate in this clinical study:

1. Men and women, ages 18 to 70 years, inclusive
2. Patients must be mentally capable of giving consent and there must be evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study
3. Patients must have SLE as defined by meeting 4 of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE (with at least 1 clinical and 1 immunologic criterion or Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies), either sequentially or simultaneously
4. At screening, patients must have at least 1 of the following:
    a. Elevated ANA $\geq$ 1:80 via immunofluorescent assay at the central laboratory
    b. Positive anti-dsDNA or anti-Smith (Sm) above the normal level as determined by the central laboratory
    c. C3 or C4 below normal as determined by central lab

5. At screening, the SLE Disease Activity Index 2000 (SLEDAI-2K) must be ≥ 6, including points from at least 1 of the following clinical components:
   a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis
      i. Excluding parameters which require central laboratory results: hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia
      ii. Points from lupus headache and organic brain syndrome will also be excluded
6. On Day 0, the SLEDAI-2K must be ≥ 6, including points from at least 1 of the following clinical components:
   a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis
      i. Excluding parameters which require central laboratory results: hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia
      ii. Points from lupus headache and organic brain syndrome will also be excluded
7. Patients must have at least 1A or 2Bs from the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer:
   a. BILAG A or B score in the mucocutaneous body system
   b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis defined as follows:
      i. "BILAG A:" Severe Arthritis, (BILAG item number 41), manifested by observed active synovitis in ≥ 2 joints with marked loss of functional range of movements and significant impairment of basic activities of daily living that has been present on several days cumulatively over the past 30 days, including at the time of the screening visit. See APPENDIX 5 for additional detailed specifications.
         - Basic ADLs are defined as the following activities which require assistance or assistive devices, (at least 1 must be present and documented in source):
            - Ambulation, toileting, grooming- including bathing and dressing; feeding oneself
      ii. "BILAG B:" Moderate Arthritis, Tendonitis or Tenosynovitis, (BILAG item number 42), defined as tendonitis/tenosynovitis, or active synovitis in ≥ 1 joint, (observed or throughout history), with some loss of functional range of movements which lead to some loss of functional range of motion as manifested by effects on instrumental ADLs such as:

- Cooking, driving, using the telephone or computer, shopping, cleaning, etc, and has been present on several days over the last 30 days, and is present at the time of the screening visit

If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in the other body systems for a total of 2 "B" BILAG body system scores

8. Patients must be currently receiving at least 1 of the following:
   a. Administration for a minimum of 12 weeks, and a stable dose for at least 56 days (8 weeks prior to signing consent) of the following permitted steroid-sparing agents:
      i. Azathioprine (AZA), mycophenolate mofetil or mycophenolic acid, chloroquine, hydroxychloroquine, or methotrexate (MTX)
   b. Prednisone (or prednisone-equivalent) cannot exceed 30 mg/day at screening for a patient to be eligible and must be stable at a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization) (see APPENDIX 3)
9. Women of childbearing potential (WOCBP; see Section 4.7 for full information regarding WOCBP, definition of menopause, and contraception):
   a. Must have a negative serum pregnancy test at screening. Urine pregnancy test must be negative prior to first dose
   b. Must not be breastfeeding
   c. Must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS161721 plus 30 days (duration of ovulatory cycle) for a total of 36 weeks after treatment completion
10. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of BOS161721 plus 90 days (duration of sperm turnover) for a total of 44 weeks after treatment completion
11. Patients must demonstrate willingness and ability to comply with the scheduled study visits, treatment plans, laboratory tests, and other procedures

4.5 Exclusion Criteria

Patients presenting with any of the following will not be included in this study:

1. Drug-induced SLE, rather than "idiopathic" SLE
2. Other systemic autoimmune disease (eg, erosive arthritis, rheumatoid arthritis [RA], multiple sclerosis [MS], systemic scleroderma, or vasculitis not related to SLE)
   a. RA-Lupus overlap (Rupus), and secondary Sjögren syndrome are allowed
3. Any major surgery within 6 weeks of study drug administration, (Day 0), or any elective surgery planned during the course of the study

4. Any history or risk for tuberculosis (TB), specifically those with:
    a. Current clinical, radiographic, or laboratory evidence of active TB
    b. History of active TB
    c. Latent TB defined as positive QuantiFERON-TB Gold In-Tube (QFT-G) or other diagnostic test in the absence of clinical manifestations. Latent TB is not excluded if the patient has documented completion of adequate course of prophylactic treatment with regimen recommended by local health authority guideline, or the patient has started treatment with isoniazid, or other regimen recommended by local health authority guidelines for at least 1 month before Day 0 and continues to receive the prophylactic treatment during study until the treatment course is completed.
5. Active or unstable lupus neuropsychiatric manifestations, including but not limited to any condition defined by BILAG A criteria, with the exception of mononeuritis multiplex and polyneuropathy, which are allowed
6. Severe proliferative lupus nephritis, (WHO Class III, IV), which requires or may require induction treatment with cytotoxic agents or high dose CS
7. Concomitant illness that, in the opinion of the investigator, is likely to require additional systemic glucocorticosteroid therapy during the study, (eg, asthma), is exclusionary
    a. However, treatment for asthma with inhalational CS therapy is allowed
8. Use or planned use of concomitant medication outside of standard of baseline treatment for SLE from Day -1 or for any time during the study. (See Section 4.6 for prohibited concomitant medication)
9. Active and clinically significant infection (bacterial, fungal, viral, or other) within 60 days prior to first dose of study drug. Clinically significant is defined as requiring systemic antibiotics or hospitalization
10. A history of opportunistic infection, or a history of recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years
11. Chronic viral hepatitis including hepatitis B (HBV) and hepatitis C (HCV), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness
12. Cryptosporidium in the stool sample at screening
13. White blood cells (WBC) < 1,200/mm^3 (1.2×10^9/L) at screening
14. Absolute neutrophil count (ANC) < 500/mm^3 at screening
15. CD4+ count < 500/µL at screening
16. Platelets < 50,000/mm^3 (50×10^9/L) or < 35,000/ mm^3 (35×10^9/L) if related to SLE, at screening
17. Hemoglobin < 8 g/dL or < 7 g/dL at screening if due to anemia related to SLE
18. Proteinuria > 3.0 g/day (3000 mg/day) at screening or equivalent level of proteinuria as assessed by protein/creatinine ratio (3 mg/mg or 339 mg/mmol)

19. Serum creatinine > 2.0 mg/dL at screening or creatinine clearance (CrCL) < 40 ml/minute based on Cockcroft-Gault calculation[39]:

    GFR = ([1 for male] or [0.85 for female]) × (140 – Age) × BW / (72 × Creatinine)

20. Serum ALT and/or serum AST > 2 × ULN at screening, unless explicitly related to lupus based on the investigator's judgment

21. Creatinine kinase (CK) > 3.0 × ULN at screening, unless it is related to lupus myositis

22. Direct bilirubin > 1.5 × ULN at screening (unless related to Gilbert's syndrome)

23. Any other laboratory test results that, in the opinion of the Investigator, might place a patient at unacceptable risk for participating in this study

24. History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody (eg, IgG protein) or molecules made of components of monoclonal antibodies

25. History substance and/or alcohol abuse or dependence within the past 1 year, at the investigator's judgment

26. History of cancer within the last 5 years (except for cutaneous basal cell or squamous cell cancer, or cervical cancer in situ resolved by excision)

27. Any other severe acute or chronic medical or psychiatric condition, including recent (within the past year) medical conditions (eg, cardiovascular conditions, respiratory illnesses) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study

28. Investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or patients who are employees of the sponsor or directly involved in the conduct of the trial

29. Currently participating in, or who have participated in other interventional (drug or device) clinical study within 30 days or 5 half-lives of baseline, whichever is longer

30. Recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4 or 5 on the C-SSRS

31. Current or pending incarceration

32. Current or pending compulsory detainment for treatment of either a psychiatric or physical (eg, infectious disease) illness

4.6 Concomitant Medications

Any medicinal product, prescribed or OTC, including herbal and other nontraditional remedies, is considered a concomitant medication. Patients should stay on stable regimen of other concomitant medications for the treatment of SLE (eg, analgesics, NSAIDs, statins, ACE inhibitors/ARBs and other antihypertensive drugs), unless changes in these treatments are

clinically indicated. Use of any other drugs for non-SLE conditions, including over-the-counter medications and herbal preparations, should remain stable unless change or addition is clinically necessary. Discussion with the medical monitor prior to initiation of new medication is strongly recommended. Any concomitant therapies must be recorded on the eCRF. Prior and concomitant medication use will be recorded for the 30 days prior to screening until the last follow-up visit. In addition, historical treatment for SLE (including immunosuppressant, anti-malarial, corticosteroid, and/or biologic agent) will be recorded for the 48 weeks prior to screening in the eCRF.

4.6.1 Oral Corticosteroid Dose

Prior to randomization, oral CSs (prednisone or prednisone equivalent), may be used in accordance with the investigator's clinical judgment and best standard of care. See APPENDIX 3 for examples of equivalents.

A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day).

After Day 0 (after initiation of study therapy), no up-titration above 10 mg/day is allowed except for up to 1 CS burst for increased disease activity.

Tapering of steroids during the course of the study will be encouraged and should be evaluated at all visits.

- Once a patient has received the first dose of study drug, prednisone (or prednisone equivalent) may be tapered down at the discretion of the investigator
    - Tapering is allowed after randomization except within 60 days of the primary (Day 210) and secondary (Day 120) endpoint assessments. Between Day 60 and Day 120, and between Day 150 and Day 210, oral CS doses must be held constant.

A maximum of 1 oral CS "burst" for increased SLE disease activity will be allowed during the study between Day 0 and Day 60, according to the following:

- An oral CS "burst" between Day 0 and Day 60; (an increase of ≤ 40 mg/day of prednisone or equivalent), which must be tapered down to a maximum of 10 mg/day within 2 weeks of initiation of the "burst"
    - Alternatively, a single intramuscular (IM) dose of methylprednisolone (40 mg or equivalent) is permitted
    - The course of the oral CS "burst" is not permitted to extend beyond Day 60

Treatment with inhalational CS therapy (eg, for asthma), or by any other route, is allowed. Other concomitant medications for SLE need to be taken at stable doses as per the inclusion criteria (Section 4.4).

4.6.2 Other Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study drug administration and during the study are described below, and washout requirements are provided in APPENDIX 4. Medications taken within 30 days prior to screening must be recorded on the eCRF.

1. Prior exposure to BOS161721
2. Patients who have received treatment with anti-CD20 monoclonal antibodies within 6 months of screening; recovery of B cells (CD19+) must be documented (record absolute number of CD19+ B cells)
3. Patients who have received treatment with cyclophosphamide within the 1 year prior to screening
4. Patients who have received treatment with cyclosporine (with exception of ophthalmic use), any other calcineurin inhibitor or other immunosuppressive medication not specified in the inclusion criteria (oral or topical) within 3 months of screening
5. Patients who are currently receiving or are scheduled to receive plasmapheresis or lymphapheresis therapy, or have received such therapy within 8 weeks prior to screening
6. Patients who have received any live vaccines within 30 days of screening. Note: Furthermore, live vaccines should not be used during the course of the study and within the 2 months following last dose. Other inactivated vaccines such as tetanus, etc, may be used according to local guidelines during treatment period
7. Patients who are scheduled or anticipated to have elective surgery during the course of the study
8. Initiation of new immunosuppressant or anti-malarial agent is not permitted. Note: Dose reduction or replacement may be allowed due to intolerability or shortage for patients on a stable dose prior to study initiation

4.7 Women of Childbearing Potential

WOCBP is defined as any woman who has experienced menarche and who has not undergone surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) and is not postmenopausal.

See Section 4.7.2 for detailed information regarding contraceptive requirements for WOCBP.

4.7.1 Determination of Menopause

Menopause is defined as at least 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. Women under the age of 55 years must have a documented serum FSH level > 40 mIU/mL at screening to confirm menopause.

4.7.2 Contraception

WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS161721 plus 30 days (duration of ovulatory cycle) for a total of 36 weeks after treatment completion.

Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS161721 plus 90 days (duration of sperm turnover) for a total of 44 weeks after treatment completion.

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

At a minimum, patients must agree to the use of 1 method of highly effective contraception from the following:

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by patients who are WOCBP or a male patient's WOCBP partner. Women who are partner of men who are patients participating in the study may use hormone-based contraceptives as 1 of the acceptable methods of contraception since they will not be receiving study drug.
- IUDs, such as ParaGard®
- Vasectomy
- Complete abstinence, defined as complete avoidance of heterosexual intercourse, is an acceptable form of contraception. Women who are abstinent while participating in the study must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the patient chooses to forego complete abstinence.

Azoospermic men and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing.

4.8 Deviation from Inclusion/Exclusion Criteria

Deviation from the inclusion or exclusion criteria will not be allowed. If deviation of inclusion/exclusion criteria is discovered after randomization, the investigator should contact the medical monitor for discussion. A decision will be made whether to allow a patient continue or withdrawal from the study medication.

See Section 6.8 for additional details.

4.8.1 Patient Withdrawal and Replacement

See Section 5.5 for reasons for removal from the trial. Withdrawn patients may be replaced during the MAD study after discussion between the principal investigator or designee and sponsor.

5 STUDY PROCEDURES

Refer to the eCRF completion guidelines for data collection requirements and documentation of study assessments/procedures.

5.1 Screening

Screening will be the same for both the MAD and POC studies.

Screening will take place from Day -28 to Day -1, and assessments may be performed over more than 1 visit. Confirmation that the most current IRB/IEC approved informed consent form (ICF) has been signed must occur before any study-specific screening procedures are performed. Procedures that are part of standard of care are not considered study-specific procedures and may be performed prior to informed consent and used to determine eligibility.

All screened patients will be assigned a unique screening number. The screening number will include a 3-digit site number and a 4-digit sequential number to identify patients from the time of screening. Only eligible patients who are confirmed by central review as meeting the inclusion/exclusion criteria, listed in Section 4.4 and Section 4.5 respectively, will be enrolled in the study. Screened patients who drop out of the clinical study before randomization will be recorded as screen failures. If rescreening occurs, the site will assign a new screening number.

Specific procedures at the screening visit will include:

- Medical history documentation
- Review of inclusion and exclusion criteria
  - Patient medical records must contain documentation of SLE diagnosis
  - C-SSRS
- Concomitant medication documentation
- Demographics
- Full physical examination
- Vital signs
- Chest x-ray
- Laboratory evaluations (nonfasting):
  - Hematology and clinical chemistry
  - Serology (Hepatitis B and C; HIV-1/2 combination)
  - TB test
  - CRP

  - Direct Coomb's test (if indicated for hemolytic anemia)
  - CD4+ count, total IgG and IgM levels, plasma CCI , CCI [redacted]
  - Serum pregnancy test (WOCBP)
  - FSH (postmenopausal women)
  - Spot urine for protein/creatinine ratio
  - Urinalysis
  - Stool sample
- 12-lead ECG
- SLE-related indices (BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, Physician's Global Assessment (PGA) of disease activity

Screening procedures are listed in the Schedule of Assessments (Section 3.4), and details are provided in Section 6.

5.1.1 Retesting During Screening Period

A single retesting of laboratory parameters and/or other assessments during the screening period is permitted (in addition to any parameters that require a confirmatory value) only if:

- medically indicated
- there is evidence a laboratory sample was mislabeled, indeterminate, inadequately processed, and/or deteriorated in transit to the central laboratory

Any new result will override the previous result (ie, the most current result prior to randomization) and is the value by which study inclusion/exclusion will be assessed, as it represents the patient's most current clinical state. This will also apply to patients who are being rescreened.

5.2 Enrollment/Randomization and Day 0 Treatment

Randomization should occur after patient eligibility for enrollment has been confirmed by the central eligibility review.

The study site will obtain a randomization number when registering the patient in IWRS. All patients will receive BOS161721 or placebo according to the kit number assigned by the IWRS randomization scheme.

After randomization, procedures include:

- PROs: CCI [redacted]
- C-SSRS
- Laboratory evaluations (fasting):
  - Hematology and clinical chemistry
  - Direct Coomb's test (if indicated for hemolytic anemia)

  - CD4+ count, total IgG and IgM levels, plasma CCI, plasma CCI and CCI, whole blood for leukocyte immunophenotype
  - ADA
  - pSTAT3 (predose [trough] samples only in Phase 1b)
  - CCI
  - CCI
  - CCI
  - See Table 1 and Table 2 for details of PK sampling in the MAD and POC studies
  - Urine pregnancy test will be collected on WOCBP prior to study drug administration
  - Spot urine for protein/creatinine ratio
  - Urinalysis
- Concomitant medication documentation
- Documentation of AEs and SAEs (see Section 6.2.2.5 on SAE reporting requirements)
- Full physical examination
- Vital signs (prior to PK blood draw, predose, and at 1 and 2 hours postdose on Day 0)
- 12-lead ECG (prior to PK blood draw)
- SLE-related indices (BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, PGA)
- SLICC/ACR damage index
- Study drug administration:
  - Administration of BOS161721 or placebo will take place on-site, and is discussed in Section 7.3

- Injection site reaction assessment performed at 2 hours postdose

Procedures on Day 0 are listed in the Schedule of Assessments (Section 3.4), and details are provided in Section 6.

All patients who are enrolled, randomized, and receive study drug, or undergo study-specific procedures should reconsent with any updated versions of IRB/IEC approved informed consents during study participation as applicable and per institutional guidelines.

5.3 Treatment Period/Follow-Up Visits

The following procedures will be performed as indicated in the Schedule of Assessments (Table 1 and Table 2). See Schedule of Assessment tables for allowable windows for each visit.

- Targeted physical examination
- Vital signs (prior to PK blood draw)
- Concomitant medication documentation
- Documentation of AEs and SAEs (see Section 6.2.2.5 on SAE reporting requirements)
- PROs: CCI
- Urine pregnancy tests will be collected on WOCBP prior to study drug administration
- Injection site reaction assessments will be performed predose

- Direct Coomb's test (if indicated for hemolytic anemia)
- Spot urine for protein to creatinine ratio
- Urinalysis
- CCI
- Plasma CCI
- PGA, BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, and the CLASI will be completed
- SLICC/ACR Damage Index will be completed at Day 180
- C-SSRS
- ECGs prior to PK blood draw
- See Table 1 and Table 2 for details of PK sampling in the MAD and POC studies, respectively
- Fasting hematology and chemistry assessments
- The CD4+ count and total IgG and IgM levels
- Plasma CCI & CCI, ADA, and whole blood for leukocyte immunophenotype
- pSTAT3 (predose [trough] samples only Phase 1b)
- CRP and nAb will be assessed if patient is positive for ADA
- CCI

5.4 Safety Follow-Up Visits

Safety follow-up visits will take place at Days 210, 240, and 270. These visits will include the following assessments as indicated in the Schedule of Assessments (Table 1 and Table 2):

- PROs: CCI
- Documentation of AEs and SAEs (see Section 6.2.2.5 on SAE reporting requirements)
- Injection site reactions
- Targeted physical examination
- Vital signs (prior to PK blood draw)
- Spot urine for protein/creatinine ratio and urinalysis
- Concomitant medication documentation
- BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, and PGA
- Fasting clinical laboratory assessments (hematology and clinical chemistry)
- Direct Coomb's test (if indicated for hemolytic anemia)
- Plasma CCI
- CCI
- 12-lead ECG (prior to PK blood draw)
- CRP
- ADA
- CCI

- See Table 1 and Table 2 for details of PK sampling in the MAD and POC studies, respectively

5.5 Premature Discontinuation

While patients are encouraged to complete all study evaluations, they may withdraw from the study at any time and for any reason. Every effort will be made to determine why any patient withdraws from the study prematurely. If the patient is unreachable by telephone, a registered letter, at the minimum, should be sent to the patient requesting him/her to contact the clinic.

All patients who withdraw from the study with an ongoing AE or SAE must be followed until the end of study or until the event is resolved or deemed stable, respectively.

If a patient withdraws prematurely after dosing, an end of treatment (EOT) visit should be performed (Day 180) and a last follow-up visit 90 days after dosing should be scheduled (Day 270). Safety follow-up visit procedures based on the Schedule of Assessments (see Section 5.4).

Patient participation may be terminated prior to completing the study and the reason recorded as follows:

- AE/SAE
- Protocol deviation
- Lost to follow-up
- Patient withdraws consent at their own request
- Investigator decision
- Decision by sponsor (other than AE/SAE, protocol deviation, or lost to follow-up)

Withdrawn patients may be replaced after discussion between the investigator or designee and sponsor.

6 ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, which may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and wellbeing of the patient. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. All protocol violations are entered directly into the eCRFs.

6.1 Medical History, Demographic and Other Baseline Information

The medical history comprises:

- General medical history

- Documentation of SLE diagnosis
- Historical medication therapy for SLE

The following demographic information will be recorded:

- Age
- Ethnic origin (Hispanic/Latino or not Hispanic/not Latino)
- Race (White, American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black/African American)
- Height (without shoes, in cm)
- Body weight, without shoes (kg)
- Body mass index (BMI [kg/m^2])

Other baseline characteristics will be recorded as follows:

- Concomitant medication documentation (see Section 4.6)
- Status of child bearing potential and contraception

6.2 Safety Assessments

6.2.1 Laboratory Assessments

Laboratory tests will be performed at times defined in the Schedule of Assessments (Section 3.4). Patient eligibility will be determined based on these tests at screening. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

A central laboratory will be used (with the exception of urine pregnancy tests and stool analysis) to ensure accuracy and consistency in test results. The central laboratory will transmit all results for protocol tests, scheduled and unscheduled, to the clinical data base. Laboratory/analyte results that could unblind the study (ie, biomarker results) will not be reported to investigative sites. Urinalysis will be performed on midstream, clean catch specimens. Some biomarkers listed above will not be drawn at some sites due to geographical logistical challenges. See the laboratory manual for details.

Endpoint analyses will be based on changes from baseline assessments at Days 120 and 210.

Table 3. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other Safety Tests
Hemoglobin	BUN	pH	Spot urine for protein/creatinine ratio
Hematocrit	Creatinine	Glucose (qual)	FSH[b]
RBC count	Glucose (fasting)	Protein (qual)	Urine pregnancy test[c]
RDW	Calcium	Blood (qual)	QuantiFERON®-TB Gold In-Tube test (QFT-G)
MCV	Sodium	Ketones	Serology[d] (Hepatitis B and C; HIV-1/2 combination)
MCH	Potassium	Nitrites	Stool sample[e]
MCHC	Chloride	Leukocyte esterase	
Platelet count	Total CO_2 (bicarbonate)	Urobilinogen	
WBC count	AST, ALT	Urine bilirubin	
CD4+ count	Total bilirubin	Microscopy[a]	
Total neutrophils (Abs)	Alkaline phosphatase		
Eosinophils (Abs)	Creatine kinase		
Monocytes (Abs)	Uric acid		
Basophils (Abs)	Albumin		
Lymphocytes (Abs)	Total cholesterol (fasting)		
	LDL-C (fasting)		
	HDL-C (fasting)		
	Triglycerides (fasting)		
	Total protein		
	PT/INR		

	Additional Tests[f] (potential Hy's Law)	Immunogenicity, PD and other Biomarker Tests
	AST, ALT (repeat)	ADA
	Total bilirubin (repeat)	nAb[g]
	Albumin (repeat)	pSTAT3 (predose [trough] samples only in Phase 1b)
	Alkaline phosphatase (repeat)	Total IgG & IgM
	Direct bilirubin	Plasma CCI
	Indirect bilirubin	Plasma CCI & CCI
	GGT	Whole blood for leukocyte immunophenotype
		CCI
		CCI
		CCI
		CRP
		Direct Coomb's test[h]

Abbreviations: Abs = absolute; ADA = anti-drug antibody; ALT = alanine aminotransferase; CCI; CCI; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C = complement; CD4+ = cluster of differentiation 4; CRP = C-reactive protein; dsDNA = double-stranded deoxyribonucleic acid;; FSH = follicle stimulating hormone; GGT = gamma-glutamyltransferase; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ration; IL-21 = interleukin 21; LDL-C = low-density lipoprotein cholesterol; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = Mean corpuscular volume; nAb = neutralizing antibody; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; PT = prothrombin time; qual = qualitative; RBC = red blood cell; RDW = RBC distribution width; SAE = serious

Table 3. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other Safety Tests

adverse event; SC = subcutaneous; CCI ; TB = tuberculosis.

a. On all urine samples.
b. At screening only, in women who are amenorrheic for at least 12 consecutive months and under 55 years old.
c. For WOCBP.
d. Screening only.
e. At screening, and if a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.
f. Additional testing for potential Hy's Law cases only (See Section 6.2.2.6.3).
g. If patient is positive for ADA.
h. If clinically indicated for hemolytic anemia.

6.2.1.1 Pregnancy testing

For WOCBP, a serum pregnancy test will be performed at screening. Following a negative serum pregnancy result at screening, appropriate contraception must be commenced or continued and a further negative urine pregnancy test results will then be required at the baseline visit before the patient may receive the investigational product. Urine pregnancy tests will also be routinely repeated at study drug administration visits prior to study drug administration, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive pregnancy test or confirmed pregnancy, the patient will be discontinued from study drug, an EOT visit should be performed (Day 180), and a last follow-up visit 90 days after last dose should be scheduled (Day 270). Safety follow-up visit procedures based on the Schedule of Assessments (see Section 5.4).

See Section 6.2.2.7.1 for information on reporting of pregnancies as AEs/SAEs during the study.

6.2.1.2 Tuberculosis Screening

During the screening period, it must be determined and documented that a patient does not have evidence of active or latent or inadequately treated TB per the exclusion criteria (Section 4.5). The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

6.2.1.2.1 Mycobacterium Tuberculosis Testing Using QuantiFERON Test[40]

QuantiFERON®-TB Gold In-Tube (QFT-G) is an in vitro diagnostic test using a peptide cocktail simulating ESAT-6, CFP-10, and TB 7.7 proteins to stimulate cells in heparinized whole blood. Detection of INFγ performed by enzyme-linked immunosorbent assay (ELISA) is used to identify in vitro responses to these peptide antigens that are associated with Mycobacterium tuberculosis infection. QFT-G is an indirect test for M. tuberculosis infection (including disease) and is intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.

Test results will be reported as positive, negative, or indeterminate. A negative QFT-G test result is required to meet the inclusion criterion. In the case of an indeterminate result, repeat tests should be permitted for the purpose of determining eligibility of patients to enroll in this study. If a repeat test is indeterminate again, the patient is a screen failure. The procedure for using this test and interpreting the results will be described fully in the laboratory manual, which will be provided to investigators.

6.2.2 Adverse Events

6.2.2.1 Definitions

An AE is defined as any untoward medical occurrence experienced by a study patient, whether or not considered drug related by the principal investigator.

AEs are unfavorable changes in a general condition, subjective or objective signs or symptoms, worsening of pre-existing concomitant disease, and clinically significant abnormality in laboratory parameters observed in a patient in the course of a clinical study.

Non-serious SLE manifestations or abnormal laboratory results related to SLE disease activity would not be recorded as AEs unless they meet the definition for SAEs (Section 6.2.2.5).

6.2.2.2 Recording of Adverse Events

AEs should be collected and recorded for each patient from the date of the first dose of study drug until the end of their participation in the study, including the safety follow up period.

AEs may be volunteered spontaneously by the study patient, or discovered by the study staff during physical examinations or by asking an open, nonleading question such as 'How have you been feeling since you were last asked?' All AEs and any required remedial action will be recorded on the Adverse Events eCRF and Safety Adverse Event Form. The details of the AE, date of AE onset (and time, if known), date of AE outcome (and time, if known), and action taken for the AE will be documented together with the principal investigator's assessment of the seriousness of the AE and causal relationship to the study drug and/or the study procedure.

All AEs should be recorded individually, using diagnostic terms where possible. If the diagnosis is not established, individual symptoms may be reported. The AEs will subsequently be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

6.2.2.3 Severity of Adverse Events

Each AE will be assessed by the principal investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03 criteria. [41] When changes in the severity (grade) of an AE occur more frequently than once a day, the maximum severity for the event should be noted for that day. Any change in severity of signs and symptoms over a number of days will be captured by recording a new AE, with the amended severity grade and the date (and time, if known) of the change.

6.2.2.4 Causality of Adverse Events

The principal investigator will assess the causal relationship between BOS161721 or placebo and the AE. One of the following categories (Table 4) should be selected based on medical judgment, considering the definitions below and all contributing factors.

Table 4. Causality Definitions	
Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment (dechallenge[a]) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge[b] procedure if necessary.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (eg, concomitant disease, environmental factors, or other drugs or chemicals).

[a] Dechallenge: Upon discontinuation of a drug suspected of causing an AE, the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation (positive dechallenge), or the symptoms continue despite withdrawal of the drug (negative dechallenge). Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists (for example, as in bone marrow suppression, fixed drug eruptions, or tardive dyskinesia).

[b] Rechallenge: Upon re-administration of a drug suspected of causing an AE in a specific patient in the past, the AE recurs upon exposure (positive rechallenge), or the AE does not recur (negative rechallenge).

An unexpected adverse drug event is any adverse drug event for which the specificity or severity is not consistent with the current IP.

6.2.2.5 Seriousness of Adverse Events

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

- Results in death
- Is life threatening; this means that the patient was at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires hospitalization or prolongation in existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly or birth defect
- Is another important medical event (see below)

Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in inpatient hospitalization
- Development of drug dependency or drug abuse

Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (eg, elective surgery for a pre-existing condition that has not worsened) need not be considered SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'nonserious' according to the usual criteria.

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are associated with the use of the drug and are serious and unexpected.

6.2.2.6 Adverse Events of Special Interest

AEs of special interest in this study include the following:

1. Anaphylaxis and serious allergic reactions
2. Grades 2 to 5 injection site reaction, including erythema, pain, and induration (See APPENDIX 6)
3. Drug Induced Liver Injury (DILI) assessed following Hy's Law
4. Malignancy
5. Opportunistic infections such as disseminated histoplasmosis, cryptococcosis, and disseminated tuberculosis
6. Cryptosporidiasis

6.2.2.6.1 Anaphylaxis and Serious Allergic Reactions

Anaphylaxis will be defined according to the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria.[42] In the event of anaphylactic reaction or severe/serious hypersensitivity/allergic reaction, the patient must discontinue IP and emergency resuscitation measures implemented. In case of other mild to moderate hypersensitivity reaction, depending on the severity, the investigator may manage in accordance with the standard-of-care.

Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus, or flushing, swollen lips-tongue-uvula) and at least 1 of the following:
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
   a. Systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from the patient's baseline

6.2.2.6.2 Injection Site Reactions

Injection site reactions are to be captured and reported as AEs. These will include Grades 2 to 5 injection site erythema, pain, and induration (see APPENDIX 6). The investigator should provide a clear description of the observed or reported AE including location and severity. All concomitant treatments used to treat injection site reactions should be recorded and captured in the eCRF, together with the AE of injection site reactions.

6.2.2.6.3 Potential Drug-Induced Liver Injury

Abnormal values in AST and/or ALT levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of DILI, and as potential Hy's Law cases, and should always be considered important medical events. If symptoms compatible with DILI precede knowledge of serum chemical test abnormalities, liver enzyme measurements should be made immediately, regardless of when the next visit or monitoring interval is scheduled. In some cases, symptoms may be an early sign of injury and although typically less sensitive than serum enzyme elevations, they may indicate a need for prompt serum testing. An increase in liver enzymes should be confirmed by a repeated test within 48 to 72 hours following the initial test, prior to reporting of a potential DILI event. Patients will continue to have weekly or biweekly liver enzyme measurements until resolution or levels return to baseline.

All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.2.2.7.2 for reporting details).

Potential DILI is defined as:

1. ALT or AST elevation > 3 × ULN

AND

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

AND

3. No other immediately apparent possible causes of ALT or AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

The patient should return to the investigational site and be evaluated as soon as possible, include laboratory tests, detailed history, and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, CK, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/International Normalized Ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

Study drug discontinuation is considered if there is marked serum AST or ALT elevation or evidence of functional impairment (as indicated by rising bilirubin or INR, which represent substantial liver injury) that is related to study drug. Discontinuation of treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5× ULN for more than 2 weeks

Discontinuation of treatment must occur if:

- ALT or AST >3 × ULN and (total bilirubin > 2 × ULN or INR > 1.5)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

6.2.2.6.4 Malignancy

The identification of a malignancy event will be made by the study site and communicated to the sponsor or designee. AEs should be reported as serious per the criteria in Section 6.2.2.5.

After the first dose of study drug, when there is a decision to biopsy a potentially malignant tumor, lymph node, or other tissue, the investigator and/or consultant(s) should contact the sponsor clinicians or designee to discuss the issue and any decisions as soon as possible.

6.2.2.6.5 Specific Infections

Any diagnosis or suggested diagnosis of opportunistic infections such as disseminated histoplasmosis, cryptococcosis, shingles, disseminated herpes simplex, or disseminated tuberculosis will be recorded as AEs of special interest.

Cryptosporidiosis is also considered an AE of special interest. Patients will be evaluated for cryptosporidium in the stool at screening, and as clinically indicated (eg, watery diarrhea) during the study. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

6.2.2.7 Reporting of Adverse Events

AE reporting will be carried out in accordance with applicable local regulations, including regulatory agency and IRB reporting requirements.

Each AE is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate, and is further outlined in Section 6.2.2.7.2.

6.2.2.7.1 Reporting of Pregnancy

As information is available, a pregnancy diagnosed during the study will be reported within 24 hours to the sponsor via the Pregnancy Notification and Outcome Form, including pregnancy in female patients who received study drug and female partners of male study patients who received study drug. The pregnancy should be followed to term and/or outcome and this outcome should also be reported to the sponsor via the Pregnancy Notification and Outcome Form. Pregnancy itself is not regarded as an AE or SAE unless there is complication.

In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an AE or SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the neonatal death as related or possibly related to exposure to investigational product.

6.2.2.7.2 Reporting of Serious Adverse Events

The principal investigator is responsible for providing notification to the sponsor of any SAE via the Safety Adverse Event Form, whether deemed study drug related or not, that a patient experiences during their participation in this study within 24 hours of becoming aware of the event.

If an SAE is fatal or life threatening, notification to the sponsor must be made aware immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding cases. In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

The principal investigator will review each SAE and evaluate the intensity and the causal relationship of the event to the study drug. All SAEs will be recorded from the time of first dose of study drug through the safety follow-up period (up to Day 270). SAEs occurring after the final follow-up visit and coming to the attention of the principal investigator must be reported only if there is (in the opinion of the principal investigator) reasonable causal relationship with the study drug.

As a minimum requirement, the initial notification should provide the following information:

- Study number
- Patient number
- Details of the SAE (verbatim details are sufficient for immediate notification)
- Criterion for classification as 'serious'
- Causality assessment (which may be updated in a follow-up report when sufficient information is available to make this classification)

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (eg, hospital reports, consultant reports, autopsy reports, etc), with the study patient's personal identifiers removed. All relevant information obtained by the principal investigator through review of these documents will be recorded and submitted to the sponsor within 24 hours of receipt of the information. If a new Safety Adverse Event Form is submitted, then the principal investigator must sign and date the form. The sponsor may also request additional information on the SAE, or clarification of omitted or discrepant information from the initial notification, which the principal investigator or an authorized delegate should submit to the sponsor within 24 hours of the request as possible.

6.2.2.7.3 Reporting of Adverse Events of Special Interest

AEs of special interest will be reported to safety immediately or within 24 hours of the site becomes aware of the event and recorded as such on the Adverse Events eCRF and Safety Adverse Event Form.

Potential DILI will be reported based on specifications mentioned in Section 6.2.2.6.3.

Each AE of special interest is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate, and is further outlined in Section 6.2.2.7.2.

6.2.2.8 Follow Up of Adverse Events

All AEs will be followed up through the safety follow-up visits. All SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the event has resolved, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the principal investigator and medical monitor, until there is a satisfactory explanation for the changes observed, or until the patient is lost to follow-up.

See Section 6.2.2.7.1 for details related to follow-up of pregnancy. See Section 6.2.2.6.3 for details related to follow-up of potential DILI. See Section 6.2.2.6.4 for details related to follow-up of malignancy.

6.2.3 Vital Signs

Vital signs (blood pressure, heart rate, and body temperature) will be assessed as specified in the Schedule of Assessments (Section 3.4). Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours postdose, as well as on each of the scheduled visit days during the study (excluding PK-only site visits). Supine BP and heart rate recordings will be made after the patient has been recumbent and at rest ≥ 5 minutes. When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

6.2.4 12-Lead Electrocardiograms

ECG will be assessed as specified in the Schedule of Assessments (Section 3.4). ECG recording will initiate after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws, though timing will be such that PK draws are collected on their scheduled times where possible.

The ECG will include all 12 standard leads and a Lead II rhythm strip on the bottom of the tracing. The ECG will be recorded at a paper speed of 25 mm/second. The following ECG parameters will be collected: PR interval, QRS interval, RR interval, QT interval, and QT interval corrected for heart rate using Fridericia's formula (QTcF).

All ECGs must be evaluated by a qualified physician or qualified designee for the presence of abnormalities and will be captured electronically and retained for future evaluation if required, up to the time of the clinical study report (CSR) completion.

6.2.5 Physical Examinations

The full physical examination will be completed at screening and Day 0. It includes an assessment of general appearance and evaluation of head, eyes, ears, nose, mouth, throat, neck,

thyroid, lymph nodes, and extremities, and dermatologic, respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurologic, and psychiatric systems.

The targeted (limited) physical examination will be completed at all other visits as indicated in the Schedule of Assessments (Section 3.4). It includes evaluation of patient complaints and SLE disease-related issues, and will exclude the genitourinary system.

6.2.6 C-SSRS

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed by Columbia University researchers for the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment. It is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening.[43]

The C-SSRS evaluation will be performed as specified in the Schedule of Assessments (Section 3.4). Patients with recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4, or 5 is exclusionary at screening will be excluded from the study. Patients with recent or active suicidal ideation or behavior at subsequent study visits will have responses to the C-SSRS reviewed in detail to assess patient risk, and appropriate consultative mental health services will be provided.

6.2.7 Injection Site Reactions

Patients will be monitored for local injection site reactions as specified in the Schedule of Assessments (Section 3.4). Local injection site reactions will be assessed at 2 hours postdose at baseline, and predose for each injection after baseline. Injection site reactions should be managed according to the standard of care. Injection site reactions, Grades 2 to 5, are to be reported as AEs of special interest (see Section 6.2.2.7.3).

6.2.8 Immunogenicity

The serum samples to measure the presence of ADA will be collected as specified in the Schedule of Assessments (Section 3.4). Blood samples (4 mL) to provide approximately 1.5 mL of plasma for anti BOS161721 antibody analysis will be collected into appropriately labeled tubes containing K_2EDTA. The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods. Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only assayed if the patient had a positive ADA on Day 90.

After the first dose, if a patient tests positive in the validated confirmatory ADA assay, the sample from this patient will be further analyzed in the neutralizing antibody (nAb) assay.

6.3 Efficacy Assessments

All efficacy assessments will be performed at times defined in the Schedule of Assessments (Section 3.4).

6.3.1 SLEDAI-2K

The SLEDAI-2K is a validated instrument that measures disease activity in SLE patients at the time of the visit and in the previous 30 days. It is a global index and includes 24 clinical and laboratory variables that are weighted by the type of manifestation, but not by severity. The total score falls between 0 and 105, with higher scores representing increased disease activity. The SLEDAI-2K has been shown to be a valid and reliable disease activity measure in multiple patient groups. A SLEDAI -2K of 6 or more generally represents moderately to severely active disease.[44]

6.3.2 BILAG 2004

The BILAG-2004 index is an organ-specific 97-question assessment based on the principle of the doctor's intent to treat. Only clinical features attributable to SLE disease activity are to be recorded and based on the patient's condition in the last 4 weeks compared with the previous 4 weeks. It will be scored as not present (0), improved (1), the same (2), worse (3), or new (4). Disease activity is graded separately for 9 body systems to 5 different grades (A to E) as follows: A ("Active") is very active disease, B ("Beware") is moderate activity, C ("Contentment") is mild stable disease, D ("Discount") is inactive now but previously active, and E ("Excluded") indicates the organ was never involved.[44] A shift from BILAG-2004 Grade A or B to a lower grade indicates a clinically relevant change in disease activity as the BILAG-2004 grades mirror the decision points for treatment interventions.

Only investigators that complete BILAG-2004 training will be allowed to perform the BILAG-2004 assessments. Preferably, the same investigator should evaluate the patient at each BILAG-2004 assessment from screening to study completion. The investigator must maintain documentation with descriptive details supporting the BILAG-2004 scoring (eg, chart, worksheet, clinic notes, and labs) at each visit.

See APPENDIX 5 for detailed specifications.

6.3.3 PGA of Disease Activity

The PGA is used to assess investigator's general impression on the patient's overall status of SLE disease activity via visual analogue scale (100 mm) with 0 being "very good, asymptomatic and no limitation of normal activities" with 100 mm being "most severe possible disease ever seen in all SLE patients".

When scoring the PGA, the assessor should always look back at the score from the previous visit.

6.3.4 Composite Endpoints: SRI-4, SRI-5, SRI-6, and BICLA Response

6.3.4.1 SRI-4 Response

The SRI-4 is a composite index of SLE disease improvement that consists of scores derived from the SLEDAI-2K and the BILAG 2004 Index. Response based on the SRI-4 is defined by:

1) ≥ 4-point reduction in SLEDAI-2K global score, 2) no new severe disease activity (BILAG A organ score) or more than 1 new moderate organ score (BILAG B), and 3) no deterioration from baseline in the PGA by ≥ 0.3 points. The SRI-4 response in patients with moderate to severe SLE is associated with broad improvements in clinical and patient-reported outcomes.[45]

6.3.4.2 SRI-5 and SRI-6 Response

Like the SRI-4, the SRI-5 and SRI-6 are composite indices of SLE disease improvement that consists of scores derived from the SLEDAI-2K and the BILAG 2004 Index. However, the SRI-5 and SRI-6 are computed with a minimal three-point or five-point improvement in SLEDAI-2K being required, respectively.[46]

6.3.4.3 BICLA Response

The BICLA is a responder index developed to measure response to therapy, and it includes scores from the BILAG, SLEDAI-2K, and PGA. BICLA response is defined as 1) at least 1 gradation of improvement in baseline BILAG 2004 scores in all body systems with moderate disease activity at entry (eg, all B [moderate disease] scores falling to C [mild], or D [no activity]); 2) no new BILAG A or more than 1 new BILAG B scores; 3) no worsening of total SLEDAI-2K score from baseline; 4) ≤ 10% deterioration in PGA score and 5) no treatment failure.[44] It is driven primarily by the BILAG, and has been used in Phase 2 and 3 mAb studies.[47]

For the endpoints of BICLA response at Days 210, 240, and 270, patient scores will be completed and response determined.

6.3.5 CLASI Response

The CLASI is a comprehensive tool for assessment of disease activity and damage in cutaneous lupus, shown to be valid, reliable, and sensitive to changes in disease activity.[48] Response is defined as 50% improvement from baseline in “A” or “B” scores. This assessment will be applied to all patients as all are required to have cutaneous disease activity.

For the secondary efficacy endpoint of CLASI response at Day 210, patient scores on MAD and POC studies will be compared with baseline for 50% improvement.

6.3.6 ACR-28 Joint Count

The ACR-28 joint count will evaluate the number of tender and swollen joints in the shoulder, elbow, wrist, hand, knee joints. Joints of the feet are excluded.

6.4 Other Variables

6.4.1 SLICC/ACR Damage Index

The SLICC/ACR damage index is a validated instrument to assess damage, defined as irreversible impairment, continuously persistent for 6 months (ascertained by clinical assessment), occurring since the onset of lupus, and it is based on a weighted scoring system. This index records damage occurring in patients with SLE regardless of cause, with demonstrated content, face, criterion, and discriminant validity.[49] It will be performed on Days 0 and 180.

6.4.2 PROs

Patients should be encouraged to complete the PROs at the clinic at the beginning of the study visit prior to any clinical assessments. A member of the staff should be available if a patient requires further instruction and to review the PRO questionnaires for completeness prior to leaving the clinic. The PROs include the CCI and the CCI and will be assessed as specified in the Schedule of Assessments (Section 3.4).

CCI

CCI

.

6.5 Pharmacokinetic Assessments

During the MAD Phase 1b (all sites) and POC Phase 2 (select sites only) studies, blood samples for PK analysis of BOS161721 or placebo concentration will be collected according to Table 1 and Table 2.

Plasma concentrations of BOS161721 will be measured using a validated immunoassay. The PK parameters will be calculated from the plasma concentration actual time profiles.

6.6 Pharmacodynamic Assessments

Blood samples for PD parameters (plasma) will be collected at times indicated in the Schedule of Assessments (Section 3.4) for each of the following parameters:

- pSTAT3 (predose [trough] samples only Phase 1b)
- Antibodies: CCI
- Plasma complement (CCI)
- Plasma CCI and CCI
- Whole blood for leukocyte immunophenotype

6.7 Pharmacokinetic/Pharmacodynamic Relationship

Evidence of any PK/PD relationships will be evaluated between BOS161721 plasma concentrations and the available PD endpoints and biomarkers.

6.8 Protocol Deviations

Protocol deviations will be documented during the study.

7 STUDY DRUG MANAGEMENT

7.1 Description

7.1.1 Formulation

CCI [redacted]

CCI [redacted]

Additional information regarding dose preparation will be provided in a separate Pharmacy Manual.

7.1.2 Storage

All supplies of BOS161721 or placebo must be stored in accordance with the manufacturer's instructions. BOS161721 or placebo will be stored in a securely locked area, accessible to authorized persons only, until needed for dosing.

Information regarding storage and dose preparation will be provided in a separate Pharmacy Manual.

7.2 Packaging and Shipment

Investigational medicinal products will be supplied by Boston Pharmaceuticals, Inc. Investigational medicinal products will be packaged and labeled according to applicable local and regulatory requirements.

7.3 Dose and Administration

Details of dosing are provided in Section 3.1.

Each unit dose will be prepared by a qualified staff member. The vials of investigational product (IP) will appear identical and will have a "blinded" label on the vials that will state CCI [redacted] mg or placebo. When the site goes into the IWRS to request the patient kit(s), the IWRS will assign the

appropriate number of kits (regardless of assignment to placebo or active treatment) per the dose (ie, CCI [redacted]). If a patient is randomized to the placebo arm, they will receive the matching number of kits.

The designated staff member (or designee under the direction of the designated staff member) will dispense BOS161721 or placebo for each patient according to the protocol, randomization list, and Pharmacy Manual, if applicable.

After receiving sponsor approval in writing, the investigational site is responsible for returning all unused or partially used BOS161721 or placebo to the sponsor or designated third party or for preparing BOS161721 or placebo for destruction via incineration.

Further details are found in a separate Pharmacy Manual.

7.4 Accountability

The Principal Investigator or designee is responsible for maintaining accurate accountability records of BOS161721 or placebo throughout the clinical study. The drug accountability log includes information such as, randomization number, amount dispensed and amount returned to the pharmacy (if any). Products returned to the pharmacy will be stored under the same conditions as products not yet dispensed. The returned products should be marked as 'returned' and kept separate from the products not yet dispensed.

All dispensing and accountability records will be available for sponsor review after database lock procedures are completed. During safety monitoring, the drug accountability log will be reconciled with the products stored in the pharmacy.

7.5 Prohibited Concomitant Therapy

Prohibited concomitant medications are discussed in Section 4.6 and APPENDIX 4 and will be listed as protocol violations if taken when not permitted.

7.6 Compliance

Dosing will be performed by trained, qualified personnel designated by the principal investigator. The date and time of dosing will be documented on each dosing day. Comments will be recorded if there are any deviations from the planned dosing procedures.

8 STATISTICS

The following analyses are planned:

- An IA will be performed during the last cohort of the MAD phase to determine dose selection for the POC phase.
- The final analysis will be performed when all patients have completed the safety follow-up or withdrawn from the study.
- Safety analyses will be performed for DMC reviews throughout the study to evaluate dose escalation decisions and accumulating safety data. The frequency and details of the

content and format of the safety review meetings will be described in the SAP and/or DMC charter.

All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9 or higher.

The following standards will be applied for the analysis unless otherwise specified. Data will be summarized descriptively by treatment and overall for each study phase. For the MAD phase, BOS161721 will be summarized overall and by each dose level, and placebo patients from each cohort will be combined. Select parameters will be summarized using patients from both study phases. Statistical testing will be performed on data from the Phase 2 study only.

Continuous data will be summarized using number, mean, standard deviation (SD), 25th and 75th percentiles, minimum, median, and maximum. Categorical data will be summarized by treatment group using frequency tables (number and percentage). Time to event data will be summarized using counts, medians, 25th and 75th percentiles, and standard error. All data will be listed for all patients.

Statistical inference will be based on a 2-tailed test with an overall 0.10 level of significance, unless stated otherwise.

The effects of noncompliance, background therapy use, treatment discontinuations, premature withdrawal from study and covariates will be assessed to determine the impact on the general applicability of results from this study. Exploratory analyses of the data will be conducted as deemed appropriate. Any deviations from the planned analyses will be described and justified in the final integrated CSR.

Protocol deviations and prohibited medications that define medication failures will be fully assigned and documented before database lock and unblinding.

Further details of the analysis, including the handling of missing data, transformations and other data handling procedures will be provided in the SAP.

8.1 Sample Size

Sample size in the Phase 1b study is based on operational consideration.

The sample size in the Phase 2 study is based on the primary endpoint, SRI-4 Response at Day 210. Approximately 156 additional patients will be randomized in a 2:1 ratio to BOS161721 versus placebo to achieve 132 evaluable subjects in the FAS. This assumes 24 subjects will drop prior to having received treatment and an evaluable post-baseline efficacy measure. Enrollment and randomization will be monitored in a blinded fashion and increased if needed to ensure at least 132 subjects are randomized into the FAS.

A total of 132 subjects randomized provides more than 80% power to detect a treatment difference of 25% in SRI-4 response rates at Day 210, based on a targeted 2-sided significance level of 10% and using a 2-sided Pearson's chi-squared test. This assumes of a response rate of 65% for BOS161721 and 40% for placebo, where missing data at Day 210 is carried forward

from most recent non-missing result and subjects are treated as a non-responder if a prohibited medication defined as a medication failure occurs.

8.2 Statistical Methods

8.2.1 Analysis Populations

The primary efficacy analysis will be based on the FAS, defined as all patients who receive at least 1 dose of study treatment and at have least 1 evaluable post-baseline efficacy evaluation. FAS analyses will be conducted on the basis of the randomized treatment.

A per protocol (PP) analysis set may be defined to exclude major protocol violations from the efficacy analysis. The PP Population will include all patients from the FAS except those with major violations to the protocol deemed to impact the analysis of the primary endpoint. These violations will be identified based on blinded data prior to study unblinding. PP analyses will be conducted on the basis of the randomized treatment.

Safety analyses will be based on the safety analysis set (SS), defined as all patients who receive at least 1 dose of study treatment. Safety analyses will be conducted on the basis of actual treatment received.

Pharmacokinetic analysis will be conducted on the PK analysis set, defined as the FAS with sufficient concentration data for the calculation of PK parameters.

8.2.2 Demographics and Baseline Characteristics

Baseline and patient characteristics will be summarized using all randomized patients.

8.2.3 Primary Efficacy Endpoint(s)

The proportion of patients who achieve a SRI-4 response at Day 210 will be assessed via Pearson's chi-squared analysis. The primary efficacy endpoint will be analyzed using the FAS and if needed repeated in the PP analysis set. Missing values will be addressed by employing a last observation carried forward (LOCF) analysis. Other imputation methods may be employed as a sensitivity analysis and will be described in the SAP. Additional analyses exploring impact of baseline factors such as baseline disease severity, race, and other characteristics may be performed.

Patients that received prohibited medications or unallowable CS usage as described in Section 4.6 will be considered "medication failures" and will be treated as non-responders for the primary efficacy analysis. Patients that received an allowable CS burst but having missing data at Day 210 will considered a medication failure and will be treated as non-responders for the primary efficacy analysis. The determination of medication failures will be reviewed using blinded data and finalized prior to unblinding.

The superiority of BOS161721 relative to placebo will be evaluated. If the proportion of SRI-4 responders for the selected POC dose in BOS161721 arm is higher than that of the placebo arm, then BOS161721 will be considered superior to placebo if the 2-sided p-value is less than or

equal to 0.10. Secondary and exploratory endpoints for this POC study will be evaluated based on the same statistical hypothesis.

8.2.4 Secondary Efficacy Endpoint(s)

Binary efficacy endpoints will be assessed via Pearson's chi-squared analysis. Continuous efficacy endpoints will be assessed via analysis of variance (ANOVA) or analysis of covariance (ANCOVA) and treatment will be compared using the F-test. Repeated measures mixed models may be performed to evaluate data collected at each visit and overall. Time-to-event endpoints will be assessed via Kaplan-Meier methodology and treatment will be compared using the log-rank test. The secondary efficacy endpoints will be analyzed on the FAS and if needed repeated in the PP analysis set. Details including handling of missing data and "medication failures" will be available in the SAP.

8.2.5 Analysis of Safety

8.2.5.1 Safety Analysis

Safety analyses will be performed on the SS. AE data will be coded to system organ class and preferred term using MedDRA. The number and percentage of patients experiencing any treatment-emergent AE, overall, and by system organ class an preferred term, will be tabulated. Treatment-emergent AEs will also be summarized by severity and relationship.

Concomitant medications will be coded using the WHO Drug dictionary. Observed values and changes from baseline in vital signs, ECG readings, and hematology and clinical chemistry parameters will be summarized at each individual visit.

8.2.6 Pharmacokinetic and Pharmacodynamic Data

8.2.6.1 Analysis of Pharmacokinetic Data

PK parameters will be calculated from concentration data collected during the MAD Phase 1b using non-compartmental analysis and include the following:

- C_{max}, T_{max}, AUC, $t_{½}$, CL, V_d

The PK parameter data will be listed and summarized descriptively in tabular format.

If data permit, the following analyses will be performed for plasma BOS161721 concentration data:

- A listing of all plasma BOS161721 concentrations by patient at actual times post dose;
- A descriptive summary of plasma BOS161721 concentrations. Summary statistics of geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum will be tabulated by study days with PK assessments.

8.2.6.2 Analysis of Pharmacodynamic Data

The PD parameter data will be listed and summarized descriptively in tabular format.

Exploratory analyses examining the relationship between PD parameters and PK concentration and PK parameters will be performed.

8.2.6.3 Population Pharmacokinetic Analysis or PK/PD Modeling

Plots of individual patient values for each relevant PD parameter on Y-axis and each relevant PK parameter on X-axis will be examined for relationship. If relationships are revealed by these diagnostic plots, PK and PD data from this study may be analyzed using modeling approaches to describe the relationship and may also be pooled with data from other studies to investigate any association between BOS161721 exposure and biomarkers or significant safety endpoints.

8.3 Interim Analysis and Power

One IA is planned for this study and will be conducted at the time of the POC decision for dose selection.

Since there is no IA during the POC phase, there is no impact on the type 1 error.

9 ETHICS AND RESPONSIBILITIES

9.1 Good Clinical Practice

The procedures set out in this protocol are designed to ensure that the sponsor and the principal investigator abide by the principles of the International Council for Harmonisation (ICH) guidelines on GCP and the Declaration of Helsinki (Version 2013). The clinical study also will be carried out in the keeping with national and local legal requirements (in accordance with US IND regulations [21 CFR 56]).

9.2 DMC

This study will use an external DMC. The DMC is an independent committee established to provide oversight of safety considerations in study and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of enrolled patients and those yet to be recruited to the trial as well as for the continuing validity and scientific merit of the study results. The DMC is charged with assessing such actions in light of an acceptable benefit/risk profile for BOS161721. The recommendations made by the DMC (ie, dose escalation, etc.) will be forwarded to the sponsor for final decision. The sponsor will forward such decisions, which may include summaries of safety data which are not endpoints, to regulatory authorities, as appropriate.

The sponsor will appoint a DMC for the periodic review of available study data. The DMC is an independent group of experts that advises the sponsor and the study investigators. The members of the DMC serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DMC are to (1) periodically review and evaluate the

accumulated study data for participant safety, study conduct, and progress, (2) make recommendations to the sponsor concerning the continuation, modification, or termination of the study and (3) suggest dose for POC portion of the study as described in Section 3.1.1.3.

The DMC considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. The DMC is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking (unblinding), and voting procedures prior to initiating any data review. The DMC is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

The DMC will have access to unblinded treatment information during the clinical trial. Details regarding management and process of this committee are found in the DMC Charter.

The DMC may recommend termination of BOS161721 treatment arm or the entire BOS161721 MAD/POC trial for any safety concern that is felt to outweigh potential benefits. The recommendation must be supported by the sponsor as indicated in the DMC Charter.

9.3 Institutional Review Board/Independent Ethics Committee

Independent Ethics Committees (IEC)/Institutional Review Boards (IRB) must meet the guidelines set out by the U.S. Food and Drug Administration (FDA) and conform to local laws and customs where appropriate. Written IRB/IEC approval for the protocol and the signed ICF must be obtained and transmitted to Boston Pharmaceuticals or representative before the study can be initiated. The IRB/IEC must be informed of and approve all protocol amendments. The investigator will ensure that this study is conducted in full conformance with all applicable local and regional laws and regulations. The complete text of the World Medical Association Declaration of Helsinki is given in APPENDIX 2.

9.4 Informed Consent

Before each patient undergoes any protocol required assessments or procedure, the written informed consent will be obtained according to the regulatory and legal requirements of the participating country. As part of this procedure, the principal investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study patient should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. The principal investigator or designee will provide the sponsor with a copy of the IRB-approved ICF prior to the start of the study.

The informed consent document must be signed and dated; 1 copy will be handed to the patient and the principal investigator will retain a copy as part of the clinical study records. The principal investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

If the informed consent document is revised, it must be reviewed and approved by the responsible IRB/IEC. Patients currently enrolled may need to sign this revision (based on IRB/IEC requirements) and all future patients enrolled in the clinical study will be required to sign this revised ICF.

9.5 Records Management

The principal investigator will ensure the accuracy, completeness, and timeliness of the data reported to the sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The principal investigator or designee will cooperate with the sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The principal investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each patient receiving BOS161721 or placebo.

The principal investigator will allow sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB to have direct access to all documents pertaining to the study.

Electronic case report forms are required and should be completed for each randomized patient. It is the principal investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported on the patients' eCRF. Electronic case report forms should be completed in a timely fashion to support the study timelines. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status. The principal investigator or designated representative should complete and the principal investigator should verify the source documents as the information is collected. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The principal investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes.

9.6 Source Documentation

The documents that will form the source data for the clinical study (eg, patient charts, laboratory reports) must be defined and documented in the in-house study master file prior to the start of the study. Data on the eCRFs which will be checked against source data during monitoring visits

must also be defined and documented in the in-house study master file including the percentage of each of the source data to be verified and the percentage of patients' eCRFs to be monitored.

9.7 Study Files and Record Retention

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of BOS161721. However, these documents should be retained for a longer period if required by the applicable legal requirements.

10 AUDITING AND MONITORING

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and on-site visits. The study will be routinely monitored to ensure compliance with the study protocol and the overall quality of data collected. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor may periodically request review of the investigator study file to assure the completeness of documentation in all respects of clinical study conduct. The study monitor will verify that each patient has proper consent documentation from the patient and/or patient's authorized representative for study procedures and for the release of medical records to the sponsor, FDA, other regulatory authorities, and the IRB. The study monitor will also verify that assent was obtained for patients not capable of providing informed consent or that documentation is provided by the investigator explaining why the patient was unable to provide assent. The investigator or appointed delegate will receive the study monitor during these on-site visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies. On completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

Throughout the course of the study, the medical monitor will determine eligibility of all screened patients, will address any medical issues that might arise, clarify medical questions, review patient safety data (eg, AE/SAE, laboratory, and ECG), and partner with the study team in the overall study management. The study medical monitoring plan will document additional details of the study medical oversight and monitoring.

11 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by Boston Pharmaceuticals. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before

implementing the changes. Boston Pharmaceuticals will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, and/or Boston Pharmaceuticals, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the patient and/or has an impact on the patient's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for patients enrolled in the study before continued participation.

12 STUDY REPORT AND PUBLICATIONS

Boston Pharmaceuticals is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

By signing the protocol, the principal investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the competent authorities will be notified of the principal investigator’s name, address, qualifications, and extent of involvement.

The principal investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted and obtained approval from the sponsor in advance.

13 STUDY DISCONTINUATION

Both Boston Pharmaceuticals and the principal investigator reserve the right to terminate the study at the investigator’s site at any time. Should this be necessary, Boston Pharmaceuticals or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the principal investigator will inform the IRB/IEC of the same. In terminating the study Boston Pharmaceuticals and the principal investigator will assure that adequate consideration is given to the protection of the patients’ interests.

14 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Boston Pharmaceuticals, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial or to comply with regulatory requirements. However, authorized regulatory officials, IRB/IEC personnel, Boston Pharmaceuticals, and its authorized representatives are allowed full access to the records.

Identification of patients and eCRFs shall be by initials, birthdate, or patient number. Documents that identify the patient (eg, the signed informed consent document) must be maintained in confidence by the principal investigator. If required, the patient's full name may be made known to an authorized regulatory agency or other authorized official.

15 REFERENCES

1 Urowitz MB, Gladman DD. How to improve morbidity and mortality in systemic lupus erythematosus. Rheumatology 2000;39:238-44.

2 Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Morbidity and Mortality in Systemic Lupus Erythematosus During a 10-Year Period. Medicine 2003;82(5):299-308.

3 Pons-Estel GJ, Alarcón GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. Semin Arthritis Rheum. 2010;39(4):257. Epub 2009 Jan 10.

4 Kanta H, Mohan C. Three Checkpoints in lupus development: central tolerance in adaptive immunity, peripheral amplification by innate immunity, and end-organ inflammation. Genes and Immunity 2009;10:390-6.

5 Dall'Aqua WF, Kiener PA, Wu H. Properties of Human IgG1s Engineered for Enhanced Binding to the Neonatal Fc Receptor (FcRn). J Biol Chem. 2006 Aug 18, 281(33):23514-24.

6 Spolski R, Leonard WJ. The Yin and Yang of interleukin-21 in allergy, autoimmunity and cancer. Curr Opin Immunol. 2008a;20:295-301.

7 Asao H, Okuyama C, Kumaki S, Ishii N, Tsuchiya S, Foster D, et al. Cutting edge: the common gamma-chain is an indispensable subunit of the IL-21 receptor complex. J Immunol. 2001;167:1-5.

8 Habib T, Senadheera S, Weinberg K, Kaushansky K. The common gamma chain (gamma c) is a required signaling component of the IL-21 receptor and supports IL-21-induced cell proliferation via JAK3. Biochemistry. 2002;41:8725-31.

9 Spolski R, Leonard WJ. Interleukin-21: basic biology and implications for cancer and autoimmunity. Annu Rev Immunol. 2008b;26:57-79.

10 Puga I, Cols M, Barra CM, He B, Cassis L, Gentile M, et al. B-cell-helper neutrophils stimulate the diversification and production of immunoglobulin in the marginal zone of the spleen. Nat Immunol. 2011;13(2):170-80.

11 Costanzo A, Chimenti MS, Botti E, Caruso R, Sarra M, Monteleone G. IL-21 in the pathogenesis and treatment of skin diseases. J Dermatol Sci. 2010;60(2):61-6.

12 Avery DT, Bryant VL, Ma CS, de Waal Malefy R, Tangye SG. IL-21-induced isotype switching to IgG and IgA by human naive B cells is differentially regulated by IL-4. J Immunol. 2008;181:1767-79.

13 Rasmussen TK, Andersen T, Bak, RO, Yiu G, Sorensen CM, Stengaard-Pedersen K, et al. Overexpression of microRNA-155 increases IL-21 mediated STAT3 signaling and IL-21 production in systemic lupus erythematosus. Arthritis Research & Therapy 2015;17(154)

14 Ettinger R, Kuchen S, Lipsky PE. The role of IL-21 in regulating B-cell function in health and disease. Immunol Rev. 2008;223:60-86.

15 Caprioli F, Sarra M, Caruso R, Stolfi C, Fina D, Sica G, et al. Autocrine regulation of IL-21 production in human T lymphocytes. J Immunol. 2008;180(3):1800-7.

16 Yang L, Anderson DE, Baecher-Allan C, Hastings WD, Bettelli E, Oukka M, et al. IL-21 and TGF-beta are required for differentiation of human T(H)17 cells. Nature. 2008;454(7202):350-2.

17 Tangye SG, Ma CS, Brink R, Deenick EK. The good, the bad and the ugly - TFH cells in human health and disease. Nat Rev Immunol. 2013;13(6):412-26.

18 Fantini MC, Rizzo A, Fina D, Caruso R, Becker C, Neurath MF, et al. IL-21 regulates experimental colitis by modulating the balance between Treg and Th17 cells. Eur J Immunol. 2007;37(11):3155-63.

19 Peluso I, Fantini MC, Fina D, Caruso R, Boirivant M, MacDonald TT, et al. IL-21 counteracts the regulatory T-cell-mediated suppression of human CD4+ T lymphocytes. J Immunol. 2007;178(2):732-9.

20 Hippen KL, Bucher C, Schirm DK, Bearl AM, Brender T, Mink KA, et al. Blocking IL-21 signaling ameliorates xenogeneic GVHD induced by human lymphocytes. Blood. 2012;119(2):619-28.

21 Davis ID, Skrumsager BK, Cebon J, Nicholaou T, Barlow JW, Moller NP, et al. An open-label, two-arm, phase I trial of recombinant human interleukin-21 in patients with metastatic melanoma. Clin Cancer Res. 2007;13:3630-6.

22 Frederiksen KS, Lundsgaard D, Freeman JA, Hughes SD, Holm TL, Skrumsager BK, et al. IL-21 induces in vivo immune activation of NK cells and CD8(+) T-cells in patients with metastatic melanoma and renal cell carcinoma. Cancer Immunol Immunother. 2008;57(10):1439-49.

23 Karrich JJ, Jachimowski LC, Nagasawa M, Kamp A, Balzarolo M, Wolkers MC, et al. IL-21- stimulated human plasmacytoid dendritic cells secrete granzyme B, which impairs their capacity to induce T-cell proliferation. Blood. 2013;121(16):3103-11.

24 Lindner S, Dahlke K, Sontheimer K, Hagn M, Kaltenmeier C, Barth TF, et al. Interleukin-21-induced granzyme B-expressing B-cells infiltrate tumors and regulate T-cells. Cancer Res. 2013;73(8):2468-79.

25 Monteleone G, Caruso R, Fina D, Peluso I, Gioia V, Stolfi C, et al. Control of matrix metalloproteinase production in human intestinal fibroblasts by interleukin 21. Gut. 2006;55(12):1774-80.

26 Nakou M, Papadimitraki ED, Fanouriakis A, Bertsias GK, Choulaki C, Goulidaki N, et al. Interleukin-21 is increased in active systemic lupus erythematosus patients and contributes to the generation of plasma B-cells. Clin Exp Rheumatol. 2013;31(2):172-9.

27 Li Q, Liu Z, Dang E, Jin L, He Z, Yang L, et al. Follicular helper T-cells (Tfh) and IL-21 involvement in the pathogenesis of bullous pemphigoid. PLoS One. 2013;8(7):e68145.

28 Liu R, Wu Q, Su D, Che N, Chen H, Geng L, et al. A regulatory effect of IL-21 on T follicular helper-like cell and B-cell in rheumatoid arthritis. Arthritis Res Ther. 2012;14(6):R255.

29 Kang KY, Kim HO, Kwok SK, Ju JH, Park KS, Sun DI, et al. Impact of interleukin-21 in the pathogenesis of primary Sjögren's syndrome: increased serum levels of interleukin-21 and its expression in the labial salivary glands. Arthritis Res Ther. 2011;13(5):R179.

30 Terrier B, Geri G, Chaara W, Allenbach Y, Rosenzwajg M, Costedoat-Chalumeau N, et al. Interleukin-21 modulates Th1 and Th17 responses in gianT-cell arteritis. Arthritis Rheum. 2012a;64(6):2001-11.

31 Terrier B, Costedoat-Chalumeau N, Garrido M, Geri G, Rosenzwajg M, Musset L, et al. Interleukin 21 correlates with T-cell and B-cell subset alterations in systemic lupus erythematosus. J Rheumatol. 2012b;39(9):1819-28.

32 International Conference on Harmonisation. Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6 (R1). 2011.

33 Wang W, Wang EQ, Balthasar JP. Monoclonal Antibody Pharmacokinetics and Pharmacodynamics. Clin Pharm & Ther 2008; 84(5):548-58.

34 Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. Journal of Allergy and Clinical Immunology 2006;117:391–7.

35 Elsaesser H, Sauer K, Brooks DG. IL-21 is required to control chronic viral infection. Science. 2009;324(5934):1569-72

36 Kotlarz D, Zietara N, Uzel G, Weidemann T, Braun CJ, Diestelhorst J, et al. Loss-of-function mutations in the IL-21 receptor gene cause a primary immunodeficiency syndrome. J Exp Med. 2013;210(3):433-43.

37 Hunter PR, Nichols G. Epidemiology and clinical features of Cryptosporidium infection in immunocompromised patients. Clinical microbiology reviews. 2002;15(1):145-54.

38 Desjardins M, Mazer BD. B-cell memory and primary immune deficiencies: interleukin-21 related defects. Curr Opin Allergy Clin Immunol. 2013;13(6):639-45.

39 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.

40 Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, US: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a4.htm.

41 NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, available at https://evs.nci.nih.gov/ftp1/CTCAE/About.html.

42 Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. Journal of Allergy and Clinical Immunology 2006;117:391–7.

43 Posner K, Melvin G a, Stanley B, Oquendo M a, Gould M. Factors in the assessment of suicidality in youth. *CNS Spectr*. 2007;12(2):156-162.

44 Castrejon I, Tani C, Jolly M, Huang A, Mosca M. Indices to assess patients with systemic lupus erythematosus in clinical trials, long-term observational studies, and clinical care. Clin Exp Rheumatol 2014; 32(85):S85-95.

45 Furie R, Wang L, Drappa J, Illei G. Systemic Lupus Erythematosus (SLE) Responder Index [SRI(4)] Response Is Associated with Global Benefit in Patients with Moderate to Severe SLE [abstract]. *Arthritis Rheumatol.* 2016; 68 (suppl 10).

46 Thanou A, Chakravarty E, James JA, Merrill JT. Which outcome measures in SLE clinical trials best reflect medical judgment? Lupus Science & Medicine 2014;1:e000005. doi:10.1136/lupus-2013-000005.

47 Wallace DJ, Kalunian K, Petri MA, Strand V, Houssiau FA, Pike M,*et al.* Efficacy and safety of epratuzumab in patients with moderate/severe active systemic lupus erythematosus: results from EMBLEM, a phase IIb, randomised, double-blind, placebo-controlled, multicentre study. *Ann Rheum Dis* 2014;73:183-90.

48 Albrecht J, Taylor L, Berlin JA, Dulay S, Ang G, Fakharzadeh S. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): An Outcome Instrument for Cutaneous Lupus Erythematosus. J Invest Derm. 2005;125(5):889-94.

49 Stoll T, Seifert B, Isenberg DA. SLICC/ACR Damage Index is Valid, and Renal and Pulmonary Organ Scores are Predictors of Sever Outcome in Patients with Systemic Lupus Erythematosus. Br J Rheumatol. 1996;35:248-54.

50 CCI [redacted].

16 APPENDICES

APPENDIX 1 NAMES OF STUDY PERSONNEL

Sponsor:	Boston Pharmaceuticals 55 Cambridge Parkway Suite 401 Cambridge, MA 02142, USA
Medical Monitor:	PPD
	PPD
Clinical Research Organizations:	PPD
	PPD
	PPD
Bioanalytical Laboratory:	PPD
Central Laboratory:	PPD

APPENDIX 2 DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles
For
Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subject."

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic, and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility, and quality.

In current medical practice and in medical research, most prophylactic, diagnostic, and therapeutic procedures involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Research investigators should be aware of the ethical, legal, and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal, or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any SAEs. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a subject of the research, even though the subject has given consent.

Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the

subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

The subjects must be volunteers and informed participants in the research project.

The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the subject's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining

informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic, or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the subjects who are research subjects.

The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists.

At the conclusion of the study, every subject entered into the study should be assured of access to the best-proven prophylactic, diagnostic, and therapeutic methods identified by the study.

The physician should fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study must never interfere with the subject-physician relationship.

In the treatment of a subject, where proven prophylactic, diagnostic, and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the subject, must be free to use unproven or new prophylactic, diagnostic, and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health, or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

APPENDIX 3 COMMONLY USED CORTICOSTEROID EQUIVALENTS

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

APPENDIX 4 MEDICATION WASHOUT PERIODS

WASHOUT TIMES OF MEDICATIONS BASED ON 5 HALF-LIVES

Medication	Discontinuing Prior to Signing Consent
Abatacept (CTLA4Ig)	24 weeks
Alefacept	12 weeks
AMG 623 (blisibimod)	24 weeks
Anifrolumab	12 weeks
Atacicept (TACI-Ig)	12 weeks
Belimumab	24 weeks
Cyclophosphamide	24 weeks
Cyclosporine (except for CSA eye drops)	4 weeks
Danazol	4 weeks
Dapsone	4 weeks
Eculizumab	12 weeks
Efalizumab	12 weeks
Epratuzumab	24 weeks
Intravenous globulin	4 weeks
Leflunomide	8 weeks (4 weeks for washout with cholestyramine)
Lenalidomide with cholestiramine	8 weeks
Lupuzor	12 weeks
Memantine	4 weeks
Natalizumab	24 weeks
Ocrelizumab	48 weeks (or 24 weeks with recovery of B cell)
Pimecrolimus	4 weeks
Plasmapheresis	24 weeks
Retinoids (oral or topical)	4 weeks
Rituximab	48 weeks (or 24 weeks with recovery of B cell)
Sirolimus	4 weeks
Tacrolimus	4 weeks
Thalidomide	8 weeks
Tocilizumab	12 weeks

APPENDIX 5 BILAG-2004 (STUDY-SPECIFIC MODIFIED CRITERIA)

CCI

APPENDIX 6 INJECTION SITE REACTION GRADING SCALE

Adverse event Injection site reaction	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection	Tenderness with or without associated symptoms (eg, warmth, erythema, itching)	Pain; Lipodystrophy; Edema; phlebitis	Ulceration or necrosis; Severe tissue damage; Operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	-
Rash maculopapular/Erythema/Induration Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally, and associated with pruritus.	Macules/papules covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness) Erythema covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness)	Macules/papules covering 10% - 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL; Erythema 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering > 30% BSA with or without associated symptoms; limiting self-care ADL Erythema covering > 30% BSA with or without associated symptoms; limiting self-careADL	-	-

ADL = active daily living

APPENDIX 7 PROTOCOL SUMMARY OF CHANGES

The protocol summary of changes was moved to the end of the protocol for easier readability.

Significant changes are described in the table below. Changed text is displayed for the first major occurrence only. Deleted text is presented in strikethrough format, and added text is presented in bold format.

Section	Description of Changes	Rationale
Global	Add: Added '**Protocol Date and Version: 21 March 2018; V3.0**' to the header.	Administrative
Global	Change: Changed Version number from V2.0 (Amendment 1) to V**3**.0 (Amendment **2**) and Version date from 14 November 2017 to **21 March 2018**.	Administrative
Global	Change: Changed subjects to **patients**.	Replaced 'subjects' to 'patients' since the enrolled participants are with SLE condition
Global	Made administrative and editorial (formatting, typographical, and grammatical) updates.	Administrative
PROTOCOL SUMMARY, Background and Rationale	Add: The Phase 2 portion will be a proof of concept (POC) study, where dose selection will be based on the **data monitoring committee (DMC) and** sponsor's assessment of safety, tolerability, immunogenicity, and PK and PD data from the MAD study of 30 patients treated with BOS161721/placebo	Clarification that POC dose selection will be based on DMC and sponsor assessment
PROTOCOL SUMMARY, Objectives **and Endpoints**	The objectives and endpoints sections were combined together and are now represented in a table format in order to demonstrate which endpoints correspond to each objective. Only primary and secondary objectives and endpoints are listed within the synopsis. Additional edits were made to some objectives and endpoints. Some new endpoints were added to the study. An exploratory objective, to examine PK and PD effects of BOS161721 in subjects with mild to moderate SLE, was changed to 'secondary objective'. Changes to the objectives and endpoints are noted below: MAD Phase 1b Study	Updated for clarity and to provide a comprehensive list of endpoints identified in the protocol

Section	Description of Changes	Rationale

OBJECTIVES	ENDPOINTS
Primary	
• To assess safety, tolerability, and immunogenicity of repeat doses of BOS161721 (20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment, in order to estimate the optimal dose.	**Safety Endpoints** • Incidence and severity of **adverse events** (AEs) **and serious adverse events (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness** • **Injection site reactions** • **Columbia Suicide severity Rating Scale (C-SSRS)** • 12-lead **electrocardiograms (**ECGs**) parameter results at each visit and change from baseline** • Vital signs (blood pressure [BP], heart rate, and temperature) **parameter results at each visit and change from baseline** • Clinical laboratory **results and change from baseline** • Physical examinations **changes from baseline** • **Anti-drug antibodies (**ADAs**)** • **Study drug exposure/compliance** • **Concomitant medication usage**
Secondary	
• **To characterize the PK of BOS161721 and select the optimal dose of BOS161721 based on safety, PK, and PD effects in patients with mild to moderate SLE.**	**Pharmacokinetic Endpoints** • **BOS161721 c**oncentration by visit and time point • Maximum observed concentration (C_{max}), first time to maximum concentration (T_{max}), area under the concentration-time curve (AUC), $t_{½}$, systematic clearance (C_L), volume of distribution (V_d) **Pharmacodynamic Endpoints** • **Results and c**hanges **(or shifts)** from baseline to **each visit** in **phosphorylated signal transducer and activator of transcription 3** (pSTAT3), C3 and C4 levels, and leukocyte immunophenotype • **Results and c**hanges **(or shifts)** from baseline in **anti-double-stranded DNA (**dsDNA**)**, antinuclear antibodies (ANA), **anti-**Sjögren syndrome A and B

Section	Description of Changes	Rationale
	(SSA, SSB), Smith (Sm), and antiphospholipid (APL) autoantibodies at **each visit** • **Results and changes (or shifts) from baseline in a**brogation of IL-21 gene signature at **each indicated visit**	
Exploratory		
• CCI	CCI - CCI • CCI	The rules for CS usage during the trial, as well as limitations of other prohibited medications, are applied on the analytical end to ensure SRI-4 responders meet all necessary criteria.

Section	Description of Changes	Rationale

POC Phase 2 Study

OBJECTIVES	ENDPOINTS
Primary	
• To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on the SLE Responder Index 4 (SRI-4)	**Primary Efficacy Endpoint** • The proportion of **subjects with a** SRI-4 **response** at Day 210 **(see Section 6.3.4.1)**
Secondary	

Section	Description of Changes		Rationale
	To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on clinical indicators of SLE activity, in adult patients with moderately to severely active SLE on limited background standard of care treatment	**Secondary Efficacy Endpoints** • The proportion of subjects **with:** - **SRI-4 response at each visit** - SRI-5 and SRI-6 **response (Section 6.3.4.2)** - **a sustained reduction of oral corticosteroid (CS) (≤ 10 mg/day and ≤ Day 0 dose) between Day 120 and Day 210** - **new BILAG A flare or > 1 BILAG B flares relative to baseline through Day 210** - **PGA worsening** - a BICLA response - a CLASI response - **medication failures** • **Results and c**hanges from baseline in: - CLASI - swollen and tender joints ACR-28 - SLEDAI-2K - **SLICC/ACR damage index** • **Time to medication failure** • **Duration of SRI-4 response** • **Time to first SRI-4 response** • Time to BILAG A **flare** or **> 1 BILAG** B flare **compared to baseline through Day 210**	
	Safety		
	• **To assess safety and tolerability of repeat doses of** BOS161721 **(20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment**	**Safety Endpoints** • Incidence and severity of **adverse events (**AEs**) and serious adverse events (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness** • **Injection site reactions** • **C-SSRS** • 12-lead ECGs **parameter results at each visit and change from baseline** • Vital signs (blood	

Section	Description of Changes	Rationale
	pressure [BP], heart rate, and temperature) **parameter results at each visit and change from baseline** • Clinical laboratory **results and change from baseline** • Physical examinations **changes from baseline** • ADAs • **Study drug exposure/compliance** • **Concomitant medication usage**	
Exploratory		
• CCI [redacted].	CCI [redacted]	
• CCI [redacted]	• CCI [redacted]	
• CCI [redacted]	• CCI [redacted]	

Section	Description of Changes	Rationale
PROTOCOL SUMMARY, Study Design	Replace: The trial will consist of a staggered MAD Phase 1b and POC Phase 2 studies. Both studies will be double blinded with each patient having the same number of doses (7), and visits; the duration will be 180 days, followed by a 90-day follow-up safety observation period. With: The trial will consist of **2 double-blinded studies:** MAD Phase 1b and POC Phase 2**. Patients may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180, followed by safety follow-up visits at Days 210, 240, and 270.**	Clarification that patients will not have the same number of visits in both studies.
PROTOCOL SUMMARY, Study Design Section 1.2.4, Risk-Benefit Assessment	Delete: Two weeks after the last patient in Cohort 3 receives the second dose, the DMC and Boston Pharmaceuticals will conduct a data review ~~for the first interim analysis (IA1). At that time, a decision will be made~~ to suggest which dose should be carried forward into the POC Phase 2 study.	The futility analysis was removed due to the modest size of the trial but more importantly because the least reliable data (high placebo response) is known to occur during the first half of the study (before week 24) when futility analysis was planned
PROTOCOL SUMMARY, Study Design Section 3.1.2.2, POC Study Design	Add: For the POC study, approximately 156 **additional** patients will be randomized to active or placebo groups in a 2:1 ratio.	Clarification on POC sample size

Section	Description of Changes	Rationale
PROTOCOL SUMMARY, Study Design	Replace: Data from 60 patients, including the 12 from the MAD study, or 6 fewer if the low dose is chosen, who are in the cohort of the chosen dose for the POC study who complete 3 months of treatment will be used in a second IA (IA2) at Day 90 to assess if the trial could stop for an early futility conclusion. If futility is not claimed in the IA2, the POC study will continue to approximately 156 patients. Following the 6 month treatment period, primary and secondary efficacy endpoints will be assessed for each patient, after providing their Day 180 disease activity assessments. DMC monitoring will be conducted periodically throughout the study as described in the DMC charter. With: DMC **safety reviews** will be conducted periodically throughout the study as described in the DMC charter.	Removed assessment information from section, and the futility analysis was removed due to the modest size of the trial but more importantly because the least reliable data (high placebo response) is known to occur during the first half of the study (before week 24) when FA was planned
PROTOCOL SUMMARY, Main Criteria for Inclusion and Exclusion (inclusion criterion 6, sub-bullet ii) Section 4.4, Inclusion Criteria (inclusion criterion 6, sub-bullet ii)	Replace: ii Points from lupus headache and organic brain syndrome are also excluded With: ii Points from lupus headache and organic brain syndrome **will** also **be** excluded	Corrected to maintain consistency

Section	Description of Changes	Rationale
PROTOCOL SUMMARY, Main Criteria for Inclusion and Exclusion (inclusion criterion 7, sub-bullets a and b)	Replace: 7 Patients must have at least 1 of the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer: a. BILAG A or B score in the mucocutaneous body system b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis as defined in the protocol Section 4.4. c If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in the other body systems for a total of 2 "B" BILAG body system scores With: 7 Patients must have at least 1**A or 2Bs from** the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer: a BILAG A or B score in the mucocutaneous body system b BILAG A or B score in the musculoskeletal body system due to active polyarthritis as defined in the protocol Section 4.4. If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in the other body systems for a total of 2 "B" BILAG body system scores	Text updated to clarify that a minimum BILAG 1 'A' or 2 'B' scores is required for screening
PROTOCOL SUMMARY, Statistical Considerations	Replace: Baseline and patient characteristics will be summarized via appropriate summary statistics by treatment group and overall, for each phase of the trial. Binary efficacy endpoints will be compared between treatments via Cochran-Mantel-Haenszel (CMH) analysis. Continuous efficacy endpoints will be assessed via analysis of covariance (ANCOVA) repeated measures mixed model analysis with factors including treatment, time, treatment-by-time interaction, baseline covariate, and covariate-by-time interaction. Summary statistics will be provided by dose/treatment for all safety endpoints. Details will be provided in the statistical analysis plan (SAP). Two IAs are planned for this study. The initial IA (IA1) will be conducted at the time of the POC decision for dose selection. The second IA (IA2)	The futility analysis was removed due to the modest size of the trial but more importantly because the least reliable data (high placebo response) is known to occur during the first half of the study (before week

Section	Description of Changes	Rationale
	will be performed for futility. IA2 is planned to be conducted when SRI-4 response is determined for approximately 60 patients (including all patients at the same dose level/matching placebo from the MAD study) after completing 3 months of treatment. The purpose of IA2 is to assess if the trial could stop for an early futility conclusion, or continue. Since there is no plan to stop the trial for an early efficacy conclusion, there is no impact on the type 1 error level. AEs will be summarized by counts and percentages of patients by treatment group. Laboratory data and vital signs will be summarized by treatment group as summary statistics for value and change from baseline at each individual time point. Summary statistics will include n, arithmetic mean, median, arithmetic SD, minimum, and maximum. The PK parameter data will be listed and summarized descriptively in tabular format. Binary PD endpoints will be assessed for the full analysis set (FAS) population via CMH analysis. Continuous PD endpoints will be assessed via ANCOVA repeated measures mixed model analysis with multiple factors. PK and PD relationships will be explored graphically and where appropriate model based methods of analysis will used. With: **Two analyses are planned: 1) an interim analysis to select the Phase 2 dose based on Phase 1 data, and 2) a final analysis at study completion. Additionally, DMC safety analyses will be performed after each Phase 1 cohort and throughout Phase 2 to monitor patient safety.** **Unless stated otherwise, statistical testing will only be performed on the Phase 2 data and will be done using 2-sided overall alpha of 0.10. Data will be summarized descriptively by treatment and overall for each study phase. For the MAD phase, BOS161721 will be summarized overall and by each dose level and placebo patients from each cohort will be combined.** **The descriptive summaries for the categorical data will include number and percentage. The descriptive summaries for the continuous data will include number, mean, standard deviations (SD), 25th and 75th percentiles, minimum, median, and maximum. Counts medians, 25th and 75th percentiles, and standard error will be presented for time-to-event data.** **All safety analyses will be performed using the safety analysis set (SS), defined as all patients who receive at least 1 dose of study treatment. All efficacy analyses will be performed using the full analysis set (FAS), defined as all patients who have receive at least 1 dose of study treatment and have at least 1 evaluable post-baseline efficacy evaluation. Select efficacy analyses may also be performed on the per protocol (PP) set.** Binary efficacy endpoints**, including the primary efficacy endpoint,** will	24) when futility analysis was planned Text updated to allow use of testing procedures that are not typical/straight forward as 1-sided (such as CMH). Simplification and consistency with binary endpoints. Allows more

Section	Description of Changes	Rationale
	be **assessed** via **Pearson's chi-squared** analysis. **Continuous efficacy endpoints will be assessed via analysis of variance (ANOVA) or analysis of** covariance (ANCOVA) **when applicable, adjusting for the baseline value. R**epeated measures mixed model**s may be performed to evaluate data collected at each visit and overall. Time-to-event endpoints will be assessed via Kaplan-Meier methodology and treatment will be compared using the log-rank test.** **Adverse event data will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients experiencing any treatment-emergent AE, overall, and by system organ class and preferred term will be tabulated. Treatment-emergent AEs will also be summarized by severity and relationship.** **Concomitant medications will be summarized, based on coded terms, using frequency and percentage of patients. Observed values and changes from baseline in vital signs, ECG readings, and hematology and clinical chemistry parameters, will be summarized at each individual visit.**	flexibility in handling missing data.
List of Abbreviations	Add: **ANOVA** **analysis of variance** **ANCOVA** **analysis of covariance** **CS** **corticosteroids** **CCI** [redacted] **FAS** **full analysis set** **MedDRA** **Medical Dictionary of Regulatory Activities** **PP** **per protocol** **SS** **safety analysis set**	Updated to align with abbreviations added throughout the protocol
List of Abbreviations	Delete: ~~RNP~~ ~~ribonucleoprotein~~	Updated to align with abbreviations deleted throughout the protocol
Section 1.2.3, Study Dose Selection	Delete: In addition, the DMC and Boston Pharmaceuticals will conduct a data review ~~for the first interim analysis (IA1). At that time, a decision will be made~~ to suggest which dose should be carried forward into the proof of concept (POC) Phase 2 study.	The futility analysis was removed due to the modest size of the trial but more importantly

Section	Description of Changes	Rationale
		because the least reliable data (high placebo response) is known to occur during the first half of the study (before week 24) when futility analysis was planned
Section 1.2.4, Risk-Benefit Assessment	Replace: Thereafter, DMC monitoring will be conducted periodically throughout the study as described in the DMC charter. With: Thereafter, DMC **safety reviews** will be conducted periodically throughout the study as described in the DMC charter.	Text updated for clarification

Section	Description of Changes	Rationale
Section 2, Study Objectives **And Endpoints**	Replace: This trial has separate primary and secondary objectives for the MAD Phase 1b and POC Phase 2 studies. With: This trial has separate objectives **and endpoints** for the MAD Phase 1b and POC Phase 2 studies. **The primary, secondary, and exploratory objectives for each phase, as applicable, are described below with their corresponding endpoints.**	Text updated to appropriately setup table
Section 2, Study Objectives **And Endpoints**	The objectives and endpoints sections (Section 2 and 3 in Amendment 1) were combined into 1 section (Section 2 of Amendment 2) and the objectives and endpoints are now in a table format to easily distinguish which endpoints align with each objective. Additional edits were made to the objectives and endpoints. Some new endpoints were added to the study. An exploratory objective, to examine PK and PD effects of BOS161721 in subjects with mild to moderate SLE, was changed to 'secondary objective'. Changes to the objectives and endpoints are noted below: 2.1 Phase 1b Multiple Ascending Dose	Updated for clarity and to provide a comprehensive list of endpoints identified in the protocol

OBJECTIVES	**ENDPOINTS**
Primary	
• To assess safety, tolerability, and immunogenicity of repeat doses of BOS161721 (20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment, in order to estimate the optimal dose.	**Safety Endpoints** • Incidence and severity of **adverse events** (AEs) **and serious adverse events (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness** • **Injection site reactions** • **Columbia Suicide severity Rating Scale (C-SSRS)** • 12-lead **electrocardiograms (**ECGs**) parameter results at each visit and change from baseline** • Vital signs (blood pressure [BP], heart rate, and temperature) **parameter results at each visit and change from baseline** • Clinical laboratory **results and change from baseline** • Physical examinations **changes from baseline** • ADAs • **Study drug**

Section	Description of Changes	Rationale

	exposure/compliance • **Concomitant medication usage**
Secondary	
• **To characterize the PK of BOS161721 and select the optimal dose of BOS161721 based on safety, PK, and PD effects in patients with mild to moderate SLE.**	**Pharmacokinetic Endpoints** • **BOS161721 c**oncentration by visit and time point • Maximum observed concentration (C_{max}), T_{max}, area under the concentration-time curve (AUC), **terminal elimination half-life ($t_{½}$)** systematic clearance (C_L), volume of distribution (V_d) **Pharmacodynamic Endpoints** • **Results and c**hanges **(or shifts)** from baseline to **each visit** in **phosphorylated signal transducer and activator of transcription 3** (pSTAT3), C3 and C4 levels, and leukocyte immunophenotype • **Results and c**hanges **(or shifts)** from baseline in **anti-double-stranded DNA (**dsDNA**)**, antinuclear antibodies (ANA), **anti-**Sjögren syndrome A and B (SSA, SSB), Smith (Sm), and antiphospholipid (APL) autoantibodies at **each visit** • **Results and changes (or shifts) from baseline in a**brogation of IL-21 gene signature at **each indicated visit**
Exploratory	
• CCI	CCI

Section	Description of Changes	Rationale

2.2 Phase 2 Proof of Concept

OBJECTIVES	ENDPOINTS
Primary	
• To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on the SLE Responder Index 4 (SRI-4)	**Primary Efficacy Endpoint** • The proportion of **subjects with a** SRI-4 **response** at Day 210 **(see Section 6.3.4.1)**
Secondary	

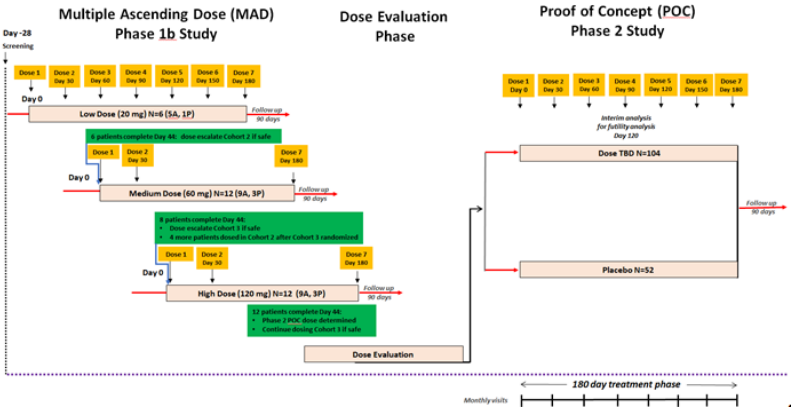
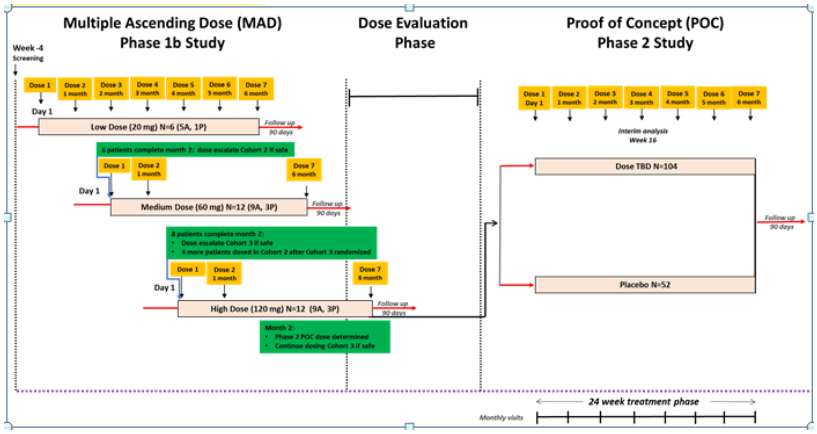
The rules for CS usage during the trial, as well as limitations of other prohibited medications, are applied on

Section	Description of Changes		Rationale
	To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on clinical indicators of SLE activity, in adult patients with moderately to severely active SLE on limited background standard of care treatment	**Secondary Efficacy Endpoints** • The proportion of subjects **with:** - **SRI-4 response at each visit** - SRI-5 and SRI-6 **response (Section 6.3.4.2)** - **a sustained reduction of oral corticosteroid (CS) (≤ 10 mg/day and ≤ Day 0 dose) between Day 120 and Day 210** - **new BILAG A flare or > 1 BILAG B flares relative to baseline through Day 210** - **PGA worsening** - a BICLA response - a CLASI response - **medication failures** • **Results and c**hanges from baseline in**:** - CLASI - swollen and tender joints ACR-28 - SLEDAI-2K - **SLICC/ACR damage index** • **Time to medication failure** • **Duration of SRI-4 response** • **Time to first SRI-4 response** • Time to BILAG A **flare** or **> 1 BILAG** B flare **compared to baseline through Day 210**	the analytical end to ensure SRI-4 responders meet all necessary criteria.
	Safety		
	• **To assess safety and tolerability of repeat doses of BOS161721 (20, 60, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment**	**Safety Endpoints** • Incidence and severity of **adverse events (**AEs**) and serious adverse events (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness** • **Injection site reactions** • **C-SSRS** • 12-lead ECGs **parameter results at each visit and change from baseline** • Vital signs (blood pressure	

Section	Description of Changes		Rationale
		[BP], heart rate, and temperature) **parameter results at each visit and change from baseline** • Clinical laboratory **results and change from baseline** • Physical examinations **changes from baseline** • ADAs • **Study drug exposure/compliance** • **Concomitant medication usage**	
	Exploratory		
	• CCI	CCI	
	• CCI	• CCI	
	• CCI	• CCI	
Section 3.1, Study Design	Replace: The trial will consist of 2 studies: MAD Phase 1b, and POC Phase 2. Both studies will be double-blinded, and patients will have the same number of visits. Patients may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180, followed by a 90-day safety follow-up visit.		Text updated to correspond with POC portion having 1 less visit.

Section	Description of Changes	Rationale
	With: The trial will consist of 2 **double-blinded** studies: MAD Phase 1b and POC Phase 2. Patients may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180, followed by **safety follow-up visits at Days 210, 240, and 270.**	
Section 3.1.1.1, Dose Escalation for the MAD Study	Replace: If > 3 patients discontinue the study in a cohort, he/she may be replaced. With: If patients discontinue the study in a cohort **prior to adequate safety follow-up**, he/she may be replaced.	Updated text to clarify that replacement may occur if any amount of subjects discontinue too early to establish safety
Section 3.1.1.3, DMC Recommendations	Delete: For the POC study, the DMC and Boston Pharmaceuticals will conduct a data review ~~for the IA1~~ to suggest which dose should be carried forward into the POC Phase 2 study.	The futility analysis was removed due to the modest size of the trial but more importantly because the least reliable data (high placebo response) is known to occur during the first half of the study (before week 24) when FA was planned.
Section 3.1.2.2, POC Study Design	Add: Dose selection will be based on the **DMC and** sponsor's assessment of safety, tolerability, immunogenicity, and PK and PD data from the MAD study of 30 patients treated with BOS161721/placebo.	Clarification that POC dose selection will be based on DMC and sponsor assessment
Section 3.1.2.2, POC Study Design	Replace: Data from approximately 60 patients (including the 12 from the MAD study, or 6 fewer if the low dose is chosen who are in the cohort of the chosen dose for the POC study) who complete 3 months of treatment will be used in the IA2 at Day 90 to assess if the trial could stop for an early futility conclusion (see Section 9.3 for details regarding the IA). If futility is not claimed in the IA2, the POC study will continue to approximately	Removed assessment information from section and the futility analysis was removed due to the modest

Section	Description of Changes	Rationale
	156 patients. Following the 6-month treatment period, primary and secondary efficacy endpoints will be assessed for each patient after providing their Day 180 disease activity assessments. DMC monitoring will be conducted periodically throughout the study as described in the DMC charter. With: DMC **safety reviews** will be conducted periodically throughout the study as described in the DMC charter.	size of the trial but more importantly because the least reliable data (high placebo response) is known to occur during the first half of the study (before week 24) when FA was planned
Section 3.2, Randomization and Blinding (new section)	Add: **3.2 Randomization and Blinding** **This is a randomized, double-blind study.** **Patients meeting all inclusion and exclusion criteria will be centrally randomized to either placebo or BOS161721 using an IWRS according to a randomization list generated by an independent, non-study statistician. Randomization will be performed separately for each study phase and separately for each cohort in the Phase 1b and 2 portion as follows:** **Phase/Cohort** | **Number of Patients** | **Randomization Ratio BOS161721:Placebo** **Phase 1b/Cohort 1** | **6** | **5:1** **Phase 1b/Cohort 2** | **12** | **3:1** **Phase 1b/Cohort 3** | **12** | **3:1** **Phase 2** | **156*** | **2:1** ***Additional patients may be enrolled to confirm sufficient numbers of patients are in the full analysis set (FAS).** **Eligible patients will be assigned to the study phase which is active at time of enrollment. Similarly, patients in the Phase 1 MAD will be assigned to the cohort which is active. Each patient will be assigned a unique randomization number which will not be reused.** **All patients, investigators, and study team participants will be blinded to treatment assignment. An independent biostatistician not otherwise involved on the study will be unblinded and prepare materials for the interim analysis (IA) and the DMC safety reviews.**	Text was added to clarify randomization and blinding process

Section	Description of Changes	Rationale
	The DMC will review unblinded data during safety reviews and the IA. A limited team at Boston Pharmaceuticals will review unblinded results from the Phase 1b MAD portion during the IA to determine the dose that will be used for the Phase 2 POC portion of the study. Details regarding maintenance of the blinding and content of data reviews will be described in the DMC charter or related study documentation.	
Section 3.3, Study Schematic	Replace:  With: 	The futility analysis was removed due to the modest size of the trial but more importantly because the least reliable data (high placebo response) is known to occur during the first half of the study (before week 24) when futility analysis was planned
Section 3.4, Schedule of Assessments (Table 1)	Replace: <table><tr><th></th><th>Screen[a]</th><th>Enroll</th><th colspan="3">Treatment Period Follow-Up</th></tr><tr><td>Days</td><td>-28 to -1</td><td>0</td><td>7 (± 1)</td><td>15 (± 3)</td><td>30 (± 3)</td></tr><tr><td>Visit Number</td><td>1</td><td>2</td><td>--</td><td>3</td><td>4</td></tr><tr><td>Injection site reaction assessment[f]</td><td></td><td>X</td><td>X</td><td></td><td>X</td></tr><tr><td>Plasma CCI & CCI</td><td>X</td><td>X</td><td></td><td>X</td><td>X</td></tr><tr><td>Whole blood for</td><td>X</td><td>X</td><td></td><td>X</td><td>X</td></tr></table>	Clarification of when certain assessments will be collected

Section **Description of Changes** **Rationale**

leukocyte immunophenotype					
CCI		X		X	X
CCI	X	X			X

With:

	Screen[a]	Enroll	Treatment Period Follow-Up		
Days	-28 to -1	0	7 (± 1)	15 (± 3)	30 (± 3)
Visit Number	1	2	--	3	4
Injection site reaction assessment		X[f]	X		X
Plasma CCI & CCI		X		X	X
Whole blood for leukocyte immunophenotype		X		X	X
CCI		X		X	
CCI	X	X			X

Section	Description of Changes	Rationale
Section 3.4, Schedule of Assessments (Table 1)	Replace: Treatment Period Follow-Up: Days 150 (± 3), 180 (± 3), 187 (± 3); Safety Follow-up: Days 195 (± 3), 210 (± 3), 240 (± 3) Visit number: 9, 10, --, --, 11, 12 pSTAT3: X, , , , , X With: Treatment Period Follow-Up: Days 150 (± 3), 180 (± 3), 187 (± 3); Safety Follow-up: Days 195 (± 3), 210 (± 3), 240 (± 3) Visit number: 9, 10, --, --, 11, 12 pSTAT3[l]	Clarification of when certain assessments will be collected
Section 3.4, Schedule of Assessments (Table 1 footnotes)	Add: i When clinically indicated **for hemolytic anemia**. **l Predose (trough) samples only.**	Text added to maintain consistency throughout the document.
Section 3.4, Schedule of Assessments (Table 1 and its footnotes)	Delete: - Predose[o] f Injection site reaction assessments to be performed ~~predose and~~ at 2 hours postdose. ~~o Predose samples occur on study drug administration visit days.~~	Clarified that no need for predose injection site reaction assessment at baseline and definition of 'o' was deleted as it was redundant.
Section 3.4, Schedule of Assessments (Table 2)	Replace: Screen[a]: Days -28 to -1; Enroll: Days 0; Treatment Period Follow-Up: Days 15 (± 3), 30 (± 3), 60 (± 3) Visit Number: 1, 2, 3, 4, 5 Injection site reaction assessment[f]: , X, , X, X Plasma CCI & CCI: X, X, X, X, X Whole blood for leukocyte immunophenotype: X, X, X, X, X	Clarification of when certain assessments will be collected

Section	Description of Changes	Rationale

CCI		X	X	X	
CCI	X	X		X	X

With:

	Screen[a]	Enroll	Treatment Period Follow-Up		
Days	-28 to -1	0	15 (± 3)	30 (± 3)	60 (± 3)
Visit Number	1	2	3	4	5
Injection site reaction assessment		X[f]		X	X
Plasma CCI & CCI		X	X	X	
Whole blood for leukocyte immunophenotype		X	X	X	
CCI		X	X		
CCI	X	X		X	X

Section 3.4, Schedule of Assessments (Table 2 footnotes)

Add:

i When clinically indicated **for hemolytic anemia**.

Text added to maintain consistency throughout the document.

Section 3.4, Schedule of Assessments (Table 2 footnotes)

Delete:

~~pSTAT3~~[l]Predose[q]

f Injection site reaction assessments to be performed ~~predose and~~ at 2 hours postdose.

~~l l Predose (trough) samples only.~~

~~q Predose samples occur on study drug administration visit days.~~

Clarified that no need for predose injection site reaction assessment at baseline, definition of 'q' was deleted as it was redundant, and footnote 'l' was removed to align with removal of pSTAT3 from the table

Section 4.2, Number of Patients

Add:

Approximately 30 patients will be randomized for the MAD Phase 1b study, and approximately 156 **additional** patients will be randomized in

Clarification on POC sample size

Section	Description of Changes	Rationale
	the POC Phase 2 study.	
Section 4.2, Number of Patients	Replace: Note that approximately 30 dropouts are assumed. With: Note that approximately **24** dropouts are assumed.	Text updated to clarify new number of dropouts assumed for the study
Section 4.4, Inclusion Criteria (Inclusion criterion 7, part b, subparts i and ii)	Replace: 7 Patients must have at least 1 of the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer: a BILAG A or B score in the mucocutaneous body system b BILAG A or B score in the musculoskeletal body system due to active polyarthritis defined as follows: i. "BILAG A:" Severe Arthritis, (BILAG item number 41), manifested by observed active synovitis in ≥ 2 joints with marked loss of functional range of movements and significant impairment of basic activities of daily living that has been present on several days cumulatively over the past 4 weeks, including at the time of the screening visit. See APPENDIX 5 for additional detailed specifications. • Basic ADLs are defined as the following activities which require assistance or assistive devices, (at least 1 must be present and documented in source): o Ambulation, toileting, grooming- including bathing and dressing; feeding oneself, (and not responsive to steroids up to 10 mg/day, antimalarials, NSAIDs) ii. "BILAG B:" Moderate Arthritis, Tendonitis or Tenosynovitis, (BILAG item number 42), defined as tendonitis/tenosynovitis, or active synovitis in ≥ 1 joint, (observed or throughout history), with some loss of functional range of movements which lead to some loss of functional range of motion as manifested by effects on instrumental ADLs such as: • Cooking, driving, using the telephone or computer, shopping, cleaning, etc, and has been present on several days over the last 4 weeks, and is present at the time of the screening visit c If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in the other body	Text updated to clarify that a minimum BILAG 1 'A' or 2 'B' scores is required for screening

Section	Description of Changes	Rationale

systems for a total of 2 “B” BILAG body system scores

With:

7 Patients must have at least 1**A or 2Bs from** the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer:

a BILAG A or B score in the mucocutaneous body system

b BILAG A or B score in the musculoskeletal body system due to active polyarthritis defined as follows:

i “BILAG A:” Severe Arthritis, (BILAG item number 41), manifested by observed active synovitis in ≥ 2 joints with marked loss of functional range of movements and significant impairment of basic activities of daily living that has been present on several days cumulatively over the past **30 days**, including at the time of the screening visit. See APPENDIX 5 for additional detailed specifications.

- Basic ADLs are defined as the following activities which require assistance or assistive devices, (at least 1 must be present and documented in source):
  - Ambulation, toileting, grooming- including bathing and dressing; feeding oneself

ii “BILAG B:” Moderate Arthritis, Tendonitis or Tenosynovitis, (BILAG item number 42), defined as tendonitis/tenosynovitis, or active synovitis in ≥ 1 joint, (observed or throughout history), with some loss of functional range of movements which lead to some loss of functional range of motion as manifested by effects on instrumental ADLs such as:

- Cooking, driving, using the telephone or computer, shopping, cleaning, etc, and has been present on several days over the last **30 days**, and is present at the time of the screening visit

If only one “B” and no “A” score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 “B” must be present in the other body systems for a total of 2 “B” BILAG body system scores

Section	Description of Changes	Rationale
Section 5.1, Screening Section 5.2, Enrollment/Randomization and Day 0 Treatment Section 5.3, Treatment Period/Follow-Up Visits Section 5.4, Safety Follow-Up Visits	Add: • Direct Coomb's test (if indicated **for hemolytic anemia**)	Text updated to clarity
Section 5.1, Screening	Delete: • CD4+ count, total IgG and IgM levels, plasma CCI , ~~plasma~~ CCI ~~and~~ CCI ~~whole blood for leukocyte immunophenotype;~~ CCI)	Updated to clarify the planned laboratory assessments
Section 5.1.1, Retesting During Screening Period	Add: • there is evidence a laboratory sample was mislabeled, **indeterminate,** inadequately processed, and/or deteriorated in transit to the central laboratory	Text added for further clarification
Section 5.2, Enrollment/Randomization and Day 0 Treatment	Replace: ○ pSTAT3 (predose [trough] samples only in Phase 2) With: ○ pSTAT3 (predose [trough] samples only in Phase **1b**)	Updated to clarify the planned laboratory assessments
Section 5.2, Enrollment/Randomization and Day 0 Treatment Section 5.3, Treatment Period/Follow-Up Visits	Delete: • CCI	Updated to clarify the planned laboratory assessments
Section 5.2, Enrollment/Randomization and Day	Replace: - Injection site reaction assessment, predose, and 2 hours post dose	Clarified that no need for predose injection site

Section	Description of Changes	Rationale
0 Treatment	With: Injection site reaction assessment, **performed at** 2 hours postdose	reaction assessment at baseline
Section 5.3, Treatment Period/Follow-Up Visits	Delete: • Injection site reaction assessments will be performed predose ~~and 2 hours postdose~~	Clarified that no need for predose injection site reaction assessment at baseline
Section 5.3, Treatment Period/Follow-Up Visits Section 5.4, Safety Follow-Up Visits Section 6.6, Pharmacodynamic Assessments	Add: • pSTAT3 **(predose [trough] samples only Phase 1b)**	Updated to clarify the planned laboratory assessments
Section 5.4, Safety Follow-Up Visits	Delete: • ~~pSTAT3~~	Updated to clarify the planned laboratory assessments
Section 6.2.1, Laboratory Assessments (Table 3)	Delete: Hematology ~~Reticulocytes (%)~~	Updated to clarify the planned laboratory assessments
Section 6.2.1, Laboratory Assessments (Table 3)	Replace: Immunogenicity, PD and other Biomarker Tests pSTAT3 (predose [trough] samples only, in Phase 2) With: Immunogenicity, PD and other Biomarker Tests pSTAT3 (predose [trough] samples only in Phase **1b**)	Updated to clarify the planned laboratory assessments
Section 6.2.1, Laboratory Assessments (Table 3 footnotes)	Add: h If clinically indicated **for hemolytic anemia**.	Text updated to clarify when Coomb's test direct will be collected

Section	Description of Changes	Rationale
Section 6.2.2.6, Adverse Events of Special Interest	Replace: 2 Injection site reaction, including erythema, pain, and induration With: 2 **Grades 2 to 5 i**njection site reaction, including erythema, pain, and induration **(See APPENDIX 6)**	Clarify that Grades 2 to 5 injection site reactions are AEs of special interest
Section 6.2.2.6.2, Injection Site Reactions	Replace: These may include injection site erythema, pain, and induration. With: These **will** include **Grades 2 to 5** injection site erythema, pain, and induration **(see APPENDIX 6)**.	Clarify that Grades 2 to 5 injection site reactions are AEs of special interest
Section 6.2.7, Injection Site Reaction	Replace: Local injection site reactions will be assessed predose and at 2 hours postdose. Injection site reactions should be managed according to the standard of care. Injection site reactions are to be reported as AEs of special interest (see Section 6.2.2.7.3). With: Local injection site reactions will be assessed **at 2 hours postdose at baseline, and** predose **for each injection after baseline**. Injection site reactions should be managed according to the standard of care. Injection site reactions**, Grades 2 to 5,** are to be reported as AEs of special interest (see Section 6.2.2.7.3).	Clarify that Grades 2 to 5 injection site reactions are AEs of special interest
Section 6.3.4.1, SRI-4 Response	Delete: ~~Patients will be evaluated for SRI-4 scores at Day 210, with evaluation for sustained reduction of oral CS (≤ 10 mg/day and ≤ Day 0 dose) between Day 120 and Day 210.~~	Differentiate assessment of SRI-4 and CS usage.
Section 6.3.4.1, SRI-4 Response	Delete: ~~Each patient, after providing their Day 210 visit SRI-4 response, will be evaluated as either a responder or non-responder.~~	Remove analysis item from assessment section

Section	Description of Changes	Rationale
Section 6.3.4.2, SRI-5 and SRI-6 Response	Delete: ~~The SRI-5 and SRI-6 are evaluated for response at Day 180, along with a sustained reduction of oral CS (≤ 10 mg/day and ≤ Day 0 dose) between Day 120 and Day 210.~~	Differentiate assessment of SRI-4 and CS usage. Remove analysis item from assessment section
Section 6.5, Pharmacokinetic Assessments	Delete: ~~PK parameters include the following:~~ • ~~C_{max}, T_{max}, AUC, $t_{½}$, CL, V_d~~ Plasma concentrations of BOS161721 will be measured using a validated immunoassay. The PK parameters will be calculated from the plasma concentration~~ nominal time profiles for the IA2 and~~ actual time profiles ~~for the final analysis. The non-compartmental analysis will be performed using appropriately validated PK/PD software.~~	Remove analysis item from assessment section
Section 6.6, Pharmacodynamic Assessments	Delete: • Antibodies: CCI [redacted] • ~~IgG and IgM and CD4+ count~~	Updated to clarify the planned PD assessments
Section 6.8, Protocol Deviations	Delete: ~~Per the statistical analysis plan (SAP), these will be listed by patient and summarized by deviation category by treatment group.~~	Remove analysis item from assessment section
Section 8, Statistics (entire section)	Replace: 9 STATISTICS There are 2 IAs planned for the study. The first IA will be conducted at the time of the POC decision for dose selection. The second IA will be performed for futility (see Section 9.3). Before the first IA, a SAP will be finalized, providing detailed methods for the analyses outlined below. Any deviations from the planned analyses will be described and justified in the final integrated CSR. The following standards will be applied for the analysis unless otherwise specified. Continuous data will be summarized by treatment group using descriptive statistics (number, mean, standard deviation [SD], minimum, median, and maximum). Categorical data will be summarized by	Updated section to clarify statistical analysis plan for the study

Section	Description of Changes	Rationale

treatment group using frequency tables (number and percentage).

9.1 Sample Size

Sample size in the Phase 1b study is based on operational consideration.

A summary of the power in the trial for the chosen sample size is provided in Table 5, with N = 132 randomized 89:43 to the chosen dose for the POC study and placebo, respectively; this includes 12 patients from the MAD study who were in the cohort of the mid or high dose if chosen for the POC study.

Table 5. Sample Size

Type 1 Error (1-Sided)	TRUE Underlying Response Rate (%)		Overall Power	Minimum OBSERVED Response Rates Yielding Statistical Significance	
	Placebo	Treatment		Placebo	Treatment
0.025	40	60	0.54	40	60
	40	65	0.75		
	40	70	0.9		
0.05	40	60	0.63	40	58
	40	65	0.81		
	40	70	0.93		

Total sample size of approximately 156 patients is planned for analysis, but may be adjusted upward according to the dropout (noncompliance) rate, which will be monitored in a blinded fashion in an ongoing basis. Note that approximately 36 dropouts are assumed.

8.2 Statistical Methods

9.2.1 Analysis Populations

The primary efficacy analysis will be based on the full analysis set (FAS), defined to be all patients with at least 1 baseline and post-baseline efficacy evaluation. A per protocol (PP) analysis set may be defined to exclude major protocol violations from the efficacy analysis. The PP Population will include all patients from the FAS except those with major violations to the protocol deemed to impact the analysis of the primary endpoint. These violations will be identified based on blinded data prior to unblinding the final analysis dataset. Safety analyses will be based on all patients who receive test treatment. Pharmacokinetic analysis will be conducted on the PK analysis set (PK), defined as the FAS with sufficient concentration data for the calculation of PK parameters. All analyses will combine data from the MAD and POC studies and focus on the active treatment dose chosen for the POC study versus placebo. The 0.05 1-sided type 1 error level is included for POC, and the 0.025 1-sided type 1 error level for potential use of this trial to support regulatory filing.

Section	Description of Changes	Rationale

9.2.2 Demographics and Baseline Characteristics

Baseline and patient characteristics will be summarized via appropriate summary statistics by treatment group and overall, for each phase of the trial.

9.2.3 Primary Endpoint(s)

The proportion of patients who achieve treatment response (measured by SRI-4 at Day 210 along with a sustained reduction of oral CS) will be analyzed via Cochran-Mantel-Haenszel (CMH) analysis. The primary endpoint will be analyzed on the FAS and if needed the PP analysis set. In addition, missing values will be addressed by employing a last observation carried forward (LOCF) analysis and/or other appropriate analytic approaches as a sensitivity analysis. Details will be available in the SAP.

9.2.4 Secondary Endpoint(s)

Binary efficacy endpoints will be assessed via CMH analysis. Continuous efficacy endpoints will be assessed via analysis of covariance (ANCOVA) repeated measures mixed model analysis with factors including treatment, time, treatment-by-time interaction, baseline covariate, and covariate-by-time interaction. The secondary efficacy endpoint will be analyzed on the FAS and if needed the PP analysis set. Details will be available in the SAP.

9.2.5 Analysis of Safety

9.2.5.1 Safety Analysis

Safety analyses will be performed on the Safety Analysis Set. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Incidences (number and percent) of AEs will be presented by treatment group. Incidences of AEs will also be presented by maximum severity and relationship to study medication. For the MAD study, the placebo patients from each cohort will be combined for the summaries. If there is a clear increase in AE rates for placebo patients across the cohorts, the AEs will also be summarized by cohort.

AEs will be summarized by counts and percentages of patients by treatment group. Laboratory data and vital signs will be summarized by treatment group as summary statistics for value and change from baseline at each individual time point. Summary statistics will include n, arithmetic mean, median, arithmetic SD, minimum, and maximum.

Additional safety parameters will be analyzed descriptively by treatment group. Descriptive statistics (n, mean, standard deviation (SD), median, minimum, maximum) will be calculated by treatment group and time point for continuous variables. Frequencies and percentages will be presented by treatment group for categorical and ordinal variables.

Section	Description of Changes	Rationale

9.2.5.2 Data Monitoring Committee

This study will use an external DMC. The DMC is an independent committee established to provide oversight of safety considerations in study and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of enrolled patients and those yet to be recruited to the trial as well as for the continuing validity and scientific merit of the study results. The DMC is charged with assessing such actions in light of an acceptable benefit/risk profile for anti-IL-21 mAb. The recommendations made by the DMC (ie, dose escalation, etc.) will be forwarded to the sponsor for final decision. The sponsor will forward such decisions, which may include summaries of safety data which are not endpoints, to regulatory authorities, as appropriate.

The DMC will have access to unblinded treatment information during the clinical trial. Details regarding management and process of this committee are found in the DMC Charter.

The DMC may recommend termination of an anti-IL-21 mAb treatment arm or the entire BOS161721 MAD/POC trial for any safety concern that is felt to outweigh potential benefits. The recommendation must be supported by the sponsor as indicated in the DMC Charter.

9.2.6 Pharmacokinetic and Pharmacodynamic Data

9.2.6.1 Analysis of Pharmacokinetic Data

The PK parameter data will be listed and summarized descriptively in tabular format.

If data permit, the following analyses will be performed for plasma BOS161721 concentration data:

- A listing of all plasma BOS161721 concentrations by patient at actual times post dose;
- A descriptive summary of plasma BOS161721 concentrations. Summary statistics of geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum will be tabulated by study days with PK assessments.

Details will be available in the SAP.

9.2.6.2 Analysis of Pharmacodynamic Data

The PD parameter data will be listed and summarized descriptively in tabular format.

Binary PD endpoints will be assessed for the FAS population. Binary PD endpoints will be assessed via CMH analysis. Continuous PD endpoints will be assessed via analysis of covariance (ANCOVA) repeated measures mixed model analysis with factors including treatment, time, treatment-

Section	Description of Changes	Rationale
	by-time interaction, baseline covariate, and covariate-by-time interaction. Normality will be assessed via diagnostic residual plots and Shapiro-Wilk statistic, but not as a formal statistical test of normality. If substantial departures from normality are observed, transformation will be used (eg, log and/or rank). Details will be available in the SAP. 9.2.6.3 Population Pharmacokinetic Analysis or PK/PD Modeling Plots of individual patient values for each relevant PD parameter on Y-axis and each relevant PK parameter on X-axis will be examined for relationship. If relationships are revealed by these diagnostic plots, PK and PD data from this study may be analyzed using modeling approaches to describe the relationship and may also be pooled with data from other studies to investigate any association between BOS161721 exposure and biomarkers or significant safety endpoints. Details will be available in the SAP. 9.3 Interim Analysis and Power Two IAs are planned for this study. The initial IA will be conducted at the time of the POC decision for dose selection. The second IA will be performed for futility. IA2 is planned to be conducted at Day 90 when SRI-4 response is determined for approximately 60 patients (including all patients at the same dose level/matching placebo from the MAD study) after completing 3 months of treatment. The purpose of the IA2 is to assess if the trial could stop for an early futility conclusion, or continue. Since there is no plan to stop the trial for an early efficacy conclusion, there is no impact on the type 1 error. If that intention changes, then $p < 0.0001$ is required for an early efficacy conclusion at the IA2 in order to not impact the planned type 1 error level. Nominal time profiles will be used for calculating PK parameters in the IA2. Details will be available in the SAP. With:	
	8 STATISTICS **The following analyses are planned:** • **An IA will be performed during the last cohort of the MAD phase to determine dose selection for the POC phase.** • **The final analysis will be performed when all patients have completed the safety follow-up or withdrawn from the study.** • **Safety analyses will be performed for DMC reviews throughout the study to evaluate dose escalation decisions and accumulating**	Updated to clarify that single alpha for a single primary hypothesis at a significance

Section	Description of Changes	Rationale
	safety data. The frequency and details of the content and format of the safety review meetings will be described in the SAP and/or DMC charter.	level is acceptable for PoC study.
	All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9 or higher. The following standards will be applied for the analysis unless otherwise specified. **Data will be summarized descriptively by** treatment **and overall for each study phase. For the MAD phase, BOS161721 will be summarized overall and by each dose level, and placebo patients from each cohort will be combined. Select parameters will be summarized using patients from both study phases. Statistical testing will be performed on data from the Phase 2 study only.** **Continuous data will be summarized** using number, mean, standard deviation **(**SD**)**, **25th and 75th percentiles,** minimum, median, and maximum. Categorical data will be summarized by treatment group using frequency tables (number and percentage). **Time to event data will be summarized using counts, medians, 25th and 75th percentiles, and standard error. All data will be listed for all patients.** **Statistical inference will be based on a 2-tailed test with an overall 0.10 level of significance, unless stated otherwise.** **The effects of noncompliance, background therapy use, treatment discontinuations, premature withdrawal from study and covariates will be assessed to determine the impact on the general applicability of results from this study. Exploratory analyses of the data will be conducted as deemed appropriate. Any deviations from the planned analyses will be described and justified in the final integrated CSR.** **Protocol deviations and prohibited medications that define medication failures will be fully assigned and documented before database lock and unblinding.** **Further details of the analysis, including the handling of missing data, transformations and other data handling procedures will be provided in the SAP.**	
	8.1 Sample Size Sample size in the Phase 1b study is based on operational consideration. **The sample size in the Phase 2 study is based on the primary endpoint, SRI-4 Response at Day 210. A**pproximately 156 **additional** patients **will be randomized in a 2:1 ratio to BOS161721 versus placebo to achieve 132 evaluable subjects in the FAS. This assumes 24 subjects will drop prior to having received treatment and an evaluable post-baseline efficacy measure. Enrollment and randomization will be monitored in a blinded fashion and increased if needed to ensure at least 132 subjects are randomized into the FAS.**	Text updated to express in terms of power for selected sample size and primary hypothesis

Section	Description of Changes	Rationale
	A total of 132 subjects randomized provides more than 80% power to detect a treatment difference of 25% in SRI-4 response rates at Day 210, based on a targeted 2-sided significance level of 10% and using a 2-sided Pearson's chi-squared test. This assumes of a response rate of 65% for BOS161721 and 40% for placebo, where missing data at Day 210 is carried forward from most recent non-missing result and subjects are treated as a non-responder if a prohibited medication defined as a medication failure occurs.	test, as well as describe alpha, beta, treatment effect assumptions used, and statistical test used for power calculation.
	8.2 Statistical Methods	
	8.2.1 Analysis Populations	
	The primary efficacy analysis will be based on the FAS, defined **as** all patients **who receive** at least 1 **dose of study treatment and have at least 1 evaluable** post-baseline efficacy evaluation. **FAS analyses will be conducted on the basis of the randomized treatment.**	
	A per protocol (PP) analysis set may be defined to exclude major protocol violations from the efficacy analysis. The PP Population will include all patients from the FAS except those with major violations to the protocol deemed to impact the analysis of the primary endpoint. These violations will be identified based on blinded data prior **study** to unblinding. **PP analyses will be conducted on the basis of the randomized treatment.**	
	Safety analyses will be based on **the safety analysis set (SS), defined as** all patients who receive **at least 1 dose of study** treatment. **Safety analyses will be conducted on the basis of actual treatment received.**	
	Pharmacokinetic analysis will be conducted on the PK analysis set, defined as the FAS with sufficient concentration data for the calculation of PK parameters.	
	8.2.2 Demographics and Baseline Characteristics	
	Baseline and patient characteristics will be summarized **using all randomized patients**.	
	8.2.3 Primary **Efficacy** Endpoint(s)	
	The proportion of patients who achieve **a** SRI-4 **response** at Day 210 will be **assessed** via **Pearson's chi-squared** analysis. The primary **efficacy** endpoint will be analyzed **using** the FAS and if needed **repeated in** the PP analysis set. **M**issing values will be addressed by employing a last observation carried forward (LOCF) analysis**. O**ther **imputation methods may be employed** as a sensitivity analysis **and will be described in** the SAP. **Additional analyses exploring impact of baseline factors such as baseline disease severity, race, and other characteristics may be performed.**	Text updated to clarify that CMH is stratified analysis, and no stratification factors were used at
	Patients that received prohibited medications or unallowable CS usage as described in Section 4.6 will be considered "medication failures" and will be treated as non-responders for the primary	

Section	Description of Changes	Rationale
	efficacy analysis. Patients that received an allowable CS burst but having missing data at Day 210 will considered a medication failure and will be treated as non-responders for the primary efficacy analysis. The determination of medication failures will be reviewed using blinded data and finalized prior to unblinding. **The superiority of BOS161721 relative to placebo will be evaluated. If the proportion of SRI-4 responders for the selected POC dose in BOS161721 arm is higher than that of the placebo arm, then BOS161721 will be considered superior to placebo if the 2-sided p-value is less than or equal to 0.10. Secondary and exploratory endpoints for this POC study will be evaluated based on the same statistical hypothesis.**	randomization. Population is expected to be relatively homogenous, so Pearson chi-square as primary and secondary analyses may be conducted with factors for adjustment.
	8.2.4 Secondary **Efficacy** Endpoint(s) Binary efficacy endpoints will be assessed via **Pearson's chi-squared** analysis. Continuous efficacy endpoints will be assessed via analysis of **variance (ANOVA) or analysis of** covariance (ANCOVA) **and treatment will be compared using the F-test. Repeated measures mixed models may be performed to evaluate data collected at each visit and overall. Time-to-event endpoints will be assessed via Kaplan-Meier methodology and treatment will be compared using the log-rank test.** The secondary efficacy endpoint**s** will be analyzed on the FAS and if needed **repeated in** the PP analysis set. Details **including handling of missing data and "medication failures"** will be available in the SAP.	Text updated to simplify and maintain consistency with binary endpoints. Allows more flexibility in handling missing data.
	8.2.5 Analysis of Safety **8**.2.5.1 Safety Analysis Safety analyses will be performed on the **SS**. AE **data** will be coded **to system organ class and preferred term** using MedDRA. **The** number and percent**age** of **patients experiencing any treatment-emergent AE, overall, and by system organ class an preferred term, will be tabulated. Treatment-emergent** AEs will also be **summarized** by severity and relationship. **Concomitant medications will be coded using the WHO Drug dictionary. Observed values and changes from baseline in vital signs, ECG readings,** and **hematology and clinical chemistry parameters** will be summarized at each individual **visit**. **8**.2.6 Pharmacokinetic and Pharmacodynamic Data **8**.2.6.1 Analysis of Pharmacokinetic Data **PK parameters will be calculated from concentration data collected during the MAD Phase 1b using non-compartmental analysis and include the following:**	

Section	Description of Changes	Rationale
	• **C_{max}, T_{max}, AUC, $t_{½}$, CL, V_d** The PK parameter data will be listed and summarized descriptively in tabular format. If data permit, the following analyses will be performed for plasma BOS161721 concentration data: • A listing of all plasma BOS161721 concentrations by patient at actual times post dose; • A descriptive summary of plasma BOS161721 concentrations. Summary statistics of geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum will be tabulated by study days with PK assessments. **8**.2.6.2 Analysis of Pharmacodynamic Data The PD parameter data will be listed and summarized descriptively in tabular format. **Exploratory analyses examining the relationship between PD parameters and PK concentration and PK parameters will be performed.** **8**.2.6.3 Population Pharmacokinetic Analysis or PK/PD Modeling Plots of individual patient values for each relevant PD parameter on Y-axis and each relevant PK parameter on X-axis will be examined for relationship. If relationships are revealed by these diagnostic plots, PK and PD data from this study may be analyzed using modeling approaches to describe the relationship and may also be pooled with data from other studies to investigate any association between BOS161721 exposure and biomarkers or significant safety endpoints **8**.3 Interim Analysis and Power **One IA is** planned for this study **and** will be conducted at the time of the POC decision for dose selection. Since there is no **IA during the POC phase**, there is no impact on the type 1 error.	The futility analysis was removed due to the modest size of the trial but more importantly because the least reliable data (high placebo response) is known to occur during the first half of

Section	Description of Changes	Rationale
		the study (before week 24) when futility analysis was planned
Section 9.2, DMC	Replace: The sponsor will appoint a DMC for the periodic review of available study data. The DMC is an independent group of experts that advises the sponsor and the study investigators. The members of the DMC serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DMC are to (1) periodically review and evaluate the accumulated study data for participant safety, study conduct, and progress, (2) make recommendations to the sponsor concerning the continuation, modification, or termination of the study and (3) suggest dose for POC portion of the study. The DMC considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. The DMC is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking (unblinding), and voting procedures prior to initiating any data review. The DMC is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it. With: **This study will use an external DMC. The DMC is an independent committee established to provide oversight of safety considerations in study and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of enrolled patients and those yet to be recruited to the trial as well as for the continuing validity and scientific merit of the study results. The DMC is charged with assessing such actions in light of an acceptable benefit/risk profile for BOS161721. The recommendations made by the DMC (ie, dose escalation, etc.) will be forwarded to the sponsor for final decision. The sponsor will forward such decisions, which may include summaries of safety data which are not endpoints, to regulatory authorities, as appropriate.** The sponsor will appoint a DMC for the periodic review of available study data. The DMC is an independent group of experts that advises the sponsor and the study investigators. The members of the DMC serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DMC are to (1) periodically review and evaluate the accumulated study data for participant safety, study conduct, and progress, (2) make recommendations to the sponsor concerning the continuation, modification, or termination of the study and (3) suggest dose for POC portion of the study **as described in Section 3.1.1.3**. The DMC considers study-specific data as well as relevant background	Clarification and to remove redundant text

Section	Description of Changes	Rationale
	knowledge about the disease, test agent, or patient population under study. The DMC is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking (unblinding), and voting procedures prior to initiating any data review. The DMC is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it. **The DMC will have access to unblinded treatment information during the clinical trial. Details regarding management and process of this committee are found in the DMC Charter.** **The DMC may recommend termination of BOS161721 treatment arm or the entire BOS161721 MAD/POC trial for any safety concern that is felt to outweigh potential benefits. The recommendation must be supported by the sponsor as indicated in the DMC Charter.**	

Section	Description of Changes	Rationale
Appendix 1, Names of Study Personnel	Replace: Clinical Research Organizations: PPD With: Clinical Research Organizations: PPD	Updated to represent change in personnel
Appendix 4, Medication Washout Periods	Replace: Medication: Belimumab; Discontinuing Prior to Signing Consent: 48 weeks With: Medication: Belimumab; Discontinuing Prior to Signing Consent: **24** weeks	Updated text to clarify when medication had to be discontinued prior to study initiation
Appendix 5, BILAG-2004 (STUDY-SPECIFIC MODIFIED CRITERIA)	Replace: CCI [redacted]	CCI [redacted]

Section	Description of Changes	Rationale
	CCI [redacted]	

Section	Description of Changes	Rationale
	CCI [redacted]	
Appendix 6, INJECTION SITE REACTION GRADING SCALE	Add:	Added table to clarify the grading scale for injection site reactions

Adverse event Injection site reaction	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection	Tenderness with or without associated symptoms (eg, warmth, erythema, itching)	Pain; Lipodystrophy; Edema; phlebitis	Ulceration or necrosis; Severe tissue damage; Operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	-
Rash maculopapular/	Macules/papules	Macules/ papules	Macules/ papules	-	-

Section	Description of Changes	Rationale

Erythema/Induration **Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally, and associated with pruritus.**	**covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness)** **Erythema covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness)**	**covering 10% - 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL;** **Erythema 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL**	**covering > 30% BSA with or without associated symptoms; limiting self-care ADL** **Erythema covering > 30% BSA with or without associated symptoms; limiting self-care ADL**		

ADL = active daily living

A RANDOMIZED DOUBLE-BLIND PHASE 1b/2 COMBINED STAGGERED MULTIPLE DOSE ESCALATION STUDY OF BOS161721 IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS ON A BACKGROUND OF LIMITED STANDARD OF CARE

SPONSOR	Boston Pharmaceuticals, Inc. 55 Cambridge Parkway, Suite 401 Cambridge, MA 02142 United States of America (USA)
INVESTIGATIONAL COMPOUND:	BOS161721
PROTOCOL NUMBER:	BOS161721-02
PHASE	Phase 1b/2
INVESTIGATIONAL NEW DRUG (IND) NUMBER:	131796
ORIGINAL PROTOCOL DATE:	05 October 2017
VERSION NUMBER:	V2.0 (Amendment 1)
VERSION DATE:	08 November 2017

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care

Study No: BOS161721-02
Original Protocol Date: 05 October 2017
Protocol Version No: v2.0 (Amendment 1)
Protocol Version Date: 08 November 2017

This study protocol was subject to critical review and has been approved by sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (APPENDIX 2), and principles of Good Clinical Practices (GCP) as described in 21 Code of Federal Regulations (CFR) parts 50, 54, 56 and 312 and according to applicable local requirements.

The investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

I agree with these statements and indicate my approval by signature for this protocol:

Name and Title	Signature	Date
PPD, MD Vice President, Clinical Development Boston Pharmaceuticals	PPD	
PPD Clinical Operations Lead Boston Pharmaceuticals	PPD	
PPD, MD, PhD Vice President, Clinical Development and Safety Officer Boston Pharmaceuticals	PPD	

SUMMARY OF CHANGES

Section	Description of Changes	Rationale
Global	Change: Changed Version number from V1.0 to **V2.0 (Amendment 1)** and Version date from 05 October 2017 to **08 November 2017**.	Administrative
Global	Change: Removed use of "Months" and "Weeks" to describe study site visits and dosing. Changed to **Day X** throughout protocol.	For clarity, site visits are based on study day number only.
Global	Change: Changed randomization day from Day 1 to **Day 0**.	Clarification (as dose is given every 30 days)
Global	Made administrative and editorial (formatting, typographical, and grammatical) updates.	Administrative
PROTOCOL SUMMARY, Background and Rationale Section 1.2.2.3, Clinical Studies	Replace: Overall, there were no clinically significant findings from this study; there were no serious adverse events (SAEs), deaths, or discontinuations due to AEs during the study, AEs reported as related to the study drug, particularly infections (flu-like symptoms, etc), were expected for the compound, and there were no clinically relevant changes in laboratory and ECG results or vital signs. With: Overall, there were no clinically significant findings from this study**, following an interim cut and review of the data at Day 90 postdose.** A**dverse event**s reported as related to the study drug, particularly infections, were expected for the compound, and there were no clinically relevant changes in laboratory and ECG results or vital signs. **There was 1 serious adverse event (SAE; death due to pulmonary embolism) that occurred 127 days after a single administration of 240 mg SC dose of BOS161721. The causality of this single SAE was not attributed to study drug and further information can be found in the Investigator's Brochure.**	Clarification and updated with new safety data.

Section	Description of Changes	Rationale
PROTOCOL SUMMARY, Study Design Section 1.2.3, Study Dose Section Section 4.1.1, Multiple Ascending Dose Phase 1b Study	Delete: Each of the 3 doses (20 mg, 60 mg, and 120 mg) selected for the MAD study are projected not to exceed the mean ~~peak levels or~~ exposure~~s~~ of that achieved in the SAD study following the single 240 mg SC dose.	Clarification to correct level of exposure
PROTOCOL SUMMARY, Study Design	Replace: Similarly, after 8 of the 12 patients in Cohort 2 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 3 begins dosing (based on the dose level determined after DMC evaluation of the safety and tolerability data from Cohort 2 and Cohort 1). Two weeks after the last patient in Cohort 3 receives the second dose, the DMC will conduct a data review for the first interim analysis (IA1) to determine which dose will be carried forward into the POC Phase 2 study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2 and 3; this dose will not exceed doses tested during the MAD study. The DMC will be reviewing all relevant data from Cohorts 1, 2, and 3 that is available when the last patient in Cohort 3 reaches 60 days (dose 2). This dose will not exceed doses tested during the MAD study. With: Similarly, after 8 of the 12 patients in Cohort 2 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 3 begins dosing after DMC evaluation of the safety and tolerability data from Cohort 2 and Cohort 1. Two weeks after the last patient in Cohort 3 receives the second dose, the DMC **and Boston Pharmaceuticals** will conduct a data review for the first interim analysis (IA1)**. At that time, a decision will be made** to **suggest** which dose **should** be carried forward into the POC Phase 2 study. This dose will not exceed doses tested during the MAD study.	Removed erroneous text and added clarity that Boston Pharmaceuticals will review data along with DMC for POC Dose selection.

Section	Description of Changes	Rationale
PROTOCOL SUMMARY, Study Design Section 4.1.2.2, POC Study Design Section 9.1, Sample Size	Add: …**approximately** 156 patients…	Clarification to allow flexibility in exact number enrolled.
PROTOCOL SUMMARY, Study Design	Replace: One oral CS "burst" for increased SLE disease activity may occur during the study either between Weeks 1 and 8 or between Weeks 16 and 20. With: One oral CS "burst" for increased SLE disease activity may occur during the study between **Day 0** and **Day 60**.	Second period for allowed CS "burst" removed as it conflicts with study endpoints.
PROTOCOL SUMMARY, Study Design Section 5.6.1, Oral Corticosteroid Dose	Replace: Tapering may occur after randomization except within 8 weeks of the primary (Week 28) and secondary (Week 16) endpoint assessments. With: Tapering may occur after randomization except within **60 days** of the primary (**Day 210**) and secondary (**Day 120**) endpoint assessments.	Replaced weeks with days to be consistent with protocol.
Section 1.2.3; Study Dose Section	Replace: In addition, the DMC will conduct a data review for the first interim analysis (IA1) to determine which dose will be carried forward into the proof of concept (POC) Phase 2 study. With: In addition, the DMC **and Boston Pharmaceuticals** will conduct a data review for the first interim analysis (IA1)**. At that time, a decision will be made** to **suggest** which dose **should** be carried forward into the proof of concept (POC) Phase 2 study.	Clarification that Boston Pharmaceuticals will review data along with DMC for POC Dose selection.

Section	Description of Changes	Rationale
Section 1.2.4, Risk-Benefit Assessment	Replace: Two weeks after the last patient in Cohort 3 receives the second dose, the DMC will conduct a data review for the IA1 to determine which dose will be carried forward into the POC Phase 2 study. With: Two weeks after the last patient in Cohort 3 receives the second dose, the DMC **and Boston Pharmaceuticals** will conduct a data review for the IA1**. At that time, a decision will be made** to **suggest** which dose **should** be carried forward into the POC Phase 2 study.	Clarification that Boston Pharmaceuticals will review data along with DMC for POC Dose selection.
Section 4.1.1.1; Dose Escalation for the MAD Study	Delete: Similarly, after 8 of the 12 patients in Cohort 2 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 3 begins dosing ~~(based on the dose level determined~~ after DMC evaluation of the safety and tolerability data from Cohorts 1 and 2~~)~~. ~~Two weeks after the last patient in Cohort 3 receives the second dose, the DMC will conduct a data review for the IA1 to determine which dose will be carried forward into the POC Phase 2 study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2, and 3; this dose will not exceed doses tested during the MAD study. The DMC will be reviewing all relevant data from Cohorts 1, 2, and 3 that is available when the last patient in Cohort 3 reaches 60 days (dose 2).~~	Removed, as this information does not fit this section.
Section 4.1.1.1; Dose Escalation for the MAD Study	Replace: If > 3 patients discontinue the study in a cohort, he/she will be replaced. With: If > 3 patients discontinue the study in a cohort, he/she **may** be replaced.	Clarified statement as it is not definitive that these patients would be replaced.
Section 4.1.1.2; Dose Limiting Toxicity (DLT)	Delete: Investigators should always manage their patients according to their medical judgment which may include interruption of study drug based on the particular clinical circumstances. ~~All dose modifications/adjustments must be clearly documented in the patient's source notes and electronic Case Report Form (eCRF).~~	Dose modifications/ adjustments are not allowed in this study.

Section	Description of Changes	Rationale
Section 4.1.1.3; DMC Recommendations	Replace: For the POC study, the DMC will conduct a data review for the IA1 to determine which dose will be carried forward into the POC Phase 2 study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2, and 3; this dose will not exceed doses tested during the MAD study. The DMC will be reviewing all relevant data from Cohorts 1, 2, and 3 that is available when the last patient in Cohort 3 reaches 60 days (dose 2). Details are provided in the DMC Charter. With: For the POC study, the DMC **and Boston Pharmaceuticals** will conduct a data review for the IA1 to **suggest** which dose **should** be carried forward into the POC Phase 2 study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2, and 3; this dose will not exceed doses tested during the MAD study. The DMC will be reviewing all relevant data from Cohorts 1, 2, and 3 that is available **at the time** the last patient in Cohort 3 **completes the Day 44 visit (2 weeks after dose 2)**. Details are provided in the DMC Charter.	Corrected error, data cut for the DMC review will be 2 weeks after dose 2 (Day 44 visit).
Section 4.1.2.1; BOS161721 Dose	Replace: The optimal dose evaluation is chosen based on MAD Phase 1b safety results. The dose will be communicated by a letter to site investigators participating in the POC Phase 2 study, and to the IRB/IEC. Once the POC dose decision has been made, screening for the POC study can begin. With: The optimal dose evaluation is chosen based on MAD Phase 1b safety**, tolerability, immunogenicity, and PK and PD data**. The dose will be communicated by a letter to site investigators participating in the POC Phase 2 study, and to the IRB/IEC.	Updated for consistency with rest of protocol.
Section 4.2, Study Schematic, Figure 2	Change: Study schematic was updated to reflect use of "Days" for dosing as well as a correction to the time point for dose escalation (change from "Day 60" to "Day **44**").	To reflect changes made to protocol body.

Section	Description of Changes	Rationale
Section 4.3, Schedule of Assessments, Table 1, Table 2	Change: Schedule of Assessments was reorganized so that all assessments are categorized as: General, Safety, Efficacy, Laboratory, or PK Labs. Footnotes were relettered accordingly.	Reorganized for better clarity
Section 4.3, Schedule of Assessments, Table 2	Change: Removed columns for Day 7 and Day 44 in POC Schedule of Assessments.	These visits are not applicable in the POC portion of this study.
Section 4.3, Schedule of Assessments, Table 1, Table 2	Change: Added assessments on Days 7 (MAD only), 187, and 195 for concomitant medications, AEs and SAEs, and injection site reactions.	Safety information should be collected even on PK-only visits.
Section 4.3, Schedule of Assessments, Table 1, Table 2 Section 6.1, Screening Section 7.2.1, Laboratory Assessments, Table 3	Delete: FSH ~~and estradiol~~ (postmenopausal women)	Estradiol is removed as FSH is sufficient to determine menopause
Section 4.3, Schedule of Assessments, Table 1, Table 2, footnote g Section 7.2.3, Vital Signs	Add: Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours postdose, as well as on each of the scheduled outpatient days in the table above **(excluding PK-only site visits at Days 7, 187, and 195)**.	Clarification
Section 4.3, Schedule of Assessments, Table 1, Table 2, footnote h	Replace: Clinical laboratory assessments will include a fasting glucose and lipid panel during screening and Week 28. With: Clinical laboratory assessments will include a fasting glucose and lipid panel**, with exception of** screening **(Visit 1) which will be nonfasting**.	Clarification

Section	Description of Changes	Rationale
Section 5.6.1, Oral Corticosteroid Dose	Delete: A maximum of 1 oral CS "burst" for increased SLE disease activity will be allowed during the study ~~either~~ between Day 0 and Day 60 ~~or between Weeks 16 and 20~~, according to the following:	Second period for allowed CS "burst" removed as it conflicts with study endpoints.
Section 5.6.1, Oral Corticosteroid Dose	Delete: • ~~An oral CS "burst" between Week 16 and Week 20 (an increase of ≤20 mg/day prednisone or equivalent), which must be tapered down to a maximum of 10 mg/day within 2 weeks of initiation of the "burst".~~ ○ ~~Alternatively, a single IM dose of methylprednisolone (40 mg or equivalent) is permitted.~~	Second period for allowed CS "burst" removed as it conflicts with study endpoints.
Section 5.6.2, Other Prohibited and/or Restricted Treatments	Replace: Prohibited and/or restricted medications taken prior to study drug administration in the study are described below, and washout requirements are provided in APPENDIX 4. With: Prohibited and/or restricted medications taken prior to study drug administration **and during** the study are described below, and washout requirements are provided in APPENDIX 4.	Clarification – this list includes not only prohibited medication prior to first dose, but also restrictions during the study.
Section 5.8.2, Exception for Non-Responders	Delete: 5.8.2 ~~Exception for Non-Responders~~ ~~Patients will be classified as non-responders if they (1) receive a second rescue medication at any time in the study or (2) take rescue medications between Week 8 and Week 16 or between Week 20 and Week 28 (as described in Section 5.6.1). If a patient has been deemed a non-responder, they will discontinue from treatment and all End of Treatment assessments will be performed. The patient will then enter the safety follow-up period. The use of rescue medications in the case of non-responders is not to be considered a protocol violation (exclusion criteria 8). Protocol violations will be identified based on blinded data prior to unblinding the final analysis dataset.~~	Section deleted. Patients requiring corticosteroid outside of the protocol allowed time should be included in safety analysis and therefore continue in study. Use of corticosteroid excluded from protocol windows would be documented as protocol violations.
Section 6.1, Screening	Delete: Screening will be the same for both the MAD and POC studies. ~~Screening for the POC study cannot begin until the POC dose decision has been made.~~	Screening for POC study can begin while dose decision is being made.

Section	Description of Changes	Rationale
Section 6.1, Screening	Add: • **Chest x-ray** • Laboratory evaluations **(nonfasting)**:	Chest x-ray was added as it was missing from V1.0 list of assessments. "(nonfasting)" was added as clarification.
Section 6.2, Enrollment/Randomization and Day 0 Treatment	Add: • Laboratory evaluations **(fasting)**:	Clarification
Section 6.3, Treatment Period/Follow-Up Visits	Replace: See Section 4.3 for allowable windows for each visit. The following procedures will be performed at every study drug administration visit (Weeks 4, 8, 12, 16, 20, and 24) and follow-up visits during the treatment period (Weeks 2 and 6): With: The following procedures will be performed **as indicated in the Schedule of Assessments (Table 1 and Table 2). See Schedule of Assessment tables for allowable windows for each visit**.	Clarification
Section 6.3, Treatment Period/Follow-Up Visits	Change: Based on change above (ie, cross-reference to Schedule of Assessments), removed timing of assessments from bulleted listed.	Clarification
Section 6.3, Treatment Period/Follow-Up Visits	Replace: • Hematology and chemistry assessments will be performed at Weeks 4 and 6 (Visits 4 and 5) for the MAD study, only, and at Weeks 8, 12, 16, 20, and 24 (Visits 6 through 10) for both studies. With: • **Fasting h**ematology and chemistry assessments	Clarification
Section 6.4, Safety Follow-Up Visits	Add: These visits will include the following **assessments as indicated in the Schedule of Assessments (Table 1 and Table 2)**:	Clarification
Section 6.4, Safety Follow-Up Visits	Change: Based on change above (ie, cross-reference to Schedule of Assessments), removed timing of assessments from bulleted listed.	Clarification

Section	Description of Changes	Rationale
Section 6.4, Safety Follow-Up Visits	Add: • **Fasting c**linical laboratory assessments (hematology and clinical chemistry)	Clarification
Section 7.2.1, Laboratory Assessments	Delete: Laboratory/analyte results that could unblind the study (ie, biomarker results) will not be reported to investigative sites ~~or other blinded personnel until the study has been unblinded~~. Urinalysis will be performed on midstream, clean catch specimens.	Text removed as Boston Pharmaceuticals will be reviewing biomarker data for POC dose selection.
Section 7.2.1, Laboratory Assessments	Add: **Endpoint analyses will be based on changes from baseline assessments at Days 120 and 210.**	Moved from redundant laboratory assessment section that was deleted from protocol.
Section 7.2.1, Laboratory Assessments, Table 3	Add: CCI	Clarification (genotype needed to establish gene signature)
Section 7.2.1.1, Pregnancy testing	Replace: Urine pregnancy tests will also be routinely repeated at study drug administration visits (Visits 2, 4, 6, 7, 8, 9, and 10) prior to study drug administration, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive pregnancy test or confirmed pregnancy, the patient will be withdrawn from study drug but may remain in the study for safety monitoring. With: Urine pregnancy tests will also be routinely repeated at study drug administration visits prior to study drug administration, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive pregnancy test or confirmed pregnancy, the patient will be **discontinued** from study drug**, an EOT visit should be performed (Day 180), and a last follow-up visit 90 days after last dose should be scheduled (Day 270). Safety follow-up visit procedures based on the Schedule of Assessments (see Section 6.4)**.	To clarify how the patient should complete the study. Also removed Visit numbers as beginning of section cross-references Schedule of Assessments.

Section	Description of Changes	Rationale
Section 7.2.4, 12-Lead Electrocardiograms	Replace: ECG will be performed at screening, and Visits 2, 4, and 7, and 13. With: ECG will be **assessed as specified in the Schedule of Assessments (Section 4.3)**.	Clarification
Section 7.2.5, Physical Examination	Replace: The targeted (limited) physical examination will be completed at Visits 3 through 13. With: The targeted (limited) physical examination will be completed at **all other visits as indicated in the Schedule of Assessments (Section 4.3)**.	Clarification
Section 7.2.6, C-SSRS	Replace: The C-SSRS evaluation will be performed at screening, Visit 2 (Day 1) and at Visits 7 and 10 (Weeks 12 and 24, respectively). With: The C-SSRS evaluation will be performed **as specified in the Schedule of Assessments (Section 4.3)**.	Clarification
Section 7.2.7, Injection Site Reactions	Replace: Patients will be monitored for local injection site reactions at dosing administration visits, Visits 2 (Day 1), Visit 4 (Week 4), and Visits 6 through 10 (Weeks 8, 12, 16, 20, and 24). Patients will also be monitored for local injection site reactions at the safety follow-up visits, Visits 11, 12, and 13 (Weeks 28, 32, and 36, respectively). With: Patients will be monitored for local injection site reactions **as specified in the Schedule of Assessments (Section 4.3)**.	Clarification

Section	Description of Changes	Rationale
Section 7.2.8, Immunogenicity	Replace: The serum samples to measure the presence of ADA will be collected as Visits 2, 3, 4, 6, 7, 10, and 13 (Week 0, 2, 4, 8, 12, 24, and 36, respectively). With: The serum samples to measure the presence of ADA will be collected **as specified in the Schedule of Assessments (Section 4.3)**.	Clarification
Section 7.3, Efficacy Assessments	Add: **All efficacy assessments will be performed at times defined in the Schedule of Assessments (Section 4.3).**	Clarification (allows for deletion of visit days from each subsection).
Section 7.3.1, SLEDAI-2K	Delete: ~~The SLEDAI-2K is completed at screening, at Visit 2, Visit 4, and Visits 6 through 13.~~	Removed based on cross-reference to Schedule of Assessments provided in Section 7.3.
Section 7.3.2, BILAG 2004	Delete: ~~The BILAG-2004 is completed at screening, Visit 2, 4, and 6 through 13.~~	Removed based on cross-reference to Schedule of Assessments provided in Section 7.3.
Section 7.3.3, PGA of Disease Activity	Delete: ~~The PGA is completed at screening, Visit 2, 4, and Visits 6 through 13.~~	Removed based on cross-reference to Schedule of Assessments provided in Section 7.3.
Section 7.3.6, ACR-28 Joint Count	Delete: ~~The ACR-28 joint count will be performed at screening, Visit 2, 4, and 6 through 13.~~	Removed based on cross-reference to Schedule of Assessments provided in Section 7.3.

Section	Description of Changes	Rationale
Section 7.3.7, Laboratory Assessments	Delete: ~~7.3.7 Laboratory Assessments~~ ~~Patients will be evaluated for laboratory parameters as specified in the Schedule of Assessments (Section 4.3), including: Fasting glucose and lipid panels, pSTAT3 (predose samples in Phase 2), total IgG & IgM, complement: CCI , Plasma CCI & CCI , whole blood for leukocyte immunophenotype and RNA, CCI , and antibodies: (CCI).~~ ~~Endpoint analyses will be based on changes from baseline assessments at Week 16 and Week 28.~~	Deletion of redundant information already presented in Section 7.2.1.
Section 7.4.2, PROs	Add: The PROs include the CCI and the CCI **and will be assessed as specified in the Schedule of Assessments (Section 4.3)**. Delete: ~~The CCI is completed by patients at screening and Day 1 (Visit 2), Week 4 (Visit 4), Week 8 (Visit 6) through Week 36 (Visit 13).~~ Delete: ~~The CCI is administered at screening, and Day 1 (Visit 2) Week 4 (Visit 4), Week 8 (Visit 6) through Week 36 (Visit 13).~~	Clarification
Section 7.5, Pharmacokinetic Assessments	Delete: PK parameters include the following: • C_{max}, T_{max}, AUC, $t_{½}$, CL, V_d ~~In addition to samples collected at the scheduled times, an additional blood sample should be collected from patients experiencing unexpected AEs and/or SAEs and the date and time documented in the eCRF.~~	This language is not applicable under PK section.
Section 7.6, Pharmacodynamic Assessments	Add: Blood samples for PD parameters (plasma) will be collected at times indicated **in the Schedule of Assessments (Section 4.3)** for each of the following parameters:	Clarification

Section	Description of Changes	Rationale
Section 7.6, Pharmacodynamic Assessments	Change: Based on change above (ie, cross-reference to Schedule of Assessments), removed timing of assessments from bulleted listed.	Clarification
Section 8.5, Prohibited Concomitant Therapy	Add: Prohibited concomitant medications are discussed in Section 5.6 and APPENDIX 4 **and will be listed as protocol violations if taken when not permitted**.	Clarification
Section 9.2.5.2, Data Monitoring Committee	Delete: The DMC will have access to unblinded treatment information during the clinical trial. ~~To prevent inadvertent unblinding of sponsor staff, reports to the DMC will describe each treatment group by a coded identifier rather than actual treatment group assignment.~~ Details regarding management and process of this committee are found in the DMC Charter.	Removed text, exact details will be provided in charter.
Section 9.3, Interim Analysis and Power	Delete: Two IAs are planned for this study. The initial IA will be conducted at the time of the POC decision for dose selection. ~~The DMC will review safety and tolerability, and PK/PD/biomarkers for dose selection. Efficacy data will not be reviewed for dose selection so there should be no impact on the type 1 error.~~	Removed as efficacy data will be reviewed by Boston Pharmaceuticals in order to make informed dose selection decision.
Section 9.3, Interim Analysis and Power	Add: Nominal time profiles will be used for calculating PK parameters in the IA2. **Details will be available in the SAP.**	Clarification
Section 10.2, DMC	Replace: The primary responsibilities of the DMC are to (1) periodically review and evaluate the accumulated study data for participant safety, study conduct, and progress, (2) make recommendations to the sponsor concerning the continuation, modification, or termination of the study and (3) make a dose recommendation for POC portion of the study. With: The primary responsibilities of the DMC are to (1) periodically review and evaluate the accumulated study data for participant safety, study conduct, and progress, (2) make recommendations to the sponsor concerning the continuation, modification, or termination of the study and (3) **suggest** dose for POC portion of the study.	Clarification

Section	Description of Changes	Rationale
Section 10.4, Informed Consent	Replace: Before each patient is enrolled in the clinical study, written informed consent will be obtained from the patient according to the regulatory and legal requirements of the participating country. With: Before each patient **undergoes any protocol required assessments or procedure**, **the** written informed consent will be obtained according to the regulatory and legal requirements of the participating country.	Clarification

BOS161721-02

A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to BOS161721 are the confidential and proprietary information of Boston Pharmaceuticals, Inc., and except as may be required by federal, state, or local laws or regulation, may not be disclosed to others without prior written permission of Boston Pharmaceuticals, Inc.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Council for Harmonisation (ICH) guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Boston Pharmaceuticals, Inc., or specified designees. I will discuss the material with them to ensure that they are fully informed about BOS161721 and the study.

_____ _____

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

PROTOCOL SUMMARY

Title:	A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care
Indication	Adults with moderately to severely active SLE
Background and Rationale	SLE is a chronic systemic autoimmune disease with considerable heterogeneity in clinical manifestations and disease course. There is evidence that B- and T-cells are critical to the development of the disease, and that T-cell-derived cytokines such as interleukin-21 (IL-21) are involved in the SLE-associated inflammatory pathological response. BOS161721 is a humanized immunoglobulin G1 (IgG1) triple mutation monoclonal antibody (mAb) intended to have an extended terminal elimination half-life ($t_{1/2}$) that selectively binds to and neutralizes IL-21, which acts on multiple cell types that drive inflammation and autoimmunity. In vivo, BOS161721 inhibits T-cell dependent antigen responses of B-cells and is being developed as a potential treatment for adults with moderately to severely active SLE. Nonclinical studies have evaluated the toxicity, pharmacodynamics (PD), toxicokinetics (TK), pharmacokinetics (PK), and immunogenicity of BOS161721 administered intravenously (IV) and subcutaneously (SC). The no observed adverse effect levels (NOAELs) in Cynomolgus monkeys were determined to be 100 mg/kg IV and 50 mg/kg SC, the highest doses tested. No SC animals had injection reactions. In a Phase 1 single ascending dose (SAD) study, BOS161721 was administered IV and SC to healthy male and female adult subjects. This double-blind, placebo-controlled study evaluated 8 ascending dose levels (1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg) for safety, tolerability, PK, PD and immunogenicity. Overall, there were no clinically significant safety or tolerability findings from this study, following an interim cut and review of the data at Day 90 postdose. Results from the Phase 1 SAD study informed the dose regimens used for the multiple ascending doses (MAD) Phase 1b study in this trial. The MAD study will involve 3 cohorts. The Phase 2 portion will be a proof of concept (POC) study, where dose selection will be based on the sponsor's assessment of safety, tolerability,

immunogenicity, and PK and PD data from the MAD study of 30 patients treated with BOS161721/placebo. The purpose of the study is to establish safe and effective dosages for adult patients with moderately to severely active SLE.

Objectives:

MAD Phase 1b Study

Primary Objective:

To assess safety, tolerability, and immunogenicity of repeat doses of BOS161721 (20 mg, 60 mg, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment, in order to estimate the optimal dose.

POC Phase 2 Study

Primary Objective:

To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on the SLE Responder Index 4 (SRI-4), with sustained reduction of oral corticosteroids (CS), in adult patients with moderately to severely active SLE on limited background standard of care treatment.

Secondary Objectives:

To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on clinical indicators of SLE activity, in adult patients with moderately to severely active SLE on limited background standard of care treatment, including:

- Changes in SLE-specific autoantibody titers
- Changes in complement 3 and 4 (C3 and C4) levels
- Responses on SRI-4, SLE Responder Index 5 and 6 (SRI-5, and SRI-6), with sustained reduction of oral CS
- Response on the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA)
- Response on the Cutaneous Lupus Erythematosus Area and Severity Index (CLASI)
- Changes in the SLE Disease Activity Index 2000 (SLEDAI-2K)
- Changes in the American College of Rheumatology (ACR)-28 joint count

Endpoints:

Phase 1b MAD Study

Primary Endpoints:

Evaluation of safety, tolerability, and immunogenicity at each dose level, to determine the optimal dose, will include the recording of the following parameters:

- Incidence and severity of adverse events (AEs) and serious adverse events (SAEs)
- 12-lead electrocardiograms (ECGs)
- Vital signs (blood pressure [BP], heart rate, and temperature)
- Clinical laboratory assessments
- Physical examinations
- Evaluation for anti-drug antibodies (ADAs)

Exploratory Endpoints:

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

Other Endpoints:

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

PRO Endpoints:

- CCI [redacted]
- CCI [redacted]

Phase 2 POC Study

Primary Efficacy Endpoint:

The primary efficacy endpoint is the proportion of patients who achieve treatment response as measured by the SRI-4 at Day 210, along with a sustained reduction of oral CS (≤ 10 mg/day and ≤ Day 0 dose) between Day 120 and Day 210.

Secondary Efficacy Endpoints:

- The proportion of patients who achieve treatment response for the SRI-5 and SRI-6 at Day 210, along with a sustained reduction of oral CS (≤ 10 mg/day and ≤ Day 0 dose) between Day 120 and Day 210
- Changes from baseline in dsDNA, ANA, SSA, SSB, RNP, Sm, APL autoantibodies, at Day 120 and Day 210
- Changes from baseline in C3 and C4 levels at Day 120 and Day 210
- Changes from baseline in the SLEDAI-2K at Day 210
- Time to BILAG A or B flare
- Changes from baseline in the CLASI at Day 210
- The proportion of patients with a BICLA response at Day 210
- The proportion of patients with CLASI response at Day 210

- Changes from baseline (percentage) in swollen joints and tender joints ACR-28 joint count
- Assessment of safety, tolerability, and immunogenicity as described for the primary endpoint in the MAD Phase 1b study

Exploratory Endpoints:

- CCI [redacted]
- CCI [redacted]

Other Endpoints:

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

PRO Endpoints:

- CCI [redacted]
- CCI [redacted]

Study Design:

This is a Phase 1b/2 combined, randomized, multicenter, double-blind, placebo-controlled trial to study the clinical efficacy, safety, and PK of multiple SC doses of BOS161721 in adult patients with moderately to severely active SLE. After successfully completing a screening phase, patients will be randomized to a specified dose of BOS161721 or placebo. The dosing schedule will be monthly. The trial will consist of a staggered MAD Phase 1b and POC Phase 2 studies. Both studies will be double-blinded with each patient having the same number of doses (7), and visits; the duration will be 180 days, followed by a 90-day follow-up safety observation period.

The MAD Phase 1b study phase will consist of 3 cohorts, with Cohort 1 containing 6 patients, where 5 of these patients will receive BOS161721 (active), and 1 will receive placebo. Cohorts 2 and 3 will each contain 12 patients, including 9 active and 3 placebo

patients. Dose selection for each cohort is based on 90-day safety, tolerability, PK, and PD data review from the Phase 1 SAD study (BOS161721-01) in healthy subjects. Each of the 3 doses (20 mg, 60 mg, and 120 mg) selected for the MAD study are projected not to exceed the mean exposure of that achieved in the SAD study following the single 240 mg SC dose. Each patient may receive a total of 7 SC monthly doses on Days 0, 30, 60, 90, 120, 150, and 180.

The MAD study design is staggered, where after the 6 patients in Cohort 1 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 2 begins dosing (after a data monitoring committee [DMC] evaluates the safety and tolerability data from Cohort 1). Similarly, after 8 of the 12 patients in Cohort 2 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 3 begins dosing after DMC evaluation of the safety and tolerability data from Cohort 2 and Cohort 1. Two weeks after the last patient in Cohort 3 receives the second dose, the DMC and Boston Pharmaceuticals will conduct a data review for the first interim analysis (IA1). At that time, a decision will be made to suggest which dose should be carried forward into the POC Phase 2 study. This dose will not exceed doses tested during the MAD study.

For the POC study, approximately 156 patients will be randomized to active or placebo groups in a 2:1 ratio. As in the MAD study, each patient in the POC study may receive a total of 7 SC monthly doses on Days 0, 30, 60, 90, 120, 150, and 180. A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). One oral CS “burst” for increased SLE disease activity may occur during the study between Day 0 and Day 60. Tapering of steroids during the course of the study will be encouraged and should be evaluated at all visits. Tapering may occur after randomization except within 60 days of the primary (Day 210) and secondary (Day 120) endpoint assessments. Between Day 60 and Day 120, and between Day 150 and Day 210, oral CS doses must be held constant otherwise the patient will be declared a non-responder in efficacy assessments.

Data from 60 patients, including the 12 from the MAD study, or 6 fewer if the low dose is chosen, who are in the cohort of the chosen dose for the POC study who complete 3 months of treatment will be used in a second IA (IA2) at Day 90 to assess if the trial could stop for an early futility conclusion. If futility is not claimed in the IA2, the POC study will continue to approximately 156 patients.

Following the 6-month treatment period, primary and secondary efficacy endpoints will be assessed for each patient, after providing their Day 180 disease activity assessments. DMC monitoring will be conducted periodically throughout the study as described in the DMC charter.

Main Criteria for Inclusion and Exclusion

Inclusion Criteria:

1. Men and women, ages 18 to 70 years, inclusive

2. Patients must be mentally capable of giving consent and there must be evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study

3. Patients must have SLE as defined by meeting 4 of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE (with at least 1 clinical and 1 immunologic criterion OR Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies), either sequentially or simultaneously

4. At screening, patients must have at least 1 of the following:

    a. Elevated ANA ≥ 1:80 via immunofluorescent assay at the central laboratory

    b. Positive anti-dsDNA or anti-Sm above the normal level as determined by the central laboratory

    c. C3 or C4 below normal as determined by the central lab

5. At screening, the SLEDAI-2K must be ≥ 6, including points from at least 1 of the following clinical components:

    a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis

        i. Excluding parameters which require central laboratory results: (hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia)

        ii. Points from lupus headache and organic brain syndrome will also be excluded

6. On Day 0, the SLEDAI-2K must be ≥ 6, including points from at

least 1 of the following clinical components:

a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis

i. Excluding parameters which require central laboratory results: hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia and leukopenia

ii. Points from lupus headache and organic brain syndrome are also excluded

7. Patients must have at least 1 of the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer:

a. BILAG A or B score in the mucocutaneous body system

b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis as defined in the protocol Section 5.4

c. If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in the other body systems for a total of 2 "B" BILAG body system scores

8. Patients must be currently receiving at least 1 of the following:

a. Administration for a minimum of 12 weeks, and a stable dose for at least 56 days (8 weeks prior to signing consent) of the following permitted steroid-sparing agents:

i. Azathioprine (AZA), mycophenolate mofetil or mycophenolic acid, chloroquine, hydroxychloroquine, or methotrexate (MTX)

b. Prednisone (or prednisone-equivalent) cannot exceed 30 mg/day at screening for a patient to be eligible and must be stable at a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization)

9. Women of childbearing potential (WOCBP; see Section 5.7 for full information regarding WOCBP, definition of menopause, and contraception):

a. Must have a negative serum pregnancy test at screening.

Urine pregnancy test must be negative prior to first dose

b. Must not be breastfeeding

c. Must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS1617219 plus 30 days (duration of ovulatory cycle) for a total of 36 weeks after treatment completion

10. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of BOS161721 plus 90 days (duration of sperm turnover) for a total of 44 weeks after treatment completion

11. Patients must demonstrate willingness and ability to comply with the scheduled study visits, treatment plans, laboratory tests, and other procedures

Exclusion Criteria

Patients presenting with any of the following will not be included in this study:

1. Drug-induced SLE, rather than "idiopathic" SLE
2. Other systemic autoimmune disease (eg, erosive arthritis, rheumatoid arthritis [RA], multiple sclerosis [MS], systemic scleroderma, or vasculitis not related to SLE)
   a. RA-Lupus overlap (Rupus), and secondary Sjögren syndrome are allowed
3. Any major surgery within 6 weeks of study drug administration, (Day 0), or any elective surgery planned during the course of the study
4. Any history or risk for tuberculosis (TB), specifically those with:
   a. Current clinical, radiographic, or laboratory evidence of active TB
   b. History of active TB
   c. Latent TB defined as positive QuantiFERON-TB Gold In-Tube (QFT-G) or other diagnostic test in the absence of clinical manifestations. Latent TB is not excluded if the patient has documented completion of adequate course of prophylactic treatment with regimen recommended by local health authority guideline, or the patient has started treatment

with isoniazid, or other regimen recommended by local health authority guidelines for at least 1 month before Day 0 and continues to receive the prophylactic treatment during study until the treatment course is completed

5. Active or unstable lupus neuropsychiatric manifestations, including but not limited to any condition defined by BILAG A criteria, with the exception of mononeuritis multiplex and polyneuropathy, which are allowed
6. Severe proliferative lupus nephritis, (WHO Class III, IV), which requires or may require induction treatment with cytotoxic agents or high dose CS
7. Concomitant illness that, in the opinion of the investigator, is likely to require additional systemic glucocorticosteroid therapy during the study, (eg, asthma), is exclusionary
    a. However, treatment for asthma with inhalational CS therapy is allowed
8. Use or planned use of concomitant medication outside of standard of baseline treatment for SLE from Day -1 or for any time during the study
9. Active and clinically significant infection (bacterial, fungal, viral, or other) within 60 days prior to first dose of study drug. Clinically significant is defined as requiring systemic antibiotics or hospitalization
10. A history of opportunistic infection, or a history of recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years
11. Chronic viral hepatitis including hepatitis B (HBV) and hepatitis C (HCV), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness
12. Cryptosporidium in the stool sample at screening
13. White blood cells (WBC) < 1,200/mm^3 (1.2×10^9/L) at screening
14. Absolute neutrophil count (ANC) < 500/mm^3 at screening
15. CD4+ count < 500/µL at screening
16. Platelets < 50,000/mm^3 (50×10^9/L) or < 35,000/ mm^3 (35×10^9/L) if related to SLE, at screening
17. Hemoglobin < 8 g/dL or < 7 g/dL at screening if due to anemia related to SLE
18. Proteinuria > 3.0 g/day (3000 mg/day) at screening or equivalent level of proteinuria as assessed by protein/creatinine ratio

(3 mg/mg or 339 mg/mmol)

19. Serum creatinine > 2.0 mg/dL at screening or creatinine clearance (CrCL) < 40 ml/minute based on Cockcroft-Gault calculation
20. Serum alanine aminotransferase (ALT) and/or serum aspartate aminotransferase (AST) > 2 × the upper limit of normal (ULN) at screening, unless explicitly related to lupus based on the investigator's judgment
21. Creatinine kinase (CK) > 3.0 × ULN at screening unless related to lupus myositis
22. Direct bilirubin > 1.5 × ULN at screening (unless related to Gilbert's syndrome)
23. Any other laboratory test results that, in the opinion of the Investigator, might place a patient at unacceptable risk for participating in this study
24. History of allergic or anaphylactic reaction to any therapeutic or diagnostic mAb (eg, IgG protein) or molecules made of components of mAbs
25. History substance and/or alcohol abuse, or dependence within the past 1 year, at the investigator's judgment
26. History of cancer within the last 5 years (except for cutaneous basal cell or squamous cell cancer, or cervical cancer in situ resolved by excision
27. Any other severe acute or chronic medical or psychiatric condition, including recent (within the past year) medical conditions (eg, cardiovascular conditions, respiratory illnesses) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study
28. Investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or patients who are employees of the sponsor or directly involved in the conduct of the trial
29. Currently participating in, or who have participated in other interventional (drug or device) clinical study within 30 days or 5 half-lives of baseline, whichever is longer
30. Recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4, or 5

on the Columbia Suicide severity Rating Scale (C-SSRS)

31. Current or pending incarceration
32. Current or pending compulsory detainment for treatment of either a psychiatric or physical (eg, infectious disease) illness

Statistical Considerations

Below is a summary of the statistical methods. Further details can be found in Section 9.

Baseline and patient characteristics will be summarized via appropriate summary statistics by treatment group and overall, for each phase of the trial.

Binary efficacy endpoints will be compared between treatments via Cochran-Mantel-Haenszel (CMH) analysis. Continuous efficacy endpoints will be assessed via analysis of covariance (ANCOVA) repeated measures mixed model analysis with factors including treatment, time, treatment-by-time interaction, baseline covariate, and covariate-by-time interaction. Summary statistics will be provided by dose/treatment for all safety endpoints. Details will be provided in the statistical analysis plan (SAP).

Two IAs are planned for this study. The initial IA (IA1) will be conducted at the time of the POC decision for dose selection. The second IA (IA2) will be performed for futility. IA2 is planned to be conducted when SRI-4 response is determined for approximately 60 patients (including all patients at the same dose level/matching placebo from the MAD study) after completing 3 months of treatment. The purpose of IA2 is to assess if the trial could stop for an early futility conclusion, or continue. Since there is no plan to stop the trial for an early efficacy conclusion, there is no impact on the type 1 error level.

AEs will be summarized by counts and percentages of patients by treatment group. Laboratory data and vital signs will be summarized by treatment group as summary statistics for value and change from baseline at each individual time point. Summary statistics will include n, arithmetic mean, median, arithmetic SD, minimum, and maximum.

The PK parameter data will be listed and summarized descriptively in tabular format. Binary PD endpoints will be assessed for the full analysis set (FAS) population via CMH analysis. Continuous PD endpoints will be assessed via ANCOVA repeated measures mixed model analysis with multiple factors. PK and PD relationships will be explored graphically and where appropriate model based methods of analysis will used.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADA	anti-drug antibody
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANC	absolute neutrophil count
APL	antiphospholipid
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AZA	azathioprine
BICLA	BILAG-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BP	blood pressure
BUN	blood urea nitrogen
BW	body weight
C	complement
C-SSRS	Columbia Suicide Severity Rating Scale
CD	cluster of differentiation
CK	creatine kinase
C_L	systematic clearance
CLASI	Cutaneous Lupus Erythematosus Area and Severity Index
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CS	corticosteroids
CSR	clinical study report
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
dsDNA	double-stranded deoxyribonucleic acid
ECG	electrocardiogram
EOT	end of treatment
eCRF	electronic case report form
F	female
Fc	fragment crystallizable
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
eGFR	estimated glomerular filtration rate

GLP	Good Laboratory Practice
GWAS	genome-wide association studies
γc	gamma chain
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCl	hydrochloride
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IL	interleukin
IL-21R	interleukin 21 receptor
IM	intramuscular
INFγ	interferon gamma
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
IVRS	interactive voice response system
JAK	Janus kinase
kg	kilogram
KLH	keyhole limpet hemocyanin
LOCF	last observation carried forward
M	male
mAb	monoclonal antibody
MAD	multiple ascending dose
MAPK	mitogen-activated protein kinase
MS	multiple sclerosis
MTX	methotrexate
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIAID/FAAN	National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network
NK	natural killer
NOAEL	no observed adverse event level
NO	nitric oxide

OTC	over-the-counter
PD	pharmacodynamics
PEF	peak expiratory flow
PGA	Physician's Global Assessment
PK	pharmacokinetics
POC	proof of concept
PR	(interval) from onset of the p-wave to the end of the r-wave
pSS	primary Sjögren's syndrome
pSTAT3	phosphorylated signal transducer and activator of transcription 3
PT	preferred term
QRS	(interval) from the onset of the q-wave to the end of the s-wave
QT	(interval) from onset of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
QFT-G	QuantiFERON-TB Gold In-Tube
RA	rheumatoid arthritis
RNP	ribonucleoprotein
RR	(interval) from the onset of the r-wave to the onset of the next consecutive r-wave
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SDMT	safety data monitoring board
CCI	[redacted]
SLE	systemic lupus erythematosus
SLEDAI-2K	SLE Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
Sm	Smith
SOC	system organ class
SRI-4	SLE Responder Index 4
SRI-5	SLE Responder Index 5
SRI-6	SLE Responder Index 6
SSA	Sjögren syndrome-A (Ro)
SSB	Sjögren syndrome-B (La)
STAT3	signal transducer and activator of transcription 3
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
TB	tuberculosis
TDAR	T-cell dependent antibody response
Tfh	T-follicular helper
Th	T-helper
TK	toxicokinetics

T_{max}	first time to maximum concentration
Treg	regulatory T-cell
TT	tetanus toxoid
ULN	upper limit of normal
US	United States
Vd	volume of distribution
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
YTE	triple mutation

1 INTRODUCTION AND RATIONALE

1.1 Indication

BOS161721 is a humanized monoclonal antibody (mAb), which binds to and inhibits interleukin-21 (IL-21) bioactivity, and is being developed for the treatment of moderately to severely active systemic lupus erythematosus (SLE) in adults.

1.2 Background and Rationale

1.2.1 Overview of the Disease State

SLE is a chronic inflammatory autoimmune disease that has variable manifestations in multiple organ systems and follows a relapsing and remitting course. The disease process includes abnormal immune responses mediated by tissue-binding autoantibodies and immune complex deposition, giving rise to tissue damage often resulting in end organ disease and even mortality. Survival of SLE has improved due to earlier detection, improved overall medical care, and standardized SLE treatment with corticosteroids, immunosuppressants, and cytotoxic agents.[1] However, some of the morbidity in patients with SLE is related to its treatment. Comparison of early and late outcomes in patients with SLE demonstrate that death in early disease is most commonly due to infections and active SLE causing multi-system organ damage, while thromboses were the most common cause of death during later disease.[2]

The reported prevalence of SLE in the United States (US) is 20 to 70 cases per 100,000 people.[3] More than 90% of cases of SLE occur in women, frequently starting at childbearing age. Women of color are disproportionately affected by SLE. This suggests multiple genetic and environmental factors are at play. Accordingly, a multifactorial view of the immunopathogenesis of SLE suggests more than 1 area of interest, including breach in central tolerance in the adaptive arm of the immune system, peripheral amplification of the autoimmune response by the innate immune system, and local processes in the target organ that facilitate end-organ disease.[4]

1.2.2 BOS161721 Development

Boston Pharmaceuticals is developing BOS161721 for the treatment of SLE. BOS161721 is a humanized immunoglobulin G1 (IgG1) mAb directed against human IL-21.

Murine mAb 19E3, the progenitor of BOS161721, was generated using mouse hybridoma technology. 19E3 has subpicomolar (pM) affinity to human IL-21 and was selected for its potent neutralization of IL-21 bioactivity. BOS161721 was generated by the humanization of mAb 19E3 where its complementarity-determining regions were grafted onto a human IgG1 kappa backbone. The fragment crystallizable (Fc) portion of BOS161721 contains a YTE (M252Y/S254T/T256E triple mutation) in the constant domain of the IgG1 heavy chain that was introduced into the parental molecule, 19E3, intended to prolong the in vivo terminal elimination half-life ($t_{1/2}$) of the mAb.[5] Thus, BOS161721 retains sub-pM binding to IL-21 and prevents IL-21 from binding to the IL-21 receptor (IL-21R), inhibiting IL-21 bioactivity.

BOS161721 binds to human IL-21 and Cynomolgus monkey IL-21, which are highly homologous, and neutralizes the bioactivity of both. BOS161721 is specific for IL-21 as it does not bind to or inhibit the other gamma-chain (γc) family of cytokines, and acts to specifically neutralize the IL-21 pathway. In *in vitro* studies, BOS161721 inhibited downstream IL-21-induced signaling, IL-21-induced plasma cell differentiation, and IL-21-induced natural killer (NK) cell activation. In *in vivo* studies, BOS161721 significantly inhibited the T-cell dependent antibody response (TDAR) to immunization with a protein antigen as well as B-cell expansion following a second protein antigen immunization in Cynomolgus monkeys.

1.2.2.1 Interleukin-21

IL-21 is an inflammatory cytokine, which belongs to a family of cytokines that also includes IL-2, IL-4, IL-7, IL-9, and IL-15, all of which bind to private receptors in complex with the common cytokine receptor γc.[6] Most cytokines in this family are critically important for both the maintenance and function of T-cell and B-cell responses. IL-21 signals through a receptor complex consisting of its own private receptor, the IL-21R and γc.[6,7] Engagement of the IL-21R/γc complex leads to the activation of several signaling pathways, including the Janus kinase/signal transducer and activator of transcription, mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase pathways.[8] IL-21 is produced mainly by T-cells and NK T-cells, but neutrophils have also been reported to produce IL-21.[9,10] The IL-21R is expressed on a broad array of cell types, including B-cells, T-cells, NK-cells, macrophages and dendritic cells, as well as other hematopoietic and nonhematopoietic cells such as fibroblasts, keratinocytes, and intestinal epithelial cells.[9,11] Activation of signal transducer and activator of transcription 3 (STAT3) via phosphorylation is critical in regulating human B-cell responses to IL-21[12]; phosphorylated STAT3 (pSTAT3) forms a homodimer, which translocates to the nucleus where it initiates transcription of the IL-21 gene, forming an autocrine loop for IL-21 production via STAT3 phosphorylation.[13] In addition, IL-21 has been shown to upregulate expression of its own receptor[14] and induces an autocrine feedback loop.[15]

IL-21 modulates various aspects of immune function. It promotes cluster of differentiation 4 (CD4+) T-cell differentiation and promotes the generation of T-helper (Th)17[16] and T-follicular helper (Tfh) cells.[15,17] In mice, IL-21 has been shown to regulate the balance between Th17 and regulatory T-cell (Treg), in that it increases Th17, while inhibiting Treg differentiation.[18] Less is understood with regards to human Tregs, although IL-21 has been reported to counteract Treg suppression of human effector T-cells[19] and blockade of IL-21 promotes Treg generation in a murine model of graft versus host disease induced by human T-cells.[20] IL-21 upregulates CD8+ T-cell and NK-cell expansion and cytolytic activity by increasing granzyme B and perforin.[21,22] IL-21 also has been reported to increase granzyme B in plasmacytoid dendritic cells and B-cells resulting in inhibition of T-cell responses.[23,24] IL-21 also has a variety of effects on nonhematopoietic cells, such as stromal cells and induces inflammation through matrix metalloproteinase release by gut intestinal fibroblasts.[25]

One principal non-redundant role of IL-21 is the promotion of B-cell activation, differentiation, or death during humoral immune responses.[14] Furthermore, increased IL-21 production is characteristic of several autoimmune diseases and is likely to contribute to autoantibody production as well as pathologic features of autoimmune disease.[26] The critical role of IL-21 in promoting humoral and other immune responses makes it an important focus of potential

therapeutic interventions in conditions characterized by overproduction of pathogenic autoantibodies. IL-21 production by Tfh cells in humans is believed to play a major role in driving the autoantibody production through its role in plasma cell differentiation. Importantly, Tfh cell populations are expanded in patients with autoimmune diseases such as lupus, bullous pemphigoid, rheumatoid arthritis (RA) and primary Sjögren's syndrome (pSS) and have been reported to correlate with IL-21 levels, autoantibodies, and disease severity.[26,27,28,29] Furthermore, loss of number and functionality of Tregs has been associated with autoimmune diseases such as SLE and giant cell arteritis, which IL-21 is expected to modulate.[30,31] Thus, neutralization of IL-21 in settings of autoimmunity is expected to impact several cell populations believed to be involved in the pathogenesis of autoimmune disorders including SLE.

BOS161721 selectively binds IL-21 with high affinity to neutralize IL-21, and due to its pleiotropic nature, neutralization of IL-21 is expected to impact several cell populations believed to be involved in the pathogenesis of SLE. Importantly, patients with SLE have elevated IL-21 plasma levels that correlate with the severity of the disease. Recently, genome-wide association studies (GWAS) have provided convincing evidence that the chromosomal 4q 27 region harbors the IL-21 genes and is associated with chronic inflammatory disorders, including SLE.[29]

1.2.2.2 Preclinical Studies

The pharmacokinetics (PK) of BOS161721 were characterized following single-dose intravenous (IV) administration of BOS161721 (0.01 to 30 mg/kg) in male Cynomolgus monkeys or repeat, every 2 weeks IV administration (15 to 100 mg/kg) and subcutaneous (SC) administration (50 mg/kg) in male and female Cynomolgus monkeys. Systemic exposure was approximately dose-proportional within the tested dose range. SC bioavailability was determined to be 64.3%. CCI [redacted]

Two single-dose (IV) non-good laboratory practice (GLP) studies conducted in Cynomolgus monkeys evaluated the toxicity, pharmacodynamics (PD), toxicokinetics (TK), and immunogenicity of BOS161721. Following a single IV administration (slow bolus), there were no BOS161721-related adverse changes, resulting in a no-observed-adverse-effect-level (NOAEL) value of 30 mg/kg, the highest dose tested among 2 studies. CCI [redacted]

In a repeat-dose GLP toxicology study in Cynomolgus monkeys, BOS161721 was administered every 2 weeks by IV or SC (50 mg/kg) administration for 3 months (a total of 7 doses). CCI [redacted]

CCI [redacted] The NOAELs were determined to be 100 mg/kg IV and 50 mg/kg SC, the highest doses tested.

1.2.2.3 Clinical Studies

BOS161721-01 was a double-blind, Phase 1, single ascending dose (SAD) study to assess the safety, PK, and PD of BOS161721 in healthy subjects. The primary objective of the study was to characterize the safety and tolerability of IV and SC SADs of BOS161721 in an otherwise healthy subject population without concomitant illnesses, immune abnormalities, or concomitant medications. Secondary objectives included characterization of the PK and immunogenicity of BOS161721, and exploratory objectives included the evaluation of the effect of BOS161721 on TDAR to keyhole limpet hemocyanin (KLH) (primary and secondary immunizations) in healthy subjects, the effects of BOS161721 on plasma levels of IL-21 (free and bound), and the evaluation of the effect of BOS161721 on IL-21 gene expression (via gene signature) in blood. This study consisted of 8 cohorts. Subjects were randomized in a 3:1 ratio (BOS161721: placebo) and received either a single dose of BOS161721 (1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg) or placebo, with safety follow-up. For the first cohort, after the first 2 subjects were dosed (1 active and 1 placebo), there was a minimum gap of 48 hours before the remaining subjects from that cohort were dosed, to allow for an initial review of any emerging safety and tolerability data. For all cohorts, escalation to the next dose was not sooner than 8 days after all the subjects in the prior cohort had been dosed and were based on a review of at least 7 days of safety and tolerability data by the Safety Data Monitoring Team (SDMT).

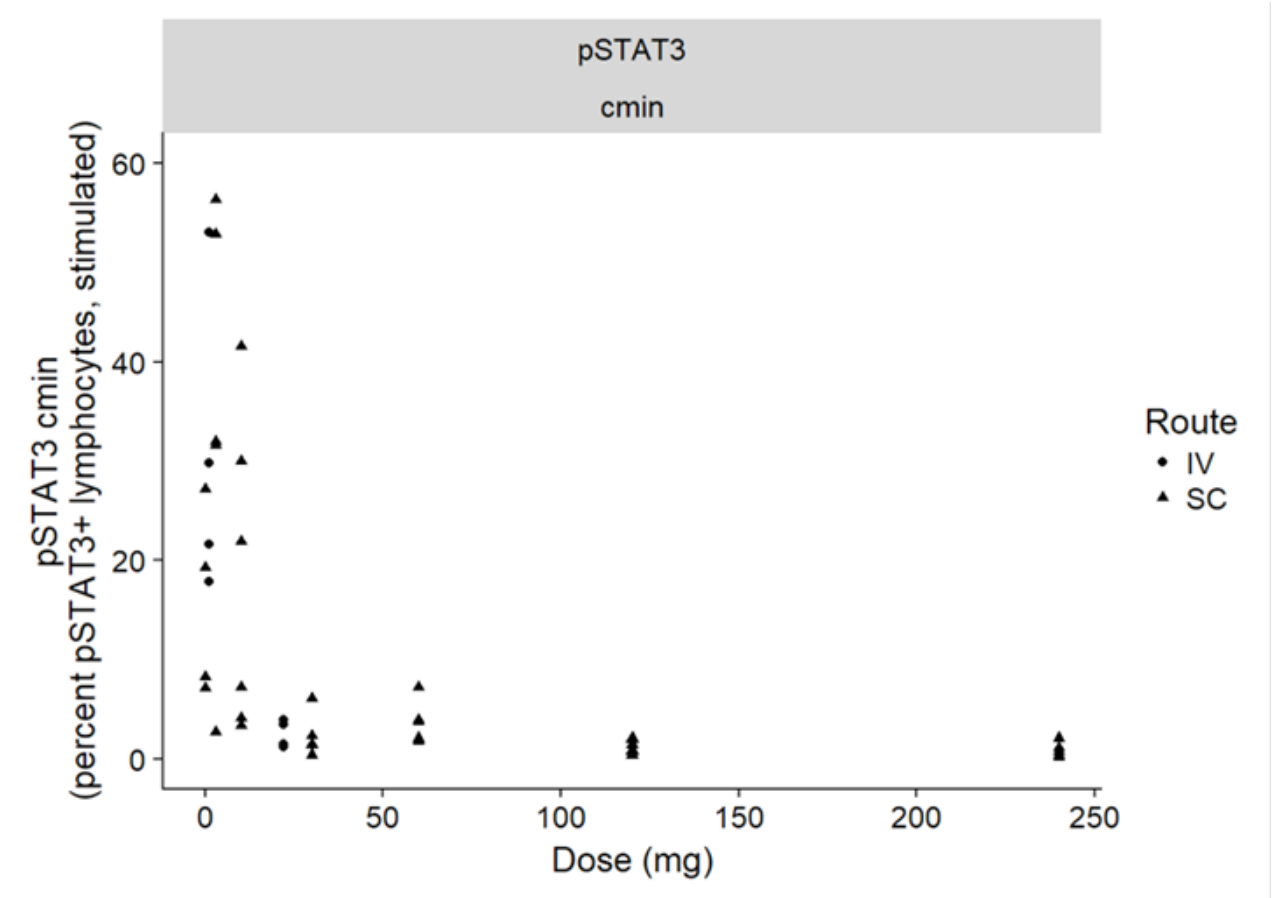
Blood samples were collected at every in-house study visit for BOS161721 concentration determinations. Blood samples were also collected for determination of IL-21 plasma levels (free and total). Safety was assessed based on the occurrence of treatment-emergent AEs, hepatic function abnormality, and acute and delayed hypersensitivity reactions. Other safety variables included electrocardiograms (ECGs), vital signs (blood pressure, heart rate, and temperature), safety laboratory assessments, blood sampling for ADAs, total IgG and IgM levels, CD4+ count, and full and targeted physical examinations. Overall, there were no clinically significant findings from this study, following an interim cut and review of the data at Day 90 postdose. Adverse events reported as related to the study drug, particularly infections, were expected for the compound, and there were no clinically relevant changes in laboratory and ECG results or vital signs. There was 1 serious adverse event (SAE; death due to pulmonary embolism) that occurred 127 days after a single administration of 240 mg SC dose of BOS161721. The causality of this single SAE was not attributed to study drug and further information can be found in the Investigator's Brochure. PK data from the SAD study demonstrates BOS161721 has an extended $t_{1/2}$ (provisional single dose data indicates this to be approximately 42-46 days) which supports evaluation of monthly dosing.

1.2.3 Study Dose Selection

Doses have been selected for the multiple ascending dose (MAD) Phase 1 study based on a 90-day safety, tolerability, PK, and PD data review from the Phase 1 SAD study (BOS161721-01); the SDMT reviewed the blinded safety data from subjects for each dose cohort (8 cohorts, evaluating 1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg), along with the accumulated safety and available PK/PD data from all subjects in the previous dose cohorts, to make a decision on whether to proceed to the next higher dose level, repeat a dose level, or stop dose escalation. Overall, there were no clinically significant safety or tolerability findings from this study.

Based on the Day-90 interim cut of the PK and biomarker data in the BOS161721-01 study, the recommended doses for evaluation in the MAD phase of this study are 20, 60, and 120 mg SC monthly. This dose recommendation is supported by evidence of linear PK with BOS161721 resulting in a median T_{max} of 6 days and an apparent terminal half-life of 44 days. Furthermore, pSTAT3 suppression, a marker of IL-21 target engagement, follows a similar time course of the mAb levels, with maximal and sustained suppression apparent with doses greater than 30 mg SC (Figure 1).

Figure 1. Individual pSTAT3 C_{min} Levels Versus Dose



IV = intravenous, pSTAT3 = phosphorylated signal transducer and activator of transcription 3; SC = subcutaneous

All doses selected for the MAD study are projected not to exceed the mean exposure of that achieved following the highest single dose of 240 mg SC administered in the Phase 1 SAD study. Cohort 1 will include randomized treatment to the 20 mg dose. Based on the staggered study design, the data monitoring committee (DMC) will perform a scheduled review of safety data and sequentially consider dose escalation for Cohorts 2 and 3. In addition, the DMC and Boston Pharmaceuticals will conduct a data review for the first interim analysis (IA1). At that time, a decision will be made to suggest which dose should be carried forward into the proof of concept (POC) Phase 2 study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2 and 3 from the MAD study (see Section 4.1.1.1).

1.2.4 Risk-Benefit Assessment

The available preclinical data on BOS161721, the findings in clinical study BOS161721-01, and existing clinical information on IL-21 inhibitors suggest that the present clinical study has an acceptable risk-benefit ratio. In this study, the risk-benefit assessment of BOS161721 in adult patients with moderately to severely active SLE will be ongoing, with step-wise evaluations during the staggered MAD study. The DMC used in this study is charged with assessing such actions in light of an acceptable benefit-risk profile for BOS161721 as an anti-IL-21 mAb. Formal DMC monitoring meetings will occur as described in the DMC Charter. Two weeks after Cohort 1 has received a second dose of study drug, the DMC will evaluate the safety and tolerability data from Cohort 1 to determine the recommended dose for Cohort 2. Two weeks after 8 patients in Cohort 2 receive a second dose, the DMC will determine if dose escalation to Cohort 3 can proceed. Two weeks after the last patient in Cohort 3 receives the second dose, the DMC and Boston Pharmaceuticals will conduct a data review for the IA1. At that time, a decision will be made to suggest which dose should be carried forward into the POC Phase 2 study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2 and 3 during the MAD study. Thereafter, DMC monitoring will be conducted periodically throughout the study as described in the DMC charter. With the agreement of the DMC and sponsor, this schedule may be modified depending on the rate of patient accrual. Additional details can be found in the DMC Charter.

The benefit of participation for all patients in this study is close monitoring of their medical condition and safety of their treatment. Those randomized to the active treatment arm may potentially experience improvement in their SLE disease. Those randomized to the placebo (in combination with standard of care) arm are not expected to obtain any additional benefit, beyond those of their background treatment, though close monitoring of their medical condition and safety may itself be associated with improving their SLE.

1.2.5 Potential Risks

Potential risks based on the mechanism of action of BOS161721 include infections, risks associated with the administration of any foreign protein or biologic agent, including injection site reaction, anaphylaxis, serious allergic reaction, and development of ADAs. ADAs could result in immune complex disease (with manifestations such as arthralgias, serum-sickness, and vasculitis), autoimmunity, or altered BOS161721 levels or activity. Further details can be found

in the current Investigator's Brochure (IB) for BOS161721, which contains comprehensive toxicology, preclinical and clinical information on BOS161721.

Two investigational drug products are considered to be in the same pharmacological class as BOS161721 based on interruption of signaling through the IL-21 signaling pathway. No potential risk generalizable across the class has been observed with these investigational products. Based on the clinical Phase 1 SAD study (BOS161721-01), AEs reported as related to the study drug, particularly infections (flu-like symptoms, etc), were expected for the compound, and there were no clinically relevant changes in laboratory and ECG results or vital signs.

The majority of IgG elimination occurs via intracellular catabolism, following fluid-phase or receptor-mediated endocytosis. This type of endocytosis and elimination is a form of target-mediated disposition where the interaction of the drug and its pharmacological target (eg, a target receptor) serves as a significant contributor to the kinetics of antibody distribution and elimination. Renal elimination, which is a primary pathway of clearance of small-molecule drugs, is relatively unimportant for IgG, as its large size prevents efficient filtration through the glomerulus. Secretion into the bile is an important pathway of elimination of IgA antibodies, but this route is not a significant contributor to the elimination of IgG antibodies. Thus, risk to renal and hepatic systems due to metabolism of BOS161721 is low.[33]

1.2.5.1 Anaphylaxis and Serious Allergic Reactions

As with the administration of any foreign protein and/or other biological agents, acute hypersensitivity reactions, including acute anaphylactic/hypersensitivity, severe allergic, and anaphylactoid reactions may follow infusion of mAbs and can be caused by various mechanisms. These acute hypersensitivity reactions may be severe and result in death.

Anaphylaxis will be defined according to the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria,[34] and are discussed in Section 7.2.2.6.1.

Based on the limited Phase 1 SAD study (BOS161721-01), anaphylaxis and serious allergic reactions in subjects who received BOS161721 was not observed.

Patients with a known history of allergy or severe hypersensitivity reaction to any component of BOS161721 formulation or patients with a history of anaphylaxis to any other biological therapy such as mAbs will be excluded from studies with BOS161721. In addition, appropriate drugs and medical equipment to treat acute hypotensive, bronchoconstrictive, or anaphylactic reactions will be immediately available at the unit and study personnel will be trained to recognize and treat these reactions.

1.2.5.2 Injection Site Reactions

In a repeat-dose GLP toxicology study in Cynomolgus monkeys, BOS161721 was administered every 2 weeks by IV or SC (50 mg/kg) for 3 months (a total of 7 doses); no SC animals had injection reactions.

Based on the Phase 1 SAD study (BOS161721-01), incidence of injection site reactions in subjects who received BOS161721 was similar to placebo.

Patients will be monitored for local injection site reactions in this study. See Section 7.2.7.

1.2.5.3 Immune Complex Disease

The potential risk of immune complex disease for BOS161721 is theoretical, based on the known risks associated with mAbs. The administration of a mAb can result in the formation of ADAs. Administration of the mAb in the presence of ADA may result in the formation of circulating antibody-antigen complexes potentially resulting in altered BOS161721 levels or activity or deposition of the complexes in microvasculature. Complement is frequently involved in the latter setting, and the breakdown products of complement attract polymorphonuclear leukocytes to the site of deposition where they can provoke local tissue damage through specific or nonspecific release of enzymes. Two of the more common end-organ targets are the blood vessels (vasculitis) and kidney (nephritis). These clinical manifestations represent immune complex disease or Type III hypersensitivity. Although BOS161721 is a humanized mAb, ADAs may develop; however, the likelihood of occurrence of immune complex disease with BOS161721 is low. The findings of immune complex disease are typically reversible when mAb administration stops and the antibody-antigen complexes are cleared from the body.

Based on the limited Phase 1 SAD study (BOS161721-01), immune complex disease in subjects who received BOS161721 was not observed.

1.2.5.4 Infections

BOS161721 is expected to diminish the activity of T-cell, B-cell and NK-cell lines. Like other medications modulating immune response, BOS161721 may increase the potential risk for infection, including serious infections. IL-21 produced by CD4+ Th cells is required to sustain the anti-viral function of CD8+ T-cells against chronic viral infections. Nonclinical evidence suggests that the risk of chronic viral infection recurrence or increased severity may occur with IL-21 inhibition.[35]

These conditions will be fully characterized with clinical descriptions and routine laboratory and/or specialty testing and treated where indicated with appropriate local standard of care.

Patients with a history of opportunistic infection, including recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years, or any other underlying pathology predisposing to serious infection, are excluded from studies with BOS161721 (for further details please refer to the current IB for BOS161721).

Patients will be assessed for hepatitis B, and C, and HIV-1/2 combination, at screening.

<u>Cryptosporidium Infection</u>

Cryptosporidium infection was noted in patients with an IL-21 receptor loss-of-function gene mutation and similar findings of cryptosporidium infection have been observed in immunosuppressed liver transplant and human immunodeficiency virus patients.[36,37] Since

BOS161721 is expected to diminish the immunosurveillance activity of T-cell, B-cell, and NK-cell lines, a similar risk is biologically plausible with prolonged exposure to BOS161721.

Since the risk of opportunistic cryptosporidium infection increases with low levels of CD4+ T-cells,[37] patients with a CD4+ count < 500 cell/mm^3 were excluded from the Phase 1 SAD study (BOS161721-01), and will be excluded from the proposed MAD/POC studies. Patients exposed to investigational product who develop diarrhea during the course of the study should immediately undergo an assessment for opportunistic infection including stool for ova and parasites and stool examination for cryptosporidium. Positive cryptosporidium in stool sample at screening is an exclusion. Treatment by the investigator where indicated should be guided by findings and be consistent with local standard of care.

Based on the limited Phase 1 SAD study (BOS161721-01), infections in subjects who received BOS161721 was not observed.

1.2.5.5 Malignancy

The stimulatory effect of IL-21 on NK cells and CD8+ T-cells suggests the cytokine may have anti-tumor activity. Nonclinical studies have demonstrated significant anti-tumor effects of IL-21 in a number of tumor models. IL-21 therapy of human metastatic melanoma and renal cell carcinoma has demonstrated POC with significant increases in levels of perforin, granzyme B, and interferon gamma (IFNγ) expression in CD8+ T-cells and NK T-cells. Clinical response has been limited in these generally unmanageable diseases.

The impact of treatment with anti-IL-21 therapy on the development or growth of malignancies is not known; however, as with other immunomodulatory biologic agents, treatment with BOS161721 may result in an increase in the risk of malignancies. NK cell suppression by IL-21 neutralization may represent a biological mechanism for a potential risk for malignancy. Patients with a history or current diagnosis of cancer within the past 5 years, with the exception of non-melanoma skin cancer or cervical cancer in situ treated with apparent success with curative therapy, are excluded from the study.

Based on the limited Phase 1 SAD study (BOS161721-01), malignancy in subjects who received BOS161721 was not observed.

1.2.5.6 Hepatic Function Abnormality

There is no substantial evidence suggesting BOS161721 is associated with liver function abnormality. However, as a precaution, patients with a history of abnormal alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), or bilirubin at screening (ALT/AST > 2 × upper limit of normal [ULN]; total bilirubin > 1.5 × [ULN] and judged by the investigator to be clinically significant) were excluded from the Phase 1 SAD study (BOS161721-01), and will be excluded from the MAD study. Patients with a positive hepatitis B or C test or a history of alcohol dependence will also be excluded.

Based on the limited Phase 1 SAD study (BOS161721-01), hepatic function abnormality in subjects who received BOS161721 was not observed.

1.2.5.7 Failure of Vaccination

IL-21 is a key cytokine in development of B-cells into immunoglobulin-secreting plasma cells. Abnormal signaling through the IL-21R/Janus Kinase (JAK)3/signal transducer and activator of transcription (STAT3) pathway leads to defective humoral immune responses to both T-dependent and T-independent antigens and impairs the establishment of long-lasting B-cell memory. Abnormal signaling through the pathway has been related to decreased specific antibody responses following vaccination, and to increased susceptibility to encapsulated bacterial infections.[38]

The effect of BOS161721 was evaluated in in vivo single dose studies in Cynomolgus monkey in which the animals received vaccination to T-cell dependent KLH antigen to stimulate a TDAR. These in vivo studies demonstrated that BOS161721 significantly inhibited B-cell proliferation and IgG antibody responses to the KLH protein antigen; however, it is worth noting that BOS161721 administration did not produce any remarkable changes in anti-KLH antibody data for IgM, IgG1, IgG3, and IgG4 or anti-tetanus toxoid (TT) antibody data for IgM, IgG, IgG1, or IgE during the dosing phase in the same study.

1.2.5.8 Potential for Drug-Drug Interactions

Drug-drug interactions were not evaluated in the Phase 1 SAD study (BOS161721-01), which included only healthy adult subjects. Use of prescription medications (with the exceptions of oral contraceptives), and over-the-counter (OTC) treatments including herbal supplements such as St John's Wort (except multivitamins), in the 2 weeks prior to screening was prohibited in the SAD study.

See Section 5.5 for other specific exclusion criteria which support lowered risk of interactions, and Section 5.6.1 for corticosteroid (CS) dosing. In addition, Section 1.2.5.6 describes considerations for hepatic function for this study.

1.2.5.9 Potential Risk to Fetal Development

No data on preclinical reproductive toxicity are available at the time of this study.

2 STUDY OBJECTIVES

This trial has separate primary and secondary objectives for the MAD Phase 1b and POC Phase 2 studies.

2.1 Phase 1b Multiple Ascending Dose

2.1.1 Primary Objective

To assess safety, tolerability, and immunogenicity of repeat doses of BOS161721 (20 mg, 60 mg, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment, in order to estimate the optimal dose.

2.2 Phase 2 Proof of Concept

2.2.1 Primary Objective

To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on the SLE Responder Index 4 (SRI-4), with sustained reduction of oral CS, in adult patients with moderately to severely active SLE on limited background standard of care treatment.

2.2.2 Secondary Objectives

To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on clinical indicators of SLE activity, in adult patients with moderately to severely active SLE on limited background standard of care treatment, including:

- Changes in SLE-specific autoantibody titers
- Changes in complement 3 and 4 (C3 and C4) levels
- Responses on SRI-4, SRI-5, and SRI-6, with sustained reduction of oral CS
- Response on the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA)
- Response on the Cutaneous Lupus Erythematosus Area and Severity Index (CLASI)
- Changes in the SLE Disease Activity Index 2000 (SLEDAI-2K)
- Changes in American College of Rheumatology (ACR)-28 joint count

3 STUDY ENDPOINTS

This trial has separate primary and secondary endpoints for the MAD Phase 1b and POC Phase 2 studies.

3.1 Phase 1b MAD Study

3.1.1 Primary Endpoints

Evaluation of safety, tolerability, and immunogenicity at each dose level, to determine the optimal dose, will include the recording of the following parameters:

- Incidence and severity of AEs, AEs of special interest, and SAEs
- 12-lead ECGs
- Vital signs (blood pressure [BP], heart rate, and temperature)

- Clinical laboratory assessments
- Physical examinations
- Evaluation for ADAs

3.1.2 Exploratory Endpoints

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

3.1.3 Other Endpoints

- CCI [redacted]
- CCI [redacted]
- CCI [redacted].

3.1.4 PRO Endpoints

- CCI [redacted]
- CCI [redacted]

3.2 Phase 2 POC Study

3.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients who achieve treatment response as measured by the SRI-4 at Day 210, along with a sustained reduction of oral CS (≤ 10 mg/day and ≤ Day 0 dose) between Day 120 and Day 210

3.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The proportion of patients who achieve treatment response for the SRI-5 and SRI-6 at Day 210, along with a sustained reduction of oral CS (≤ 10 mg/day and ≤ Day 0 dose) between Day 120 and Day 210
- Changes from baseline in dsDNA, ANA, SSA, SSB, RNP, Sm, APL autoantibodies, at Day 120 and Day 210
- Changes from baseline in C3 and C4 levels at Day 120 and Day 210
- Changes from baseline in the SLEDAI-2K at Day 210
- Time to BILAG A or B flare
- Changes from baseline in the CLASI at Day 210
- The proportion of patients with a BICLA response at Day 210
- The proportion of patients with CLASI response at Day 210
- Changes from baseline (percentage) in swollen joints and tender joints ACR-28 joint count
- Incidence and severity of AEs, AEs of special interest, and SAEs
- 12-lead ECGs
- Vital signs (BP, heart rate, and temperature)
- Clinical laboratory assessments

- Physical examinations and targeted physical examinations
- Evaluation for ADAs

3.2.3 Exploratory Endpoints

- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI

3.2.4 Other Endpoints

- CCI

3.2.5 PRO Endpoints

- CCI
- CCI

4 STUDY PLAN

4.1 Study Design

This is a Phase 1b/2 combined, randomized, multicenter, double-blind, placebo-controlled trial to study the clinical efficacy, safety, and PK of SC doses of BOS161721 in adult patients with

moderately to severely active SLE. After successfully completing a screening phase, patients will be randomized to a specified dose of BOS161721 or placebo. The dosing schedule will be monthly.

The trial will consist of 2 studies: MAD Phase 1b, and POC Phase 2. Both studies will be double-blinded, and patients will have the same number of visits. Patients may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180, followed by a 90-day safety follow-up visit.

SLE disease activity assessment data will be centrally reviewed by medical monitor and sponsor to ensure the scores are clinically meaningful and compliant with specific definition. The scope of responsibility includes, but is not limited to, review and confirmation of "A" and "B" BILAG system organ disease, confirmation of clinical components of the SLEDAI-2K score at screening and during the study, and cross-validation of the instruments used in this study to assess the disease being studied. Further details on the content and methods of data reports by the medical monitor and sponsor will be outlined in the Medical Data Review Plan along with the processes and procedures that will be followed.

4.1.1 Multiple Ascending Dose Phase 1b Study

The MAD study will consist of 3 cohorts:

- Cohort 1 (20 mg SC) will include 6 patients
    - 5 patients will receive BOS161721 (active group) and 1 patient will receive placebo (placebo group)
- Cohorts 2 (60 mg SC) and 3 (120 mg SC) will include 12 patients each
    - 9 patients in the active group and 3 in the placebo group

Doses selected for each of the 3 cohorts is based on a 90-day safety, tolerability, PK and PD data review from the Phase 1 SAD study (BOS161721-01) in healthy subjects. All doses selected for the MAD study are projected not to exceed the mean exposure of that achieved in the SAD study.

4.1.1.1 Dose Escalation for the MAD Study

The MAD study design is staggered, where after the 6 patients in Cohort 1 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 2 begins dosing (after DMC evaluation of the safety and tolerability data from Cohort 1). Similarly, after 8 of the 12 patients in Cohort 2 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 3 begins dosing after DMC evaluation of the safety and tolerability data from Cohorts 1 and 2. Each cohort will continue at their assigned dose level through their respective 6-month treatment periods (See Study Schematic, Section 4.1). If > 3 patients discontinue the study in a cohort, he/she may be replaced.

Criteria for dose escalation are further described in the DMC Charter. See Section 4.1.1.2 for additional details about DLTs.

4.1.1.2 Dose Limiting Toxicity (DLT)

Severity of adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. For the purpose of dose escalation, any of the following AEs occurring after study drug administration, which are attributable to the study drug, will be considered DLTs:

Hematologic:

- Grade 4 neutropenia
- Grade 3 neutropenic infection
- Grade 3 thrombocytopenia with bleeding
- Grade 4 thrombocytopenia

Non-Hematologic:

- Grade 3 or above toxicities, persisting after optimal treatment with standard medical therapy (eg, anti-emetics, anti-diarrheals)
- Drug-induced liver injury ([DILI], Hy's Law), as defined in Section 7.2.2.6.3

Investigators should always manage their patients according to their medical judgment which may include interruption of study drug based on the particular clinical circumstances.

4.1.1.3 DMC Recommendations

During scheduled meetings, the DMC will review relevant study data for safety or benefit-risk concern. During the MAD study, the DMC may provide the following recommendations to the sponsor:

- Expanding a cohort at a specific dosing level, or repeating a lower dose in a subsequent cohort
- Continuing a dose level for a given cohort
- Escalating a dose level for a subsequent cohort
- Termination of current or previous cohort(s)

Further dosing in a given cohort will be halted if 2 or more DLTs are identified intra- and inter-patients dosed. For the POC study, the DMC and Boston Pharmaceuticals will conduct a data review for the IA1 to suggest which dose should be carried forward into the POC Phase 2

study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2, and 3; this dose will not exceed doses tested during the MAD study. The DMC will be reviewing all relevant data from Cohorts 1, 2, and 3 that is available at the time the last patient in Cohort 3 completes the Day 44 visit (2 weeks after dose 2). Details are provided in the DMC Charter.

4.1.2 POC Phase 2 Study

4.1.2.1 BOS161721 Dose

The optimal dose evaluation is chosen based on MAD Phase 1b safety, tolerability, immunogenicity, and PK and PD data. The dose will be communicated by a letter to site investigators participating in the POC Phase 2 study, and to the IRB/IEC.

4.1.2.2 POC Study Design

For the POC study, approximately 156 patients will be randomized to active or placebo groups in a 2:1 ratio.

As in the MAD study, each patient in the POC study may receive a total of 7 SC monthly doses of study drug on Days 0, 30, 60, 90, 120, 150, and 180. Assessments will be completed according to the Schedule of Assessments (Section 4.3). Dose selection will be based on the sponsor's assessment of safety, tolerability, immunogenicity, and PK and PD data from the MAD study of 30 patients treated with BOS161721/placebo.

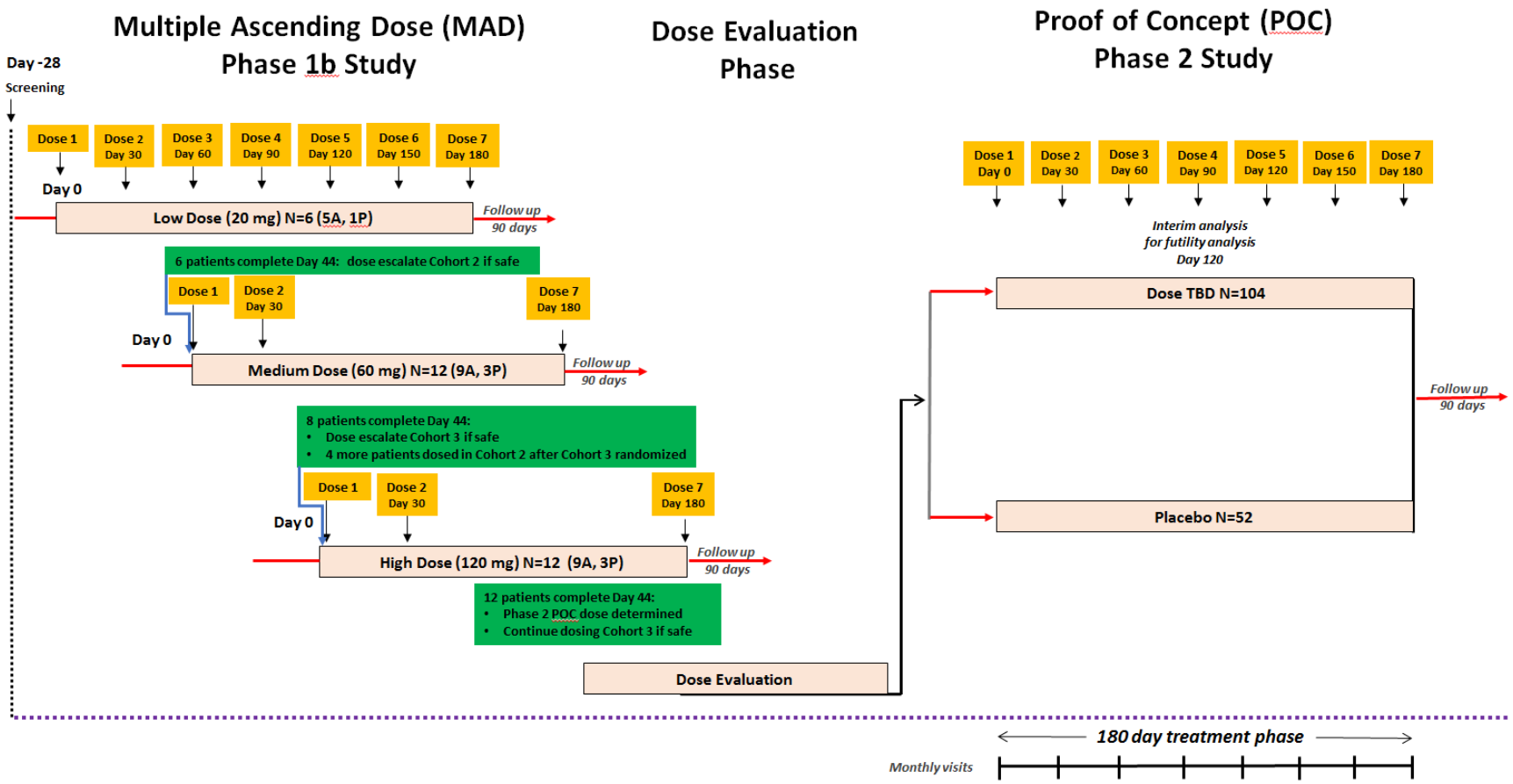
Data from approximately 60 patients (including the 12 from the MAD study, or 6 fewer if the low dose is chosen who are in the cohort of the chosen dose for the POC study) who complete 3 months of treatment will be used in the IA2 at Day 90 to assess if the trial could stop for an early futility conclusion (see Section 9.3 for details regarding the IA). If futility is not claimed in the IA2, the POC study will continue to approximately 156 patients.

Following the 6-month treatment period, primary and secondary efficacy endpoints will be assessed for each patient after providing their Day 180 disease activity assessments.

DMC monitoring will be conducted periodically throughout the study as described in the DMC charter.

4.2 Study Schematic

Figure 2. Study Diagram for MAD Phase 1b and POC Phase 2 Studies



A = active drug (BOS161721); P = placebo

4.3 Schedule of Assessments

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
GENERAL ASSESSMENTS																
Informed consent	X															
Inclusion/Exclusion criteria	X															
Medical history	X															
Demographics	X															
SLICC Criteria for SLE	X															
Concomitant medication[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[c]		X														
BOS161721 or placebo dosing		X			X		X	X	X	X	X					
SAFETY ASSESSMENTS																
Full physical exam	X	X														
Chest x-ray[d]	X															
C-SSRS	X	X						X			X					
AEs and SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	X	X			X			X								X
Injection site reaction assessment[f]		X	X		X		X	X	X	X	X	X	X	X	X	X
Targeted physical examination				X	X	X	X	X	X	X	X			X	X	X
Vital signs (BP, HR, and temperature)[g]	X	X		X	X	X	X	X	X	X	X			X	X	X
EFFICACY ASSESSMENTS																
BILAG-2004 Index	X	X			X		X	X	X	X	X			X	X	X

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
SLEDAI-2K	X	X			X		X	X	X	X	X			X	X	X
PGA of disease activity	X	X			X		X	X	X	X	X			X	X	X
ACR-28 joint count	X	X			X		X	X	X	X	X			X	X	X
CLASI	X	X			X		X	X	X	X	X			X	X	X
CCI		X			X		X	X	X	X	X			X	X	X
SLICC/ACR Damage Index		X									X					
CCI		X			X		X	X	X	X	X			X	X	X
LABORATORY ASSESSMENTS																
CD4+ count	X	X		X	X	X		X			X					
Clinical laboratory assessments (hematology and clinical chemistry)[h]	X	X			X	X	X	X	X	X	X			X	X	X
Coomb's test direct[i]	X	X			X		X	X	X	X	X			X	X	X
Total IgG and IgM	X	X		X	X	X		X			X					
Plasma CCI	X	X			X		X	X	X	X	X			X	X	X
Plasma CCI & CCI	X	X		X	X		X	X			X					
Whole blood for leukocyte immunophenotype	X	X		X	X		X	X			X					
ADA[j]		X		X	X		X	X			X					X
nAb[k]								X			X					
pSTAT3		X			X	X	X	X			X					X
CCI		X									X					
Whole blood RNA collection		X		X	X			X								X

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**
CCI [redacted]	X	X			X		X	X	X	X	X			X[l]	X[l]	X[l]
CRP	X							X								X
Serum pregnancy test (women)	X															
FSH (postmenopausal women)	X															
Urine pregnancy test (women)[m]		X			X		X	X	X	X	X					
TB test (QuantiFERON-TB Gold In-Tube)[d]	X															
Serology (hepatitis B and C, HIV-1/2 combination)	X															
Stool sample[n]	X															
Spot urine for protein/creatinine ratio	X	X			X		X	X	X	X	X			X	X	X
Urinalysis	X	X			X		X	X	X	X	X			X	X	X
PK Labs																
Predose[o]		X			X		X	X	X	X	X					
Postdose		X[p]	X	X	X[p]						X[p]	X	X	X	X	X

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Days	**-28 to -1**	**0**	**7 (± 1)**	**15 (± 3)**	**30 (± 3)**	**44 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**--**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**--**	**--**	**11**	**12**	**13**

Abbreviations: ACR = American College of Rheumatology; ADA= anti-drug antibody; AE = adverse event; CCI [redacted]; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; C = complement; CD4+ = cluster of differentiation 4; CLASI = Cutaneous Lupus Area and Severity Index; CRP = C-reactive protein; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; CCI [redacted]; FSH = follicle stimulating hormone; HR = heart rate; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IL-21 = interleukin 21; IV = intravenous; nAb = neutralizing antibody; PGA = Physician's Global Assessment; PK = pharmacokinetic; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; RNA = ribonucleic acid; RNP = ribonucleoprotein; SAE = serious adverse event; SC = subcutaneous; CCI [redacted]; SLEDAI-2K = SLE Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; CCI [redacted]; TB = tuberculosis; TDAR = T-cell dependent antigen response.

[a] Screening assessments will be performed over more than 1 visit.

[b] Concomitant use of oral corticosteroids: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). See Section 5.6.1 for further details.

[c] Randomization should occur after patient eligibility has been confirmed by central eligibility review.

[d] If patients have had a TB test and chest x ray within 3 months prior to screening, then these assessments do not need to be repeated during screening. The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

[e] ECGs will be performed after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws.

[f] Injection site reaction assessments to be performed predose and at 2 hours postdose.

[g] Vital signs will be assessed after the patient has been supine and at rest ≥ 5 minutes. Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours postdose, as well as on each of the scheduled outpatient days in the table above (excluding PK-only site visits at Days 7, 187, and 195). When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

[h] Clinical laboratory assessments will include a fasting glucose and lipid panel, with exception of screening (Visit 1) which will be nonfasting.

[i] When clinically indicated.

[j] Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only assayed if the patient had a positive ADA on Day 90.

[k] nAb is assessed if patient is positive for ADA.

[l] Only dsDNA collected during safety follow-up visits.

[m] Urine pregnancy test will be collected on WOCBP prior to study drug administration on dosing visits.

[n] Cryptosporidium test is required at screening. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

[o] Predose samples occur on study drug administration visit days.

[p] Postdose samples will be collected at 4, 8, and 24 hours after study drug administration on Days 0, 30, and 180.

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC) Study

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
GENERAL ASSESSMENTS														
Informed consent	X													
Inclusion/Exclusion criteria	X													
Medical history	X													
Demographics	X													
SLICC Criteria for SLE	X													
Concomitant medication[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[c]		X												
BOS161721 or placebo dosing		X		X	X	X	X	X	X					
SAFETY ASSESSMENTS														
Full physical exam	X	X												
Chest x-ray[d]	X													
C-SSRS	X	X				X			X					
AEs and SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[e]	X	X		X		X								X
Injection site reaction assessment[f]		X		X	X	X	X	X	X	X	X	X	X	X
Targeted physical examination			X	X	X	X	X	X	X			X	X	X
Vital signs (BP, HR, and temperature)[g]	X	X	X	X	X	X	X	X	X			X	X	X
EFFICACY ASSESSMENTS														
BILAG-2004 Index	X	X		X	X	X	X	X	X			X	X	X
SLEDAI-2K	X	X		X	X	X	X	X	X			X	X	X
PGA	X	X		X	X	X	X	X	X			X	X	X
ACR-28 joint count	X	X		X	X	X	X	X	X			X	X	X
CLASI	X	X		X	X	X	X	X	X			X	X	X
CCI		X		X	X	X	X	X	X			X	X	X

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC) Study

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
SLICC/ACR Damage Index		X							X					
CCI		X		X	X	X	X	X	X			X	X	X
LABORATORY ASSESSMENTS														
CD4+ count	X	X	X	X		X			X					
Clinical laboratory assessments (hematology and clinical chemistry)[h]	X	X		X	X	X	X	X	X			X	X	X
Coomb's test direct[i]	X	X		X	X	X	X	X	X			X	X	X
Total IgG and IgM	X	X	X	X		X			X					
Plasma CCI	X	X		X	X	X	X	X	X			X	X	X
Plasma CCI & CCI	X	X	X	X	X	X			X					
Whole blood for leukocyte immunophenotype	X	X	X	X	X	X			X					
ADA[j]		X	X	X	X	X			X					X
nAb[k]						X			X					
pSTAT3[l]		X		X	X	X			X					
CCI		X							X					
Whole blood RNA collection		X	X	X		X								X
CCI	X	X		X	X	X	X	X	X			X[m]	X[m]	X[m]
CRP	X					X								X
Serum pregnancy test (women)	X													
FSH (postmenopausal women)	X													
Urine pregnancy test (women)[n]		X		X	X	X	X	X	X					
TB test (QuantiFERON-TB Gold In-Tube)[d]	X													
Serology (hepatitis B and C, HIV-1/2 combination)	X													

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC) Study

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**
Stool sample[o]	X													
Spot urine for protein/creatinine ratio	X	X		X	X	X	X	X	X			X	X	X
Urinalysis	X	X		X	X	X	X	X	X			X	X	X
PK Labs[p]														
Predose[q]		X		X	X	X	X	X	X					
Postdose			X							X	X	X	X	X

Abbreviations: ACR = American College of Rheumatology; ADA= anti-drug antibody; AE = adverse event; CCI [redacted]; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; C = complement; CD4+ = cluster of differentiation 4; CLASI = Cutaneous Lupus Area and Severity Index; CRP = C-reactive protein; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; CCI [redacted]; FSH = follicle stimulating hormone; HR = heart rate; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IL-21 = interleukin 21; IV = intravenous; nAb = neutralizing antibody; PGA = Physician's Global Assessment; PK = pharmacokinetic; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; RNA = ribonucleic acid; RNP = ribonucleoprotein; SAE = serious adverse event; SC = subcutaneous; CCI [redacted]; SLEDAI-2K = SLE Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; CCI [redacted]; TB = tuberculosis; TDAR = T-cell dependent antigen response.

[a] Screening assessments will be performed over more than 1 visit.

[b] Concomitant use of oral corticosteroids: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day). See Section 5.6.1 for further details.

[c] Randomization should occur after patient eligibility has been confirmed. The actual randomization procedure can be completed on Day -1 after eligibility confirmation or the morning of Day 0 prior to dosing for logistical purposes.

[d] If patients have had a TB test and chest x ray within 3 months prior to screening, then these assessments do not need to be repeated during screening. The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

[e] ECGs will be performed after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws.

[f] Injection site reaction assessments to be performed predose and at 2 hours postdose.

[g] Vital signs will be assessed after the patient has been supine and at rest ≥ 5 minutes. Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours postdose, as well as on each of the scheduled outpatient days in the table above (excluding PK-only site visits at Days 187 and 195). When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

[h] Clinical laboratory assessments will include a fasting glucose and lipid panel, with exception of screening (Visit 1) which will be nonfasting.

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC) Study

	Screen[a]	Enroll	Treatment Period Follow-up									Safety Follow-Up		
Days	**-28 to -1**	**0**	**15 (± 3)**	**30 (± 3)**	**60 (± 3)**	**90 (± 3)**	**120 (± 3)**	**150 (± 3)**	**180 (± 3)**	**187 (± 3)**	**195 (± 3)**	**210 (± 3)**	**240 (± 3)**	**270 (± 3)**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**--**	**--**	**10**	**11**	**12**

[i] When clinically indicated.

[j] Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only assayed if the patient had a positive ADA on Day 90.

[k] nAb is assessed if patient is positive for ADA.

[l] Predose (trough) samples only.

[m] Only CCI collected during safety follow-up visits.

[n] Urine pregnancy test will be collected on WOCBP prior to study drug administration on dosing visits.

[o] Cryptosporidium test is required at screening. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

[p] PK samples will only be collected at the investigational sites that will be participating in the PK portion of the study.

[q] Predose samples occur on study drug administration visit days.

5 POPULATION

5.1 Participant Recruitment

Advertisements approved by the IRB, and investigator databases, may be used as recruitment procedures for adult men and women with moderately to severely active SLE.

5.2 Number of Patients

Approximately 186 male and female patients are planned for enrollment, but may be adjusted upward according to the dropout (noncompliance) rate, which will be monitored in a blinded fashion in an ongoing basis. Approximately 30 patients will be randomized for the MAD Phase 1b study, and approximately 156 patients will be randomized in the POC Phase 2 study. Note that approximately 30 dropouts are assumed.

5.3 Patient Screening

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular individual. Patient eligibility will be reviewed and confirmed by the medical monitor or designee prior to randomization. Screening assessments (see the Schedule of Assessments [Section 4.3]) for this study must be performed between Day -28 and Day -1.

5.4 Inclusion Criteria

Patients who meet the following criteria will be considered eligible to participate in this clinical study:

1. Men and women, ages 18 to 70 years, inclusive
2. Patients must be mentally capable of giving consent and there must be evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study
3. Patients must have SLE as defined by meeting 4 of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE (with at least 1 clinical and 1 immunologic criterion or Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies), either sequentially or simultaneously
4. At screening, patients must have at least 1 of the following:
    a. Elevated ANA ≥ 1:80 via immunofluorescent assay at the central laboratory
    b. Positive anti-dsDNA or anti-Smith (Sm) above the normal level as determined by the central laboratory
    c. C3 or C4 below normal as determined by central lab

5. At screening, the SLE Disease Activity Index 2000 (SLEDAI-2K) must be ≥ 6, including points from at least 1 of the following clinical components:
   a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis
      i. Excluding parameters which require central laboratory results: (hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia)
      ii. Points from lupus headache and organic brain syndrome will also be excluded
6. On Day 0, the SLEDAI-2K must be ≥ 6, including points from at least 1 of the following clinical components:
   a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis
      i. Excluding parameters which require central laboratory results: (hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia)
      ii. Points from lupus headache and organic brain syndrome are also excluded
7. Patients must have at least 1 of the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer:
   a. BILAG A or B score in the mucocutaneous body system
   b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis defined as follows:
      i. "BILAG A:" Severe Arthritis, (BILAG item number 41), manifested by observed active synovitis in ≥ 2 joints with marked loss of functional range of movements and significant impairment of basic activities of daily living that has been present on several days cumulatively over the past 4 weeks, including at the time of the screening visit. See APPENDIX 5 for additional detailed specifications.
         - Basic ADLs are defined as the following activities which require assistance or assistive devices, (at least 1 must be present and documented in source):
            - Ambulation, toileting, grooming- including bathing and dressing; feeding oneself, (and not responsive to steroids up to 10 mg/day, antimalarials, NSAIDs)
      ii. "BILAG B:" Moderate Arthritis, Tendonitis or Tenosynovitis, (BILAG item number 42), defined as tendonitis/tenosynovitis, or active synovitis in ≥ 1 joint, (observed or throughout history), with some loss of functional range of movements which lead to some loss of functional range of motion as manifested by effects on instrumental ADLs such as:

- Cooking, driving, using the telephone or computer, shopping, cleaning, etc, and has been present on several days over the last 4 weeks, and is present at the time of the screening visit

c. If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in the other body systems for a total of 2 "B" BILAG body system scores

8. Patients must be currently receiving at least 1 of the following:
   a. Administration for a minimum of 12 weeks, and a stable dose for at least 56 days (8 weeks prior to signing consent) of the following permitted steroid-sparing agents:
      i. Azathioprine (AZA), mycophenolate mofetil or mycophenolic acid, chloroquine, hydroxychloroquine, or methotrexate (MTX)
   b. Prednisone (or prednisone-equivalent) cannot exceed 30 mg/day at screening for a patient to be eligible and must be stable at a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization) (see APPENDIX 3)
9. Women of childbearing potential (WOCBP; see Section 5.7 for full information regarding WOCBP, definition of menopause, and contraception):
   a. Must have a negative serum pregnancy test at screening. Urine pregnancy test must be negative prior to first dose
   b. Must not be breastfeeding
   c. Must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS161721 plus 30 days (duration of ovulatory cycle) for a total of 36 weeks after treatment completion
10. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of BOS161721 plus 90 days (duration of sperm turnover) for a total of 44 weeks after treatment completion
11. Patients must demonstrate willingness and ability to comply with the scheduled study visits, treatment plans, laboratory tests, and other procedures

5.5 Exclusion Criteria

Patients presenting with any of the following will not be included in this study:

1. Drug-induced SLE, rather than "idiopathic" SLE
2. Other systemic autoimmune disease (eg, erosive arthritis, rheumatoid arthritis [RA], multiple sclerosis [MS], systemic scleroderma, or vasculitis not related to SLE)
   a. RA-Lupus overlap (Rupus), and secondary Sjögren syndrome are allowed
3. Any major surgery within 6 weeks of study drug administration, (Day 0), or any elective surgery planned during the course of the study

4. Any history or risk for tuberculosis (TB), specifically those with:
   a. Current clinical, radiographic, or laboratory evidence of active TB
   b. History of active TB
   c. Latent TB defined as positive QuantiFERON-TB Gold In-Tube (QFT-G) or other diagnostic test in the absence of clinical manifestations. Latent TB is not excluded if the patient has documented completion of adequate course of prophylactic treatment with regimen recommended by local health authority guideline, or the patient has started treatment with isoniazid, or other regimen recommended by local health authority guidelines for at least 1 month before Day 0 and continues to receive the prophylactic treatment during study until the treatment course is completed.
5. Active or unstable lupus neuropsychiatric manifestations, including but not limited to any condition defined by BILAG A criteria, with the exception of mononeuritis multiplex and polyneuropathy, which are allowed
6. Severe proliferative lupus nephritis, (WHO Class III, IV), which requires or may require induction treatment with cytotoxic agents or high dose CS
7. Concomitant illness that, in the opinion of the investigator, is likely to require additional systemic glucocorticosteroid therapy during the study, (eg, asthma), is exclusionary
   a. However, treatment for asthma with inhalational CS therapy is allowed
8. Use or planned use of concomitant medication outside of standard of baseline treatment for SLE from Day -1 or for any time during the study. (See Section 5.6 for prohibited concomitant medication)
9. Active and clinically significant infection (bacterial, fungal, viral, or other) within 60 days prior to first dose of study drug. Clinically significant is defined as requiring systemic antibiotics or hospitalization
10. A history of opportunistic infection, or a history of recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years
11. Chronic viral hepatitis including hepatitis B (HBV) and hepatitis C (HCV), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness
12. Cryptosporidium in the stool sample at screening
13. White blood cells (WBC) < 1,200/mm^3 (1.2×10^9/L) at screening
14. Absolute neutrophil count (ANC) < 500/mm^3 at screening
15. CD4+ count < 500/µL at screening
16. Platelets < 50,000/mm^3 (50×10^9/L) or < 35,000/ mm^3 (35×10^9/L) if related to SLE, at screening
17. Hemoglobin < 8 g/dL or < 7 g/dL at screening if due to anemia related to SLE
18. Proteinuria > 3.0 g/day (3000 mg/day) at screening or equivalent level of proteinuria as assessed by protein/creatinine ratio (3 mg/mg or 339 mg/mmol)

19. Serum creatinine > 2.0 mg/dL at screening or creatinine clearance (CrCL) < 40 ml/minute based on Cockcroft-Gault calculation[39]:

    GFR = ([1 for male] or [0.85 for female]) × (140 – Age) × BW / (72 × Creatinine)

20. Serum ALT and/or serum AST > 2 × ULN at screening, unless explicitly related to lupus based on the investigator's judgment
21. Creatinine kinase (CK) > 3.0 × ULN at screening, unless it is related to lupus myositis
22. Direct bilirubin > 1.5 × ULN at screening (unless related to Gilbert's syndrome)
23. Any other laboratory test results that, in the opinion of the Investigator, might place a patient at unacceptable risk for participating in this study
24. History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody (eg, IgG protein) or molecules made of components of monoclonal antibodies
25. History substance and/or alcohol abuse or dependence within the past 1 year, at the investigator's judgment
26. History of cancer within the last 5 years (except for cutaneous basal cell or squamous cell cancer, or cervical cancer in situ resolved by excision)
27. Any other severe acute or chronic medical or psychiatric condition, including recent (within the past year) medical conditions (eg, cardiovascular conditions, respiratory illnesses) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study
28. Investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or patients who are employees of the sponsor or directly involved in the conduct of the trial
29. Currently participating in, or who have participated in other interventional (drug or device) clinical study within 30 days or 5 half-lives of baseline, whichever is longer
30. Recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4 or 5 on the Columbia Suicide severity Rating Scale (C-SSRS)
31. Current or pending incarceration
32. Current or pending compulsory detainment for treatment of either a psychiatric or physical (eg, infectious disease) illness

5.6 Concomitant Medications

Any medicinal product, prescribed or OTC, including herbal and other nontraditional remedies, is considered a concomitant medication. Patients should stay on stable regimen of other concomitant medications for the treatment of SLE (eg, analgesics, NSAIDs, statins, ACE

inhibitors/ARBs and other antihypertensive drugs), unless changes in these treatments are clinically indicated. Use of any other drugs for non-SLE conditions, including over-the-counter medications and herbal preparations, should remain stable unless change or addition is clinically necessary. Discussion with the medical monitor prior to initiation of new medication is strongly recommended. Any concomitant therapies must be recorded on the eCRF. Prior and concomitant medication use will be recorded for the 30 days prior to screening until the last follow-up visit. In addition, historical treatment for SLE (including immunosuppressant, anti-malarial, corticosteroid, and/or biologic agent) will be recorded for the 48 weeks prior to screening in the eCRF.

5.6.1 Oral Corticosteroid Dose

Prior to randomization, oral CSs (prednisone or prednisone equivalent), may be used in accordance with the investigator's clinical judgment and best standard of care. See APPENDIX 3 for examples of equivalents.

A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 0 (randomization day).

After Day 0 (after initiation of study therapy), no up-titration above 10 mg/day is allowed except for up to 1 CS burst for increased disease activity.

Tapering of steroids during the course of the study will be encouraged and should be evaluated at all visits.

- Once a patient has received the first dose of study drug, prednisone (or prednisone equivalent) may be tapered down at the discretion of the investigator
    - Tapering is allowed after randomization except within 60 days of the primary (Day 210) and secondary (Day 120) endpoint assessments. Between Day 60 and Day 120, and between Day 150 and Day 210, oral CS doses must be held constant otherwise the patient will be declared a non-responder in efficacy assessments.

A maximum of 1 oral CS "burst" for increased SLE disease activity will be allowed during the study between Day 0 and Day 60, according to the following:

- An oral CS "burst" between Day 0 and Day 60; (an increase of ≤ 40 mg/day of prednisone or equivalent), which must be tapered down to a maximum of 10 mg/day within 2 weeks of initiation of the "burst"
    - Alternatively, a single intramuscular (IM) dose of methylprednisolone (40 mg or equivalent) is permitted
    - The course of the oral CS "burst" is not permitted to extend beyond Day 60

Treatment with inhalational CS therapy (eg, for asthma), or by any other route, is allowed. Other concomitant medications for SLE need to be taken at stable doses as per the inclusion criteria (Section 5.4).

5.6.2 Other Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study drug administration and during the study are described below, and washout requirements are provided in APPENDIX 4. Medications taken within 30 days prior to screening must be recorded on the eCRF.

1. Prior exposure to BOS161721
2. Patients who have received treatment with anti-CD20 monoclonal antibodies within 6 months of screening; recovery of B cells (CD19+) must be documented (record absolute number of CD19+ B cells)
3. Patients who have received treatment with cyclophosphamide within the 1 year prior to screening
4. Patients who have received treatment with cyclosporine (with exception of ophthalmic use), any other calcineurin inhibitor or other immunosuppressive medication not specified in the inclusion criteria (oral or topical) within 3 months of screening
5. Patients who are currently receiving or are scheduled to receive plasmapheresis or lymphapheresis therapy, or have received such therapy within 8 weeks prior to screening
6. Patients who have received any live vaccines within 30 days of screening. Note: Furthermore, live vaccines should not be used during the course of the study and within the 2 months following last dose. Other inactivated vaccines such as tetanus, etc, may be used according to local guidelines during treatment period
7. Patients who are scheduled or anticipated to have elective surgery during the course of the study
8. Initiation of new immunosuppressant or anti-malarial agent is not permitted. Note: Dose reduction or replacement may be allowed due to intolerability or shortage for patients on a stable dose prior to study initiation

5.7 Women of Childbearing Potential

WOCBP is defined as any woman who has experienced menarche and who has not undergone surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) and is not postmenopausal.

See Section 5.7.2 for detailed information regarding contraceptive requirements for WOCBP.

5.7.1 Determination of Menopause

Menopause is defined as at least 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. Women under the age of 55 years must have a documented serum FSH level > 40 mIU/mL at screening to confirm menopause.

5.7.2 Contraception

WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS161721 plus 30 days (duration of ovulatory cycle) for a total of 36 weeks after treatment completion.

Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS161721 plus 90 days (duration of sperm turnover) for a total of 44 weeks after treatment completion.

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

At a minimum, patients must agree to the use of 1 method of highly effective contraception from the following:

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by patients who are WOCBP or a male patient's WOCBP partner. Women who are partner of men who are patients participating in the study may use hormone-based contraceptives as 1 of the acceptable methods of contraception since they will not be receiving study drug.
- IUDs, such as ParaGard®
- Vasectomy
- Complete abstinence, defined as complete avoidance of heterosexual intercourse, is an acceptable form of contraception. Women who are abstinent while participating in the study must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the patient chooses to forego complete abstinence.

Azoospermic men and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing.

5.8 Deviation from Inclusion/Exclusion Criteria

Deviation from the inclusion or exclusion criteria will not be allowed. If deviation of inclusion/exclusion criteria is discovered after randomization, the investigator should contact the medical monitor for discussion. A decision will be made whether to allow a patient continue or withdrawal from the study medication.

See Section 7.8 for additional details.

5.8.1 Patient Withdrawal and Replacement

See Section 6.5 for reasons for removal from the trial. Withdrawn patients may be replaced during the MAD study after discussion between the principal investigator or designee and sponsor.

6 STUDY PROCEDURES

Refer to the eCRF completion guidelines for data collection requirements and documentation of study assessments/procedures.

6.1 Screening

Screening will be the same for both the MAD and POC studies.

Screening will take place from Day -28 to Day -1, and assessments may be performed over more than 1 visit. Confirmation that the most current IRB/IEC approved informed consent form (ICF) has been signed must occur before any study-specific screening procedures are performed. Procedures that are part of standard of care are not considered study-specific procedures and may be performed prior to informed consent and used to determine eligibility.

All screened patients will be assigned a unique screening number. The screening number will include a 3-digit site number and a 4-digit sequential number to identify patients from the time of screening. Only eligible patients who are confirmed by central review as meeting the inclusion/exclusion criteria, listed in Section 5.4 and Section 5.5 respectively, will be enrolled in the study. Screened patients who drop out of the clinical study before randomization will be recorded as screen failures. If rescreening occurs, the site will assign a new screening number.

Specific procedures at the screening visit will include:

- Medical history documentation
- Review of inclusion and exclusion criteria
    - Patient medical records must contain documentation of SLE diagnosis
    - C-SSRS
- Concomitant medication documentation
- Demographics
- Full physical examination
- Vital signs

- Chest x-ray
- Laboratory evaluations (nonfasting):
  - Hematology and clinical chemistry
  - Serology (Hepatitis B and C; HIV-1/2 combination)
  - TB test
  - CRP
  - Direct Coomb's test (if indicated)
  - CD4+ count, total IgG and IgM levels, plasma CCI, plasma CCI and CCI, whole blood for leukocyte immunophenotype; CCI
  - Serum pregnancy test (WOCBP)
  - FSH (postmenopausal women)
  - Spot urine for protein/creatinine ratio
  - Urinalysis
  - Stool sample
- 12-lead ECG
- SLE-related indices (BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, Physician's Global Assessment (PGA) of disease activity

Screening procedures are listed in the Schedule of Assessments (Section 4.3), and details are provided in Section 7.

6.1.1 Retesting During Screening Period

A single retesting of laboratory parameters and/or other assessments during the screening period is permitted (in addition to any parameters that require a confirmatory value) only if:

- medically indicated
- there is evidence a laboratory sample was mislabeled, inadequately processed, and/or deteriorated in transit to the central laboratory

Any new result will override the previous result (ie, the most current result prior to randomization) and is the value by which study inclusion/exclusion will be assessed, as it

represents the patient's most current clinical state. This will also apply to patients who are being rescreened.

6.2 Enrollment/Randomization and Day 0 Treatment

Randomization should occur after patient eligibility for enrollment has been confirmed by the central eligibility review.

The study site will obtain a randomization number when registering the patient in IWRS. All patients will receive BOS161721 or placebo according to the kit number assigned by the IWRS randomization scheme.

After randomization, procedures include:

- PROs: CCI
- C-SSRS
- Laboratory evaluations (fasting):
  - Hematology and clinical chemistry
  - Direct Coomb's test (if indicated)
  - CD4+ count, total IgG and IgM levels, plasma CCI, plasma CCI and CCI, whole blood for leukocyte immunophenotype
  - ADA
  - pSTAT3 (predose [trough] samples only in Phase 2)
  - CCI
  - Whole blood RNA collection
  - CCI
  - See Table 1 and Table 2 for details of PK sampling in the MAD and POC studies
  - Urine pregnancy test will be collected on WOCBP prior to study drug administration
  - Spot urine for protein/creatinine ratio
  - Urinalysis
- Concomitant medication documentation
- Documentation of AEs and SAEs (see Section 7.2.2.5 on SAE reporting requirements)

- Full physical examination
- Vital signs (prior to PK blood draw, predose, and at 1 and 2 hours postdose on Day 0)
- 12-lead ECG (prior to PK blood draw)
- SLE-related indices (BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, PGA)
- SLICC/ACR damage index
- Study drug administration:
    - Administration of BOS161721 or placebo will take place on-site, and is discussed in Section 8.3
- Injection site reaction assessment, predose, and 2 hours postdose

Procedures on Day 0 are listed in the Schedule of Assessments (Section 4.3), and details are provided in Section 7.

All patients who are enrolled, randomized, and receive study drug, or undergo study-specific procedures should reconsent with any updated versions of IRB/IEC approved informed consents during study participation as applicable and per institutional guidelines.

6.3 Treatment Period/Follow-Up Visits

The following procedures will be performed as indicated in the Schedule of Assessments (Table 1 and Table 2). See Schedule of Assessment tables for allowable windows for each visit.

- Targeted physical examination
- Vital signs (prior to PK blood draw)
- Concomitant medication documentation
- Documentation of AEs and SAEs (see Section 7.2.2.5 on SAE reporting requirements)
- PROs: CCI
- Urine pregnancy tests will be collected on WOCBP prior to study drug administration
- Injection site reaction assessments will be performed predose and 2 hours postdose
- Direct Coomb's test (if indicated)
- Spot urine for protein to creatinine ratio
- Urinalysis

- CCI [redacted]
- Plasma CCI [redacted]
- PGA, BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, and the CLASI will be completed
- SLICC/ACR Damage Index will be completed at Day 180
- C-SSRS
- ECGs prior to PK blood draw
- See Table 1 and Table 2 for details of PK sampling in the MAD and POC studies, respectively
- Fasting hematology and chemistry assessments
- The CD4+ count and total IgG and IgM levels
- Plasma CCI [redacted] & CCI [redacted], ADA, and whole blood for leukocyte immunophenotype
- pSTAT3
- Whole blood RNA
- CRP and nAb will be assessed if patient is positive for ADA
- CCI [redacted]

6.4 Safety Follow-Up Visits

Safety follow-up visits will take place at Days 210, 240, and 270. These visits will include the following assessments as indicated in the Schedule of Assessments (Table 1 and Table 2):

- PROs: CCI [redacted]
- Documentation of AEs and SAEs (see Section 7.2.2.5 on SAE reporting requirements)
- Injection site reactions
- Targeted physical examination
- Vital signs (prior to PK blood draw)
- Spot urine for protein/creatinine ratio and urinalysis
- Concomitant medication documentation

- BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, and PGA
- Fasting clinical laboratory assessments (hematology and clinical chemistry)
- Direct Coomb's test (if indicated)
- Plasma CCI
- CCI
- pSTAT3
- 12-lead ECG (prior to PK blood draw)
- CRP
- ADA
- Whole blood RNA collection
- See Table 1 and Table 2 for details of PK sampling in the MAD and POC studies, respectively

6.5 Premature Discontinuation

While patients are encouraged to complete all study evaluations, they may withdraw from the study at any time and for any reason. Every effort will be made to determine why any patient withdraws from the study prematurely. If the patient is unreachable by telephone, a registered letter, at the minimum, should be sent to the patient requesting him/her to contact the clinic.

All patients who withdraw from the study with an ongoing AE or SAE must be followed until the end of study or until the event is resolved or deemed stable, respectively.

If a patient withdraws prematurely after dosing, an end of treatment (EOT) visit should be performed (Day 180) and a last follow-up visit 90 days after dosing should be scheduled (Day 270). Safety follow-up visit procedures based on the Schedule of Assessments (see Section 6.4).

Patient participation may be terminated prior to completing the study and the reason recorded as follows:

- AE/SAE
- Protocol deviation
- Lost to follow-up
- Patient withdraws consent at their own request

- Investigator decision
- Decision by sponsor (other than AE/SAE, protocol deviation, or lost to follow-up)

Withdrawn patients may be replaced after discussion between the investigator or designee and sponsor.

7 ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, which may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and wellbeing of the patient. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. All protocol violations are entered directly into the eCRFs.

7.1 Medical History, Demographic and Other Baseline Information

The medical history comprises:

- General medical history
- Documentation of SLE diagnosis
- Historical medication therapy for SLE

The following demographic information will be recorded:

- Age
- Ethnic origin (Hispanic/Latino or not Hispanic/not Latino)
- Race (White, American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black/African American)
- Height (without shoes, in cm)
- Body weight, without shoes (kg)
- Body mass index (BMI [kg/m^2])

Other baseline characteristics will be recorded as follows:

- Concomitant medication documentation (see Section 5.6)
- Status of child bearing potential and contraception

7.2 Safety Assessments

7.2.1 Laboratory Assessments

Laboratory tests will be performed at times defined in the Schedule of Assessments (Section 4.3). Patient eligibility will be determined based on these tests at screening. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

A central laboratory will be used (with the exception of urine pregnancy tests and stool analysis) to ensure accuracy and consistency in test results. The central laboratory will transmit all results for protocol tests, scheduled and unscheduled, to the clinical data base. Laboratory/analyte results that could unblind the study (ie, biomarker results) will not be reported to investigative sites. Urinalysis will be performed on midstream, clean catch specimens. Some biomarkers listed above will not be drawn at some sites due to geographical logistical challenges. See the laboratory manual for details.

Endpoint analyses will be based on changes from baseline assessments at Days 120 and 210.

Table 3. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other Safety Tests
Hemoglobin	BUN	pH	Spot urine for protein/creatinine ratio
Hematocrit	Creatinine	Glucose (qual)	FSH[b]
RBC count	Glucose (fasting)	Protein (qual)	Urine pregnancy test[c]
RDW	Calcium	Blood (qual)	QuantiFERON®-TB Gold In-Tube test (QFT-G)
MCV	Sodium	Ketones	Serology[d] (Hepatitis B and C; HIV-1/2 combination)
MCH	Potassium	Nitrites	Stool sample[e]
MCHC	Chloride	Leukocyte esterase	
Platelet count	Total CO_2 (bicarbonate)	Urobilinogen	
WBC count	AST, ALT	Urine bilirubin	
CD4+ count	Total bilirubin	Microscopy[a]	
Total neutrophils (Abs)	Alkaline phosphatase		
Eosinophils (Abs)	Creatine kinase		
Monocytes (Abs)	Uric acid		
Basophils (Abs)	Albumin		
Lymphocytes (Abs)	Total cholesterol (fasting)		
Reticulocytes (%)	LDL-C (fasting)		
	HDL-C (fasting)		
	Triglycerides (fasting)		
	Total protein		
	PT/INR		

	Additional Tests[f] (potential Hy's Law)	Immunogenicity, PD and other Biomarker Tests
	AST, ALT (repeat)	ADA
	Total bilirubin (repeat)	nAb[g]
	Albumin (repeat)	pSTAT3 (predose [trough] samples only, in Phase 2)
	Alkaline phosphatase (repeat)	Total IgG & IgM
	Direct bilirubin	Plasma CCI
	Indirect bilirubin	Plasma CCI & CCI
	GGT	Whole blood for leukocyte immunophenotype and RNA
		CCI CCI
		Antibodies CCI
		CRP
		Direct Coomb's test[h]

Abbreviations: Abs = absolute; ADA = anti-drug antibody; ALT = alanine aminotransferase; CCI ; CCI ; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C = complement; CD4+ = cluster of differentiation 4; CRP = C-reactive protein; dsDNA = double-stranded deoxyribonucleic acid;; FSH = follicle stimulating hormone; GGT = gamma-glutamyltransferase; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ration; IL-21 = interleukin 21; LDL-C = low-density lipoprotein cholesterol; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = Mean corpuscular volume; nAb = neutralizing antibody; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; PT = prothrombin time; qual = qualitative; RBC = red blood cell; RDW = RBC distribution width; RNA = ribonucleic acid;

Table 3. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other Safety Tests

RNP = ribonucleoprotein; SAE = serious adverse event; SC = subcutaneous; CCI ; TB = tuberculosis.

a. On all urine samples.
b. At screening only, in women who are amenorrheic for at least 12 consecutive months and under 55 years old.
c. For WOCBP.
d. Screening only.
e. At screening, and if a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.
f. Additional testing for potential Hy's Law cases only (See Section 7.2.2.6.3).
g. If patient is positive for ADA.
h. If clinically indicated.

7.2.1.1 Pregnancy testing

For WOCBP, a serum pregnancy test will be performed at screening. Following a negative serum pregnancy result at screening, appropriate contraception must be commenced or continued and a further negative urine pregnancy test results will then be required at the baseline visit before the patient may receive the investigational product. Urine pregnancy tests will also be routinely repeated at study drug administration visits prior to study drug administration, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive pregnancy test or confirmed pregnancy, the patient will be discontinued from study drug, an EOT visit should be performed (Day 180), and a last follow-up visit 90 days after last dose should be scheduled (Day 270). Safety follow-up visit procedures based on the Schedule of Assessments (see Section 6.4).

See Section 7.2.2.7.1 for information on reporting of pregnancies as AEs/SAEs during the study.

7.2.1.2 Tuberculosis Screening

During the screening period, it must be determined and documented that a patient does not have evidence of active or latent or inadequately treated TB per the exclusion criteria (Section 5.5). The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 0).

7.2.1.2.1 Mycobacterium Tuberculosis Testing Using QuantiFERON Test[40]

QuantiFERON®-TB Gold In-Tube (QFT-G) is an in vitro diagnostic test using a peptide cocktail simulating ESAT-6, CFP-10, and TB 7.7 proteins to stimulate cells in heparinized whole blood. Detection of INFγ performed by enzyme-linked immunosorbent assay (ELISA) is used to identify in vitro responses to these peptide antigens that are associated with Mycobacterium tuberculosis infection. QFT-G is an indirect test for M. tuberculosis infection (including disease) and is intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.

Test results will be reported as positive, negative, or indeterminate. A negative QFT-G test result is required to meet the inclusion criterion. In the case of an indeterminate result, repeat tests should be permitted for the purpose of determining eligibility of patients to enroll in this study. If a repeat test is indeterminate again, the patient is a screen failure. The procedure for using this test and interpreting the results will be described fully in the laboratory manual, which will be provided to investigators.

7.2.2 Adverse Events

7.2.2.1 Definitions

An AE is defined as any untoward medical occurrence experienced by a study patient, whether or not considered drug related by the principal investigator.

AEs are unfavorable changes in a general condition, subjective or objective signs or symptoms, worsening of pre-existing concomitant disease, and clinically significant abnormality in laboratory parameters observed in a patient in the course of a clinical study.

Non-serious SLE manifestations or abnormal laboratory results related to SLE disease activity would not be recorded as AEs unless they meet the definition for SAEs (Section 7.2.2.5).

7.2.2.2 Recording of Adverse Events

AEs should be collected and recorded for each patient from the date of the first dose of study drug until the end of their participation in the study, including the safety follow up period.

AEs may be volunteered spontaneously by the study patient, or discovered by the study staff during physical examinations or by asking an open, nonleading question such as 'How have you been feeling since you were last asked?' All AEs and any required remedial action will be recorded on the Adverse Events eCRF and Safety Adverse Event Form. The details of the AE, date of AE onset (and time, if known), date of AE outcome (and time, if known), and action taken for the AE will be documented together with the principal investigator's assessment of the seriousness of the AE and causal relationship to the study drug and/or the study procedure.

All AEs should be recorded individually, using diagnostic terms where possible. If the diagnosis is not established, individual symptoms may be reported. The AEs will subsequently be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

7.2.2.3 Severity of Adverse Events

Each AE will be assessed by the principal investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03 criteria. [41] When changes in the severity (grade) of an AE occur more frequently than once a day, the maximum severity for the event should be noted for that day. Any change in severity of signs and symptoms over a number of days will be captured by recording a new AE, with the amended severity grade and the date (and time, if known) of the change.

7.2.2.4 Causality of Adverse Events

The principal investigator will assess the causal relationship between BOS161721 or placebo and the AE. One of the following categories (Table 4) should be selected based on medical judgment, considering the definitions below and all contributing factors.

Table 4. Causality Definitions	
Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment (dechallenge[a]) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge[b] procedure if necessary.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (eg, concomitant disease, environmental factors, or other drugs or chemicals).

[a] Dechallenge: Upon discontinuation of a drug suspected of causing an AE, the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation (positive dechallenge), or the symptoms continue despite withdrawal of the drug (negative dechallenge). Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists (for example, as in bone marrow suppression, fixed drug eruptions, or tardive dyskinesia).

[b] Rechallenge: Upon re-administration of a drug suspected of causing an AE in a specific patient in the past, the AE recurs upon exposure (positive rechallenge), or the AE does not recur (negative rechallenge).

An unexpected adverse drug event is any adverse drug event for which the specificity or severity is not consistent with the current IP.

7.2.2.5 Seriousness of Adverse Events

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

- Results in death
- Is life threatening; this means that the patient was at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires hospitalization or prolongation in existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly or birth defect
- Is another important medical event (see below)

Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in inpatient hospitalization
- Development of drug dependency or drug abuse

Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (eg, elective surgery for a pre-existing condition that has not worsened) need not be considered SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'nonserious' according to the usual criteria.

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are associated with the use of the drug and are serious and unexpected.

7.2.2.6 Adverse Events of Special Interest

AEs of special interest in this study include the following:

1. Anaphylaxis and serious allergic reactions
2. Injection site reaction, including erythema, pain, and induration
3. Drug Induced Liver Injury (DILI) assessed following Hy's Law
4. Malignancy
5. Opportunistic infections such as disseminated histoplasmosis, cryptococcosis, and disseminated tuberculosis
6. Cryptosporidiasis

7.2.2.6.1 Anaphylaxis and Serious Allergic Reactions

Anaphylaxis will be defined according to the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria.[42] In the event of anaphylactic reaction or severe/serious hypersensitivity/allergic reaction, the patient must discontinue IP and emergency resuscitation measures implemented. In case of other mild to moderate hypersensitivity reaction, depending on the severity, the investigator may manage in accordance with the standard-of-care.

Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus, or flushing, swollen lips-tongue-uvula) and at least 1 of the following:

a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)

b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   c. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):

   a. Systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from the patient's baseline

7.2.2.6.2 Injection Site Reactions

Injection site reactions are to be captured and reported as AEs. These may include injection site erythema, pain, and induration. The investigator should provide a clear description of the observed or reported AE including location and severity. All concomitant treatments used to treat injection site reactions should be recorded and captured in the eCRF, together with the AE of injection site reactions.

7.2.2.6.3 Potential Drug-Induced Liver Injury

Abnormal values in AST and/or ALT levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of DILI, and as potential Hy's Law cases, and should always be considered important medical events. If symptoms compatible with DILI precede knowledge of serum chemical test abnormalities, liver enzyme measurements should be made immediately, regardless of when the next visit or monitoring interval is scheduled. In some cases, symptoms may be an early sign of injury and although typically less sensitive than serum enzyme elevations, they may indicate a need for prompt serum testing. An increase in liver enzymes should be confirmed by a repeated test within 48 to 72 hours following the initial test, prior to reporting of a potential DILI event. Patients will continue to have weekly or biweekly liver enzyme measurements until resolution or levels return to baseline.

All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 7.2.2.7.2 for reporting details).

Potential DILI is defined as:

1. ALT or AST elevation > 3 × ULN

AND

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

AND

3. No other immediately apparent possible causes of ALT or AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

The patient should return to the investigational site and be evaluated as soon as possible, include laboratory tests, detailed history, and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, CK, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/International Normalized Ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

Study drug discontinuation is considered if there is marked serum AST or ALT elevation or evidence of functional impairment (as indicated by rising bilirubin or INR, which represent substantial liver injury) that is related to study drug. Discontinuation of treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5× ULN for more than 2 weeks

Discontinuation of treatment must occur if:

- ALT or AST >3 × ULN and (total bilirubin > 2 × ULN or INR > 1.5)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

7.2.2.6.4 Malignancy

The identification of a malignancy event will be made by the study site and communicated to the sponsor or designee. AEs should be reported as serious per the criteria in Section 7.2.2.5.

After the first dose of study drug, when there is a decision to biopsy a potentially malignant tumor, lymph node, or other tissue, the investigator and/or consultant(s) should contact the sponsor clinicians or designee to discuss the issue and any decisions as soon as possible.

7.2.2.6.5 Specific Infections

Any diagnosis or suggested diagnosis of opportunistic infections such as disseminated histoplasmosis, cryptococcosis, shingles, disseminated herpes simplex, or disseminated tuberculosis will be recorded as AEs of special interest.

Cryptosporidiosis is also considered an AE of special interest. Patients will be evaluated for cryptosporidium in the stool at screening, and as clinically indicated (eg, watery diarrhea) during the study. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

7.2.2.7 Reporting of Adverse Events

AE reporting will be carried out in accordance with applicable local regulations, including regulatory agency and IRB reporting requirements.

Each AE is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate, and is further outlined in Section 7.2.2.7.2.

7.2.2.7.1 Reporting of Pregnancy

As information is available, a pregnancy diagnosed during the study will be reported within 24 hours to the sponsor via the Pregnancy Notification and Outcome Form, including pregnancy in female patients who received study drug and female partners of male study patients who received study drug. The pregnancy should be followed to term and/or outcome and this outcome should also be reported to the sponsor via the Pregnancy Notification and Outcome Form. Pregnancy itself is not regarded as an AE or SAE unless there is complication.

In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an AE or SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the neonatal death as related or possibly related to exposure to investigational product.

7.2.2.7.2 Reporting of Serious Adverse Events

The principal investigator is responsible for providing notification to the sponsor of any SAE via the Safety Adverse Event Form, whether deemed study drug related or not, that a patient experiences during their participation in this study within 24 hours of becoming aware of the event.

If an SAE is fatal or life threatening, notification to the sponsor must be made aware immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding cases. In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

The principal investigator will review each SAE and evaluate the intensity and the causal relationship of the event to the study drug. All SAEs will be recorded from the time of first dose of study drug through the safety follow-up period (up to Day 270). SAEs occurring after the final follow-up visit and coming to the attention of the principal investigator must be reported only if there is (in the opinion of the principal investigator) reasonable causal relationship with the study drug.

As a minimum requirement, the initial notification should provide the following information:

- Study number
- Patient number
- Details of the SAE (verbatim details are sufficient for immediate notification)
- Criterion for classification as ‘serious’
- Causality assessment (which may be updated in a follow-up report when sufficient information is available to make this classification)

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (eg, hospital reports, consultant reports, autopsy reports, etc), with the study patient’s personal identifiers removed. All relevant information

obtained by the principal investigator through review of these documents will be recorded and submitted to the sponsor within 24 hours of receipt of the information. If a new Safety Adverse Event Form is submitted, then the principal investigator must sign and date the form. The sponsor may also request additional information on the SAE, or clarification of omitted or discrepant information from the initial notification, which the principal investigator or an authorized delegate should submit to the sponsor within 24 hours of the request as possible.

7.2.2.7.3 Reporting of Adverse Events of Special Interest

AEs of special interest will be reported to safety immediately or within 24 hours of the site becomes aware of the event and recorded as such on the Adverse Events eCRF and Safety Adverse Event Form.

Potential DILI will be reported based on specifications mentioned in Section 7.2.2.6.3.

Each AE of special interest is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate, and is further outlined in Section 7.2.2.7.2.

7.2.2.8 Follow Up of Adverse Events

All AEs will be followed up through the safety follow-up visits. All SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the event has resolved, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the principal investigator and medical monitor, until there is a satisfactory explanation for the changes observed, or until the patient is lost to follow-up.

See Section 7.2.2.7.1 for details related to follow-up of pregnancy. See Section 7.2.2.6.3 for details related to follow-up of potential DILI. See Section 7.2.2.6.4 for details related to follow-up of malignancy.

7.2.3 Vital Signs

Vital signs (blood pressure, heart rate, and body temperature) will be assessed as specified in the Schedule of Assessments (Section 4.3). Vital signs will be assessed on Day 0 at predose and at 1 and 2 hours postdose, as well as on each of the scheduled visit days during the study (excluding PK-only site visits). Supine BP and heart rate recordings will be made after the patient has been recumbent and at rest ≥ 5 minutes. When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

7.2.4 12-Lead Electrocardiograms

ECG will be assessed as specified in the Schedule of Assessments (Section 4.3). ECG recording will initiate after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws, though timing will be such that PK draws are collected on their scheduled times where possible.

The ECG will include all 12 standard leads and a Lead II rhythm strip on the bottom of the tracing. The ECG will be recorded at a paper speed of 25 mm/second. The following ECG parameters will be collected: PR interval, QRS interval, RR interval, QT interval, and QT interval corrected for heart rate using Fridericia's formula (QTcF).

All ECGs must be evaluated by a qualified physician or qualified designee for the presence of abnormalities and will be captured electronically and retained for future evaluation if required, up to the time of the clinical study report (CSR) completion.

7.2.5 Physical Examinations

The full physical examination will be completed at screening and Day 0. It includes an assessment of general appearance and evaluation of head, eyes, ears, nose, mouth, throat, neck, thyroid, lymph nodes, and extremities, and dermatologic, respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurologic, and psychiatric systems.

The targeted (limited) physical examination will be completed at all other visits as indicated in the Schedule of Assessments (Section 4.3). It includes evaluation of patient complaints and SLE disease-related issues, and will exclude the genitourinary system.

7.2.6 C-SSRS

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed by Columbia University researchers for the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment. It is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening.[43]

The C-SSRS evaluation will be performed as specified in the Schedule of Assessments (Section 4.3). Patients with recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4, or 5 is exclusionary at screening will be excluded from the study. Patients with recent or active suicidal ideation or behavior at subsequent study visits will have responses to the C-SSRS reviewed in detail to assess patient risk, and appropriate consultative mental health services will be provided.

7.2.7 Injection Site Reactions

Patients will be monitored for local injection site reactions as specified in the Schedule of Assessments (Section 4.3). Local injection site reactions will be assessed predose and at 2 hours postdose. Injection site reactions should be managed according to the standard of care. Injection site reactions are to be reported as AEs of special interest (see Section 7.2.2.7.3).

7.2.8 Immunogenicity

The serum samples to measure the presence of ADA will be collected as specified in the Schedule of Assessments (Section 4.3). Blood samples (4 mL) to provide approximately 1.5 mL

of plasma for anti BOS161721 antibody analysis will be collected into appropriately labeled tubes containing K_2EDTA. The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods. Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only assayed if the patient had a positive ADA on Day 90.

After the first dose, if a patient tests positive in the validated confirmatory ADA assay, the sample from this patient will be further analyzed in the neutralizing antibody (nAb) assay.

7.3 Efficacy Assessments

All efficacy assessments will be performed at times defined in the Schedule of Assessments (Section 4.3).

7.3.1 SLEDAI-2K

The SLEDAI-2K is a validated instrument that measures disease activity in SLE patients at the time of the visit and in the previous 30 days. It is a global index and includes 24 clinical and laboratory variables that are weighted by the type of manifestation, but not by severity. The total score falls between 0 and 105, with higher scores representing increased disease activity. The SLEDAI-2K has been shown to be a valid and reliable disease activity measure in multiple patient groups. A SLEDAI -2K of 6 or more generally represents moderately to severely active disease.[44]

7.3.2 BILAG 2004

The BILAG-2004 index is an organ-specific 97-question assessment based on the principle of the doctor's intent to treat. Only clinical features attributable to SLE disease activity are to be recorded and based on the patient's condition in the last 4 weeks compared with the previous 4 weeks. It will be scored as not present (0), improved (1), the same (2), worse (3), or new (4). Disease activity is graded separately for 9 body systems to 5 different grades (A to E) as follows: A ("Active") is very active disease, B ("Beware") is moderate activity, C ("Contentment") is mild stable disease, D ("Discount") is inactive now but previously active, and E ("Excluded") indicates the organ was never involved.[44] A shift from BILAG-2004 Grade A or B to a lower grade indicates a clinically relevant change in disease activity as the BILAG-2004 grades mirror the decision points for treatment interventions.

Only investigators that complete BILAG-2004 training will be allowed to perform the BILAG-2004 assessments. Preferably, the same investigator should evaluate the patient at each BILAG-2004 assessment from screening to study completion. The investigator must maintain documentation with descriptive details supporting the BILAG-2004 scoring (eg, chart, worksheet, clinic notes, and labs) at each visit.

See APPENDIX 5 for detailed specifications.

7.3.3 PGA of Disease Activity

The PGA is used to assess investigator's general impression on the patient's overall status of SLE disease activity via visual analogue scale (100 mm) with 0 being "very good, asymptomatic and no limitation of normal activities" with 100 mm being "most severe possible disease ever seen in all SLE patients".

When scoring the PGA, the assessor should always look back at the score from the previous visit.

7.3.4 Composite Endpoints: SRI-4, SRI-5, SRI-6, and BICLA Response

7.3.4.1 SRI-4 Response

Patients will be evaluated for SRI-4 scores at Day 210, with evaluation for sustained reduction of oral CS (≤ 10 mg/day and ≤ Day 0 dose) between Day 120 and Day 210.

The SRI-4 is a composite index of SLE disease improvement that consists of scores derived from the SLEDAI-2K and the BILAG 2004 Index. Response based on the SRI-4 is defined by:

1) ≥ 4-point reduction in SLEDAI-2K global score, 2) no new severe disease activity (BILAG A organ score) or more than 1 new moderate organ score (BILAG B), and 3) no deterioration from baseline in the PGA by ≥ 0.3 points. The SRI-4 response in patients with moderate to severe SLE is associated with broad improvements in clinical and patient-reported outcomes.[45]

Each patient, after providing their Day 210 visit SRI-4 response, will be evaluated as either a responder or non-responder.

7.3.4.2 SRI-5 and SRI-6 Response

Like the SRI-4, the SRI-5 and SRI-6 are composite indices of SLE disease improvement that consists of scores derived from the SLEDAI-2K and the BILAG 2004 Index. However, the SRI-5 and SRI-6 are computed with a minimal three-point or five-point improvement in SLEDAI-2K being required, respectively.[46]

The SRI-5 and SRI-6 are evaluated for response at Day 180, along with a sustained reduction of oral CS (≤ 10 mg/day and ≤ Day 0 dose) between Day 120 and Day 210.

7.3.4.3 BICLA Response

The BICLA is a responder index developed to measure response to therapy, and it includes scores from the BILAG, SLEDAI-2K, and PGA. BICLA response is defined as 1) at least 1 gradation of improvement in baseline BILAG 2004 scores in all body systems with moderate disease activity at entry (eg, all B [moderate disease] scores falling to C [mild], or D [no activity]); 2) no new BILAG A or more than 1 new BILAG B scores; 3) no worsening of total SLEDAI-2K score from baseline; 4) ≤ 10% deterioration in PGA score and 5) no treatment failure.[44] It is driven primarily by the BILAG, and has been used in Phase 2 and 3 mAb studies.[47]

For the endpoints of BICLA response at Days 210, 240, and 270, patient scores will be completed and response determined.

7.3.5 CLASI Response

The CLASI is a comprehensive tool for assessment of disease activity and damage in cutaneous lupus, shown to be valid, reliable, and sensitive to changes in disease activity.[48] Response is defined as 50% improvement from baseline in "A" or "B" scores. This assessment will be applied to all patients as all are required to have cutaneous disease activity.

For the secondary efficacy endpoint of CLASI response at Day 210, patient scores on MAD and POC studies will be compared with baseline for 50% improvement.

7.3.6 ACR-28 Joint Count

The ACR-28 joint count will evaluate the number of tender and swollen joints in the shoulder, elbow, wrist, hand, knee joints. Joints of the feet are excluded.

7.4 Other Variables

7.4.1 SLICC/ACR Damage Index

The SLICC/ACR damage index is a validated instrument to assess damage, defined as irreversible impairment, continuously persistent for 6 months (ascertained by clinical assessment), occurring since the onset of lupus, and it is based on a weighted scoring system. This index records damage occurring in patients with SLE regardless of cause, with demonstrated content, face, criterion, and discriminant validity.[49] It will be performed on Days 0 and 180.

7.4.2 PROs

Patients should be encouraged to complete the PROs at the clinic at the beginning of the study visit prior to any clinical assessments. A member of the staff should be available if a patient requires further instruction and to review the PRO questionnaires for completeness prior to leaving the clinic. The PROs include the CCI and the CCI and will be assessed as specified in the Schedule of Assessments (Section 4.3).

CCI .

CCI .

7.5 Pharmacokinetic Assessments

During the MAD Phase 1b (all sites) and POC Phase 2 (select sites only) studies, blood samples for PK analysis of BOS161721 or placebo concentration will be collected according to Table 1 and Table 2.

PK parameters include the following:

- C_{max}, T_{max}, AUC, $t_{½}$, CL, V_d

Plasma concentrations of BOS161721 will be measured using a validated immunoassay. The PK parameters will be calculated from the plasma concentration-nominal time profiles for the IA2 and actual time profiles for the final analysis. The non-compartmental analysis will be performed using appropriately validated PK/PD software.

7.6 Pharmacodynamic Assessments

Blood samples for PD parameters (plasma) will be collected at times indicated in the Schedule of Assessments (Section 4.3) for each of the following parameters:

- pSTAT3
- Antibodies: CCI [redacted]
- Plasma complement ([redacted])
- Plasma [redacted] and [redacted]
- Whole blood for leukocyte immunophenotype
- Whole blood RNA
- IgG and IgM and CD4+ count

7.7 Pharmacokinetic/Pharmacodynamic Relationship

Evidence of any PK/PD relationships will be evaluated between BOS161721 plasma concentrations and the available PD endpoints and biomarkers.

7.8 Protocol Deviations

Protocol deviations will be documented during the study. Per the statistical analysis plan (SAP), these will be listed by patient and summarized by deviation category by treatment group.

8 STUDY DRUG MANAGEMENT

8.1 Description

8.1.1 Formulation

CCI [redacted]

CCI [redacted]

Additional information regarding dose preparation will be provided in a separate Pharmacy Manual.

8.1.2 Storage

All supplies of BOS161721 or placebo must be stored in accordance with the manufacturer's instructions. BOS161721 or placebo will be stored in a securely locked area, accessible to authorized persons only, until needed for dosing.

Information regarding storage and dose preparation will be provided in a separate Pharmacy Manual.

8.2 Packaging and Shipment

Investigational medicinal products will be supplied by Boston Pharmaceuticals, Inc. Investigational medicinal products will be packaged and labeled according to applicable local and regulatory requirements.

8.3 Dose and Administration

Details of dosing are provided in Section 4.1.

Each unit dose will be prepared by a qualified staff member. The vials of investigational product (IP) will appear identical and will have a "blinded" label on the vials that will state CCI [redacted] mg or placebo. When the site goes into the IWRS to request the patient kit(s), the IWRS will assign the appropriate number of kits (regardless of assignment to placebo or active treatment) per the dose (ie, CCI [redacted]). If a patient is randomized to the placebo arm, they will receive the matching number of kits.

The designated staff member (or designee under the direction of the designated staff member) will dispense BOS161721 or placebo for each patient according to the protocol, randomization list, and Pharmacy Manual, if applicable.

After receiving sponsor approval in writing, the investigational site is responsible for returning all unused or partially used BOS161721 or placebo to the sponsor or designated third party or for preparing BOS161721 or placebo for destruction via incineration.

Further details are found in a separate Pharmacy Manual.

8.4 Accountability

The Principal Investigator or designee is responsible for maintaining accurate accountability records of BOS161721 or placebo throughout the clinical study. The drug accountability log includes information such as, randomization number, amount dispensed and amount returned to the pharmacy (if any). Products returned to the pharmacy will be stored under the same conditions as products not yet dispensed. The returned products should be marked as 'returned' and kept separate from the products not yet dispensed.

All dispensing and accountability records will be available for sponsor review after database lock procedures are completed. During safety monitoring, the drug accountability log will be reconciled with the products stored in the pharmacy.

8.5 Prohibited Concomitant Therapy

Prohibited concomitant medications are discussed in Section 5.6 and APPENDIX 4 and will be listed as protocol violations if taken when not permitted.

8.6 Compliance

Dosing will be performed by trained, qualified personnel designated by the principal investigator. The date and time of dosing will be documented on each dosing day. Comments will be recorded if there are any deviations from the planned dosing procedures.

9 STATISTICS

There are 2 IAs planned for the study. The first IA will be conducted at the time of the POC decision for dose selection. The second IA will be performed for futility (see Section 9.3). Before the first IA, a SAP will be finalized, providing detailed methods for the analyses outlined below. Any deviations from the planned analyses will be described and justified in the final integrated CSR.

The following standards will be applied for the analysis unless otherwise specified. Continuous data will be summarized by treatment group using descriptive statistics (number, mean, standard deviation [SD], minimum, median, and maximum). Categorical data will be summarized by treatment group using frequency tables (number and percentage).

9.1 Sample Size

Sample size in the Phase 1b study is based on operational consideration.

A summary of the power in the trial for the chosen sample size is provided in Table 5, with N = 132 randomized 89:43 to the chosen dose for the POC study and placebo, respectively; this includes 12 patients from the MAD study who were in the cohort of the mid or high dose if chosen for the POC study.

Table 5. Sample Size

Type 1 Error (1-Sided)	TRUE Underlying Response Rate (%)		Overall Power	Minimum OBSERVED Response Rates Yielding Statistical Significance	
	Placebo	Treatment		Placebo	Treatment
0.025	40	60	0.54	40	60
	40	65	0.75		
	40	70	0.9		
0.05	40	60	0.63	40	58
	40	65	0.81		
	40	70	0.93		

Total sample size of approximately 156 patients is planned for analysis, but may be adjusted upward according to the dropout (noncompliance) rate, which will be monitored in a blinded fashion in an ongoing basis. Note that approximately 36 dropouts are assumed.

9.2 Statistical Methods

9.2.1 Analysis Populations

The primary efficacy analysis will be based on the full analysis set (FAS), defined to be all patients with at least 1 baseline and post-baseline efficacy evaluation. A per protocol (PP) analysis set may be defined to exclude major protocol violations from the efficacy analysis. The PP Population will include all patients from the FAS except those with major violations to the protocol deemed to impact the analysis of the primary endpoint. These violations will be identified based on blinded data prior to unblinding the final analysis dataset. Safety analyses will be based on all patients who receive test treatment. Pharmacokinetic analysis will be conducted on the PK analysis set (PK), defined as the FAS with sufficient concentration data for the calculation of PK parameters. All analyses will combine data from the MAD and POC studies and focus on the active treatment dose chosen for the POC study versus placebo. The 0.05 1-sided type 1 error level is included for POC, and the 0.025 1-sided type 1 error level for potential use of this trial to support regulatory filing.

9.2.2 Demographics and Baseline Characteristics

Baseline and patient characteristics will be summarized via appropriate summary statistics by treatment group and overall, for each phase of the trial.

9.2.3 Primary Endpoint(s)

The proportion of patients who achieve treatment response (measured by SRI-4 at Day 210 along with a sustained reduction of oral CS) will be analyzed via Cochran-Mantel-Haenszel (CMH) analysis. The primary endpoint will be analyzed on the FAS and if needed the PP analysis set. In addition, missing values will be addressed by employing a last observation carried forward (LOCF) analysis and/or other appropriate analytic approaches as a sensitivity analysis. Details will be available in the SAP.

9.2.4 Secondary Endpoint(s)

Binary efficacy endpoints will be assessed via CMH analysis. Continuous efficacy endpoints will be assessed via analysis of covariance (ANCOVA) repeated measures mixed model analysis with factors including treatment, time, treatment-by-time interaction, baseline covariate, and covariate-by-time interaction. The secondary efficacy endpoint will be analyzed on the FAS and if needed the PP analysis set. Details will be available in the SAP.

9.2.5 Analysis of Safety

9.2.5.1 Safety Analysis

Safety analyses will be performed on the Safety Analysis Set. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Incidences (number and percent) of AEs will be presented by treatment group. Incidences of AEs will also be presented by maximum severity and relationship to study medication. For the MAD study, the placebo patients from each cohort will be combined for the summaries. If there is a clear increase in AE rates for placebo patients across the cohorts, the AEs will also be summarized by cohort.

AEs will be summarized by counts and percentages of patients by treatment group. Laboratory data and vital signs will be summarized by treatment group as summary statistics for value and change from baseline at each individual time point. Summary statistics will include n, arithmetic mean, median, arithmetic SD, minimum, and maximum.

Additional safety parameters will be analyzed descriptively by treatment group. Descriptive statistics (n, mean, standard deviation (SD), median, minimum, maximum) will be calculated by treatment group and time point for continuous variables. Frequencies and percentages will be presented by treatment group for categorical and ordinal variables.

9.2.5.2 Data Monitoring Committee

This study will use an external DMC. The DMC is an independent committee established to provide oversight of safety considerations in study and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of enrolled patients and those yet to be recruited to the trial as well as for the continuing validity and scientific merit of the study results. The DMC is charged with assessing such actions in light of an acceptable benefit/risk profile for anti-IL-21 mAb. The recommendations made by the DMC (ie, dose escalation, etc.) will be forwarded to the sponsor for final decision. The sponsor will

forward such decisions, which may include summaries of safety data which are not endpoints, to regulatory authorities, as appropriate.

The DMC will have access to unblinded treatment information during the clinical trial. Details regarding management and process of this committee are found in the DMC Charter.

The DMC may recommend termination of an anti-IL-21 mAb treatment arm or the entire BOS161721 MAD/POC trial for any safety concern that is felt to outweigh potential benefits. The recommendation must be supported by the sponsor as indicated in the DMC Charter.

9.2.6 Pharmacokinetic and Pharmacodynamic Data

9.2.6.1 Analysis of Pharmacokinetic Data

The PK parameter data will be listed and summarized descriptively in tabular format.

If data permit, the following analyses will be performed for plasma BOS161721 concentration data:

- A listing of all plasma BOS161721 concentrations by patient at actual times post dose;
- A descriptive summary of plasma BOS161721 concentrations. Summary statistics of geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum will be tabulated by study days with PK assessments.

Details will be available in the SAP.

9.2.6.2 Analysis of Pharmacodynamic Data

The PD parameter data will be listed and summarized descriptively in tabular format.

Binary PD endpoints will be assessed for the FAS population. Binary PD endpoints will be assessed via CMH analysis. Continuous PD endpoints will be assessed via analysis of covariance (ANCOVA) repeated measures mixed model analysis with factors including treatment, time, treatment-by-time interaction, baseline covariate, and covariate-by-time interaction. Normality will be assessed via diagnostic residual plots and Shapiro-Wilk statistic, but not as a formal statistical test of normality. If substantial departures from normality are observed, transformation will be used (eg, log and/or rank).

Details will be available in the SAP.

9.2.6.3 Population Pharmacokinetic Analysis or PK/PD Modeling

Plots of individual patient values for each relevant PD parameter on Y-axis and each relevant PK parameter on X-axis will be examined for relationship. If relationships are revealed by these diagnostic plots, PK and PD data from this study may be analyzed using modeling approaches to describe the relationship and may also be pooled with data from other studies to investigate any association between BOS161721 exposure and biomarkers or significant safety endpoints.

Details will be available in the SAP.

9.3 Interim Analysis and Power

Two IAs are planned for this study. The initial IA will be conducted at the time of the POC decision for dose selection.

The second IA will be performed for futility. IA2 is planned to be conducted at Day 90 when SRI-4 response is determined for approximately 60 patients (including all patients at the same dose level/matching placebo from the MAD study) after completing 3 months of treatment. The purpose of the IA2 is to assess if the trial could stop for an early futility conclusion, or continue. Since there is no plan to stop the trial for an early efficacy conclusion, there is no impact on the type 1 error. If that intention changes, then $p < 0.0001$ is required for an early efficacy conclusion at the IA2 in order to not impact the planned type 1 error level.

Nominal time profiles will be used for calculating PK parameters in the IA2. Details will be available in the SAP.

10 ETHICS AND RESPONSIBILITIES

10.1 Good Clinical Practice

The procedures set out in this protocol are designed to ensure that the sponsor and the principal investigator abide by the principles of the International Council for Harmonisation (ICH) guidelines on GCP and the Declaration of Helsinki (Version 2013). The clinical study also will be carried out in the keeping with national and local legal requirements (in accordance with US IND regulations [21 CFR 56]).

10.2 DMC

The sponsor will appoint a DMC for the periodic review of available study data. The DMC is an independent group of experts that advises the sponsor and the study investigators. The members of the DMC serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DMC are to (1) periodically review and evaluate the accumulated study data for participant safety, study conduct, and progress, (2) make recommendations to the sponsor concerning the continuation, modification, or termination of the study and (3) suggest dose for POC portion of the study.

The DMC considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. The DMC is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking (unblinding), and voting procedures prior to initiating any data review. The DMC is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

10.3 Institutional Review Board/Independent Ethics Committee

Independent Ethics Committees (IEC)/Institutional Review Boards (IRB) must meet the guidelines set out by the U.S. Food and Drug Administration (FDA) and conform to local laws and customs where appropriate. Written IRB/IEC approval for the protocol and the signed ICF must be obtained and transmitted to Boston Pharmaceuticals or representative before the study can be initiated. The IRB/IEC must be informed of and approve all protocol amendments. The investigator will ensure that this study is conducted in full conformance with all applicable local and regional laws and regulations. The complete text of the World Medical Association Declaration of Helsinki is given in APPENDIX 2.

10.4 Informed Consent

Before each patient undergoes any protocol required assessments or procedure, the written informed consent will be obtained according to the regulatory and legal requirements of the participating country. As part of this procedure, the principal investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study patient should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. The principal investigator or designee will provide the sponsor with a copy of the IRB-approved ICF prior to the start of the study.

The informed consent document must be signed and dated; 1 copy will be handed to the patient and the principal investigator will retain a copy as part of the clinical study records. The principal investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

If the informed consent document is revised, it must be reviewed and approved by the responsible IRB/IEC. Patients currently enrolled may need to sign this revision (based on IRB/IEC requirements) and all future subjects enrolled in the clinical study will be required to sign this revised ICF.

10.5 Records Management

The principal investigator will ensure the accuracy, completeness, and timeliness of the data reported to the sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The principal investigator or designee will cooperate with the sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The principal investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each patient receiving BOS161721 or placebo.

The principal investigator will allow sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB to have direct access to all documents pertaining to the study.

Electronic case report forms are required and should be completed for each randomized patient. It is the principal investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported on the patients' eCRF. Electronic case report forms should be completed in a timely fashion to support the study timelines. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status. The principal investigator or designated representative should complete and the principal investigator should verify the source documents as the information is collected. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The principal investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes.

10.6 Source Documentation

The documents that will form the source data for the clinical study (eg, patient charts, laboratory reports) must be defined and documented in the in-house study master file prior to the start of the study. Data on the eCRFs which will be checked against source data during monitoring visits must also be defined and documented in the in-house study master file including the percentage of each of the source data to be verified and the percentage of patients' eCRFs to be monitored.

10.7 Study Files and Record Retention

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of BOS161721. However, these documents should be retained for a longer period if required by the applicable legal requirements.

11 AUDITING AND MONITORING

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and on-site visits. The study will be routinely monitored to ensure compliance with the study protocol and the overall quality of data collected. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the

study monitor. The study monitor may periodically request review of the investigator study file to assure the completeness of documentation in all respects of clinical study conduct. The study monitor will verify that each patient has proper consent documentation from the patient and/or patient's authorized representative for study procedures and for the release of medical records to the sponsor, FDA, other regulatory authorities, and the IRB. The study monitor will also verify that assent was obtained for patients not capable of providing informed consent or that documentation is provided by the investigator explaining why the patient was unable to provide assent. The investigator or appointed delegate will receive the study monitor during these on-site visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies. On completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

Throughout the course of the study, the medical monitor will determine eligibility of all screened patients, will address any medical issues that might arise, clarify medical questions, review patient safety data (eg, AE/SAE, laboratory, and ECG), and partner with the study team in the overall study management. The study medical monitoring plan will document additional details of the study medical oversight and monitoring.

12 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by Boston Pharmaceuticals. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. Boston Pharmaceuticals will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, and/or Boston Pharmaceuticals, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the patient and/or has an impact on the patient's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for patients enrolled in the study before continued participation.

13 STUDY REPORT AND PUBLICATIONS

Boston Pharmaceuticals is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

By signing the protocol, the principal investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the competent authorities will be notified of the principal investigator's name, address, qualifications, and extent of involvement.

The principal investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted and obtained approval from the sponsor in advance.

14 STUDY DISCONTINUATION

Both Boston Pharmaceuticals and the principal investigator reserve the right to terminate the study at the investigator's site at any time. Should this be necessary, Boston Pharmaceuticals or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the principal investigator will inform the IRB/IEC of the same. In terminating the study Boston Pharmaceuticals and the principal investigator will assure that adequate consideration is given to the protection of the patients' interests.

15 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Boston Pharmaceuticals, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial or to comply with regulatory requirements. However, authorized regulatory officials, IRB/IEC personnel, Boston Pharmaceuticals, and its authorized representatives are allowed full access to the records.

Identification of patients and eCRFs shall be by initials, birthdate, or patient number. Documents that identify the patient (eg, the signed informed consent document) must be maintained in confidence by the principal investigator. If required, the patient's full name may be made known to an authorized regulatory agency or other authorized official.

16 REFERENCES

1 Urowitz MB, Gladman DD. How to improve morbidity and mortality in systemic lupus erythematosus. Rheumatology 2000;39:238-44.

2 Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Morbidity and Mortality in Systemic Lupus Erythematosus During a 10-Year Period. Medicine 2003;82(5):299-308.

3 Pons-Estel GJ, Alarcón GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. Semin Arthritis Rheum. 2010;39(4):257. Epub 2009 Jan 10.

4 Kanta H, Mohan C. Three Checkpoints in lupus development: central tolerance in adaptive immunity, peripheral amplification by innate immunity, and end-organ inflammation. Genes and Immunity 2009;10:390-6.

5 Dall'Aqua WF, Kiener PA, Wu H. Properties of Human IgG1s Engineered for Enhanced Binding to the Neonatal Fc Receptor (FcRn). J Biol Chem. 2006 Aug 18, 281(33):23514-24.

6 Spolski R, Leonard WJ. The Yin and Yang of interleukin-21 in allergy, autoimmunity and cancer. Curr Opin Immunol. 2008a;20:295-301.

7 Asao H, Okuyama C, Kumaki S, Ishii N, Tsuchiya S, Foster D, et al. Cutting edge: the common gamma-chain is an indispensable subunit of the IL-21 receptor complex. J Immunol. 2001;167:1-5.

8 Habib T, Senadheera S, Weinberg K, Kaushansky K. The common gamma chain (gamma c) is a required signaling component of the IL-21 receptor and supports IL-21-induced cell proliferation via JAK3. Biochemistry. 2002;41:8725-31.

9 Spolski R, Leonard WJ. Interleukin-21: basic biology and implications for cancer and autoimmunity. Annu Rev Immunol. 2008b;26:57-79.

10 Puga I, Cols M, Barra CM, He B, Cassis L, Gentile M, et al. B-cell-helper neutrophils stimulate the diversification and production of immunoglobulin in the marginal zone of the spleen. Nat Immunol. 2011;13(2):170-80.

11 Costanzo A, Chimenti MS, Botti E, Caruso R, Sarra M, Monteleone G. IL-21 in the pathogenesis and treatment of skin diseases. J Dermatol Sci. 2010;60(2):61-6.

12 Avery DT, Bryant VL, Ma CS, de Waal Malefy R, Tangye SG. IL-21-induced isotype switching to IgG and IgA by human naive B cells is differentially regulated by IL-4. J Immunol. 2008;181:1767-79.

13 Rasmussen TK, Andersen T, Bak, RO, Yiu G, Sorensen CM, Stengaard-Pedersen K, et al. Overexpression of microRNA-155 increases IL-21 mediated STAT3 signaling and IL-21 production in systemic lupus erythematosus. Arthritis Research & Therapy 2015;17(154)

14 Ettinger R, Kuchen S, Lipsky PE. The role of IL-21 in regulating B-cell function in health and disease. Immunol Rev. 2008;223:60-86.

15 Caprioli F, Sarra M, Caruso R, Stolfi C, Fina D, Sica G, et al. Autocrine regulation of IL-21 production in human T lymphocytes. J Immunol. 2008;180(3):1800-7.

16 Yang L, Anderson DE, Baecher-Allan C, Hastings WD, Bettelli E, Oukka M, et al. IL-21 and TGF-beta are required for differentiation of human T(H)17 cells. Nature. 2008;454(7202):350-2.

17 Tangye SG, Ma CS, Brink R, Deenick EK. The good, the bad and the ugly - TFH cells in human health and disease. Nat Rev Immunol. 2013;13(6):412-26.

18 Fantini MC, Rizzo A, Fina D, Caruso R, Becker C, Neurath MF, et al. IL-21 regulates experimental colitis by modulating the balance between Treg and Th17 cells. Eur J Immunol. 2007;37(11):3155-63.

19 Peluso I, Fantini MC, Fina D, Caruso R, Boirivant M, MacDonald TT, et al. IL-21 counteracts the regulatory T-cell-mediated suppression of human CD4+ T lymphocytes. J Immunol. 2007;178(2):732-9.

20 Hippen KL, Bucher C, Schirm DK, Bearl AM, Brender T, Mink KA, et al. Blocking IL-21 signaling ameliorates xenogeneic GVHD induced by human lymphocytes. Blood. 2012;119(2):619-28.

21 Davis ID, Skrumsager BK, Cebon J, Nicholaou T, Barlow JW, Moller NP, et al. An open-label, two-arm, phase I trial of recombinant human interleukin-21 in patients with metastatic melanoma. Clin Cancer Res. 2007;13:3630-6.

22 Frederiksen KS, Lundsgaard D, Freeman JA, Hughes SD, Holm TL, Skrumsager BK, et al. IL-21 induces in vivo immune activation of NK cells and CD8(+) T-cells in patients with metastatic melanoma and renal cell carcinoma. Cancer Immunol Immunother. 2008;57(10):1439-49.

23 Karrich JJ, Jachimowski LC, Nagasawa M, Kamp A, Balzarolo M, Wolkers MC, et al. IL-21- stimulated human plasmacytoid dendritic cells secrete granzyme B, which impairs their capacity to induce T-cell proliferation. Blood. 2013;121(16):3103-11.

24 Lindner S, Dahlke K, Sontheimer K, Hagn M, Kaltenmeier C, Barth TF, et al. Interleukin-21-induced granzyme B-expressing B-cells infiltrate tumors and regulate T-cells. Cancer Res. 2013;73(8):2468-79.

25 Monteleone G, Caruso R, Fina D, Peluso I, Gioia V, Stolfi C, et al. Control of matrix metalloproteinase production in human intestinal fibroblasts by interleukin 21. Gut. 2006;55(12):1774-80.

26 Nakou M, Papadimitraki ED, Fanouriakis A, Bertsias GK, Choulaki C, Goulidaki N, et al. Interleukin-21 is increased in active systemic lupus erythematosus patients and contributes to the generation of plasma B-cells. Clin Exp Rheumatol. 2013;31(2):172-9.

27 Li Q, Liu Z, Dang E, Jin L, He Z, Yang L, et al. Follicular helper T-cells (Tfh) and IL-21 involvement in the pathogenesis of bullous pemphigoid. PLoS One. 2013;8(7):e68145.

28 Liu R, Wu Q, Su D, Che N, Chen H, Geng L, et al. A regulatory effect of IL-21 on T follicular helper-like cell and B-cell in rheumatoid arthritis. Arthritis Res Ther. 2012;14(6):R255.

29 Kang KY, Kim HO, Kwok SK, Ju JH, Park KS, Sun DI, et al. Impact of interleukin-21 in the pathogenesis of primary Sjögren's syndrome: increased serum levels of interleukin-21 and its expression in the labial salivary glands. Arthritis Res Ther. 2011;13(5):R179.

30 Terrier B, Geri G, Chaara W, Allenbach Y, Rosenzwajg M, Costedoat-Chalumeau N, et al. Interleukin-21 modulates Th1 and Th17 responses in gianT-cell arteritis. Arthritis Rheum. 2012a;64(6):2001-11.

31 Terrier B, Costedoat-Chalumeau N, Garrido M, Geri G, Rosenzwajg M, Musset L, et al. Interleukin 21 correlates with T-cell and B-cell subset alterations in systemic lupus erythematosus. J Rheumatol. 2012b;39(9):1819-28.

32 International Conference on Harmonisation. Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6 (R1). 2011.

33 Wang W, Wang EQ, Balthasar JP. Monoclonal Antibody Pharmacokinetics and Pharmacodynamics. Clin Pharm & Ther 2008; 84(5):548-58.

34 Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. Journal of Allergy and Clinical Immunology 2006;117:391–7.

35 Elsaesser H, Sauer K, Brooks DG. IL-21 is required to control chronic viral infection. Science. 2009;324(5934):1569-72

36 Kotlarz D, Zietara N, Uzel G, Weidemann T, Braun CJ, Diestelhorst J, et al. Loss-of-function mutations in the IL-21 receptor gene cause a primary immunodeficiency syndrome. J Exp Med. 2013;210(3):433-43.

37 Hunter PR, Nichols G. Epidemiology and clinical features of Cryptosporidium infection in immunocompromised patients. Clinical microbiology reviews. 2002;15(1):145-54.

38 Desjardins M, Mazer BD. B-cell memory and primary immune deficiencies: interleukin-21 related defects. Curr Opin Allergy Clin Immunol. 2013;13(6):639-45.

39 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.

40 Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, US: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a4.htm.

41 NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, available at https://evs.nci.nih.gov/ftp1/CTCAE/About.html.

42 Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. Journal of Allergy and Clinical Immunology 2006;117:391–7.

43 Posner K, Melvin G a, Stanley B, Oquendo M a, Gould M. Factors in the assessment of suicidality in youth. *CNS Spectr*. 2007;12(2):156-162.

44 Castrejon I, Tani C, Jolly M, Huang A, Mosca M. Indices to assess patients with systemic lupus erythematosus in clinical trials, long-term observational studies, and clinical care. Clin Exp Rheumatol 2014; 32(85):S85-95.

45 Furie R, Wang L, Drappa J, Illei G. Systemic Lupus Erythematosus (SLE) Responder Index [SRI(4)] Response Is Associated with Global Benefit in Patients with Moderate to Severe SLE [abstract]. *Arthritis Rheumatol.* 2016; 68 (suppl 10).

46 Thanou A, Chakravarty E, James JA, Merrill JT. Which outcome measures in SLE clinical trials best reflect medical judgment? Lupus Science & Medicine 2014;1:e000005. doi:10.1136/lupus-2013-000005.

47 Wallace DJ, Kalunian K, Petri MA, Strand V, Houssiau FA, Pike M,*et al.* Efficacy and safety of epratuzumab in patients with moderate/severe active systemic lupus erythematosus: results from EMBLEM, a phase IIb, randomised, double-blind, placebo-controlled, multicentre study. *Ann Rheum Dis* 2014;73:183-90.

48 Albrecht J, Taylor L, Berlin JA, Dulay S, Ang G, Fakharzadeh S. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): An Outcome Instrument for Cutaneous Lupus Erythematosus. J Invest Derm. 2005;125(5):889-94.

49 Stoll T, Seifert B, Isenberg DA. SLICC/ACR Damage Index is Valid, and Renal and Pulmonary Organ Scores are Predictors of Sever Outcome in Patients with Systemic Lupus Erythematosus. Br J Rheumatol. 1996;35:248-54.

50 CCI [redacted].

17 APPENDICES

APPENDIX 1 NAMES OF STUDY PERSONNEL

Sponsor:	Boston Pharmaceuticals 55 Cambridge Parkway Suite 401 Cambridge, MA 02142, USA
Medical Monitor:	PPD
	PPD
Clinical Research Organizations:	PPD
	PPD
	PPD
Bioanalytical Laboratory:	PPD
Central Laboratory:	PPD

APPENDIX 2 DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles
For
Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subject."

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic, and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility, and quality.

In current medical practice and in medical research, most prophylactic, diagnostic, and therapeutic procedures involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Research investigators should be aware of the ethical, legal, and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal, or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any SAEs. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a subject of the research, even though the subject has given consent.

Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the

subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

The subjects must be volunteers and informed participants in the research project.

The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the subject's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining

informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic, or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the subjects who are research subjects.

The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists.

At the conclusion of the study, every subject entered into the study should be assured of access to the best-proven prophylactic, diagnostic, and therapeutic methods identified by the study.

The physician should fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study must never interfere with the subject-physician relationship.

In the treatment of a subject, where proven prophylactic, diagnostic, and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the subject, must be free to use unproven or new prophylactic, diagnostic, and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health, or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

APPENDIX 3 COMMONLY USED CORTICOSTEROID EQUIVALENTS

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

APPENDIX 4 MEDICATION WASHOUT PERIODS

WASHOUT TIMES OF MEDICATIONS BASED ON 5 HALF-LIVES

Medication	Discontinuing Prior to Signing Consent
Abatacept (CTLA4Ig)	24 weeks
Alefacept	12 weeks
AMG 623 (blisibimod)	24 weeks
Anifrolumab	12 weeks
Atacicept (TACI-Ig)	12 weeks
Belimumab	48 weeks
Cyclophosphamide	24 weeks
Cyclosporine (except for CSA eye drops)	4 weeks
Danazol	4 weeks
Dapsone	4 weeks
Eculizumab	12 weeks
Efalizumab	12 weeks
Epratuzumab	24 weeks
Intravenous globulin	4 weeks
Leflunomide	8 weeks (4 weeks for washout with cholestyramine)
Lenalidomide with cholestiramine	8 weeks
Lupuzor	12 weeks
Memantine	4 weeks
Natalizumab	24 weeks
Ocrelizumab	48 weeks (or 24 weeks with recovery of B cell)
Pimecrolimus	4 weeks
Plasmapheresis	24 weeks
Retinoids (oral or topical)	4 weeks
Rituximab	48 weeks (or 24 weeks with recovery of B cell)
Sirolimus	4 weeks
Tacrolimus	4 weeks
Thalidomide	8 weeks
Tocilizumab	12 weeks

APPENDIX 5 BILAG-2004 (STUDY-SPECIFIC MODIFIED CRITERIA)

CCI

A RANDOMIZED DOUBLE-BLIND PHASE 1b/2 COMBINED STAGGERED MULTIPLE DOSE ESCALATION STUDY OF BOS161721 IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS ON A BACKGROUND OF LIMITED STANDARD OF CARE

SPONSOR	Boston Pharmaceuticals, Inc. 55 Cambridge Parkway, Suite 401 Cambridge, MA 02142 United States of America (USA)
INVESTIGATIONAL COMPOUND:	BOS161721
PROTOCOL NUMBER:	BOS161721-02
PHASE	Phase 1b/2
INVESTIGATIONAL NEW DRUG (IND) NUMBER:	131796
ORIGINAL PROTOCOL DATE:	05 October 2017
VERSION NUMBER:	V1.0
VERSION DATE:	06 October 2017

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care

Study No: BOS161721-02
Original Protocol Date: 05 October 2017
Protocol Version No: v1.0
Protocol Version Date: 06 October 2017

This study protocol was subject to critical review and has been approved by sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (APPENDIX 2), and principles of Good Clinical Practices (GCP) as described in 21 Code of Federal Regulations (CFR) parts 50, 54, 56 and 312 and according to applicable local requirements.

The investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

I agree with these statements and indicate my approval by signature for this protocol:

Name and Title	Signature	Date
PPD, MD Vice President, Clinical Development Boston Pharmaceuticals	PPD	10/6/2017
PPD Clinical Operations Lead Boston Pharmaceuticals	PPD	10/6/2017
PPD, MD, PhD Vice President, Clinical Development and Safety Officer Boston Pharmaceuticals	PPD	10/6/2017

BOS161721-02

A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to BOS161721 are the confidential and proprietary information of Boston Pharmaceuticals, Inc., and except as may be required by federal, state, or local laws or regulation, may not be disclosed to others without prior written permission of Boston Pharmaceuticals, Inc.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Council for Harmonisation (ICH) guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Boston Pharmaceuticals, Inc., or specified designees. I will discuss the material with them to ensure that they are fully informed about BOS161721 and the study.

_____ _____

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

PROTOCOL SUMMARY

Title:	A Randomized Double-Blind Phase 1b/2 Combined Staggered Multiple Dose Escalation Study of BOS161721 in Systemic Lupus Erythematosus (SLE) Patients on a Background of Limited Standard of Care
Indication	Adults with moderately to severely active SLE
Background and Rationale	SLE is a chronic systemic autoimmune disease with considerable heterogeneity in clinical manifestations and disease course. There is evidence that B- and T-cells are critical to the development of the disease, and that T-cell-derived cytokines such as interleukin-21 (IL-21) are involved in the SLE-associated inflammatory pathological response. BOS161721 is a humanized immunoglobulin G1 (IgG1) triple mutation monoclonal antibody (mAb) intended to have an extended terminal elimination half-life ($t_{1/2}$) that selectively binds to and neutralizes IL-21, which acts on multiple cell types that drive inflammation and autoimmunity. In vivo, BOS161721 inhibits T-cell dependent antigen responses of B-cells and is being developed as a potential treatment for adults with moderately to severely active SLE. Nonclinical studies have evaluated the toxicity, pharmacodynamics (PD), toxicokinetics (TK), pharmacokinetics (PK), and immunogenicity of BOS161721 administered intravenously (IV) and subcutaneously (SC). The no observed adverse effect levels (NOAELs) in Cynomolgus monkeys were determined to be 100 mg/kg IV and 50 mg/kg SC, the highest doses tested. No SC animals had injection reactions. In a Phase 1 single ascending dose (SAD) study, BOS161721 was administered IV and SC to healthy male and female adult subjects. This double-blind, placebo-controlled study evaluated 8 ascending dose levels (1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg) for safety, tolerability, PK, PD and immunogenicity. Overall, there were no clinically significant safety or tolerability findings from this study. Results from the Phase 1 SAD study informed the dose regimens used for the multiple ascending doses (MAD) Phase 1b study in this trial. The MAD study will involve 3 cohorts. The Phase 2 portion will be a proof of concept (POC) study, where dose selection will be based on the sponsor's assessment of safety, tolerability, immunogenicity, and PK and PD data from the MAD study of

30 patients treated with BOS161721/placebo. The purpose of the study is to establish safe and effective dosages for adult patients with moderately to severely active SLE.

Objectives:

MAD Phase 1b Study

Primary Objective:

To assess safety, tolerability, and immunogenicity of repeat doses of BOS161721 (20 mg, 60 mg, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment, in order to estimate the optimal dose.

POC Phase 2 Study

Primary Objective:

To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on the SLE Responder Index 4 (SRI-4), with sustained reduction of oral corticosteroids (CS), in adult patients with moderately to severely active SLE on limited background standard of care treatment.

Secondary Objectives:

To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on clinical indicators of SLE activity, in adult patients with moderately to severely active SLE on limited background standard of care treatment, including:

- Changes in SLE-specific autoantibody titers;
- Changes in complement 3 and 4 (C3 and C4) levels;
- Responses on SRI-4, SLE Responder Index 5 and 6 (SRI-5, and SRI-6), with sustained reduction of oral CS;
- Response on the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA);
- Response on the Cutaneous Lupus Erythematosus Area and Severity Index (CLASI);
- Changes in the SLE Disease Activity Index 2000 (SLEDAI-2K);
- Changes in the American College of Rheumatology (ACR)-28 joint count.

Endpoints:

Phase 1b MAD Study

Primary Endpoints:

Evaluation of safety, tolerability, and immunogenicity at each dose level, to determine the optimal dose, will include the recording of the following parameters:

- Incidence and severity of adverse events (AEs) and serious adverse events (SAEs);
- 12-lead electrocardiograms (ECGs);
- Vital signs (blood pressure [BP], heart rate, and temperature);
- Clinical laboratory assessments;
- Physical examinations;
- Evaluation for anti-drug antibodies (ADAs).

Exploratory Endpoints:

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted].

Other Endpoints:

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

PRO Endpoints:

- CCI [redacted]
- CCI [redacted]

Phase 2 POC Study

Primary Efficacy Endpoint:

The primary efficacy endpoint is the proportion of patients who achieve treatment response as measured by the SRI-4 at Week 28, along with a sustained reduction of oral CS (≤ 10 mg/day and ≤ Day 1 dose) between Week 16 and Week 28.

Secondary Efficacy Endpoints:

- The proportion of patients who achieve treatment response for the SRI-5 and SRI-6 at Week 28, along with a sustained reduction of oral CS (≤ 10 mg/day and ≤ Day 1 dose) between Week 16 and Week 28;
- Changes from baseline in dsDNA, ANA, SSA, SSB, RNP, Sm, APL autoantibodies, at Week 16 and Week 28;
- Changes from baseline in C3 and C4 levels at Week 16 and Week 28;
- Changes from baseline in the SLEDAI-2K at Week 28;
- Time to BILAG A or B flare;
- Changes from baseline in the CLASI at Week 28;
- The proportion of patients with a BICLA response at Week 28;

- The proportion of patients with CLASI response at Week 28;
- Changes from baseline (percentage) in swollen joints and tender joints ACR-28 joint count;
- Assessment of safety, tolerability, and immunogenicity as described for the primary endpoint in the MAD Phase 1b study.

Exploratory Endpoints:

- CCI [redacted]
- CCI [redacted]

Other Endpoints:

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

PRO Endpoints:

- CCI [redacted]
- CCI [redacted]

Study Design:

This is a Phase 1b/2 combined, randomized, multicenter, double-blind, placebo-controlled trial to study the clinical efficacy, safety, and PK of multiple SC doses of BOS161721 in adult patients with moderately to severely active SLE. After successfully completing a screening phase, patients will be randomized to a specified dose of BOS161721 or placebo. The dosing schedule will be monthly. The trial will consist of a staggered MAD Phase 1b and POC Phase 2 studies. Both studies will be double-blinded with each patient having the same number of doses (7), and visits; the duration will be 180 days, followed by a 90-day follow-up safety observation period.

The MAD Phase 1b study phase will consist of 3 cohorts, with Cohort 1 containing 6 patients, where 5 of these patients will receive

BOS161721 (active), and 1 will receive placebo. Cohorts 2 and 3 will each contain 12 patients, including 9 active and 3 placebo patients. Dose selection for each cohort is based on 90-day safety, tolerability, PK, and PD data review from the Phase 1 SAD study (BOS161721-01) in healthy subjects. Each of the 3 doses (20 mg, 60 mg, and 120 mg) selected for the MAD study are projected not to exceed the mean peak levels or exposures of that achieved in the SAD study following the single 240 mg SC dose. Each patient may receive a total of 7 SC monthly doses on Days 1, 30, 60, 90, 120, 150, and 180.

The MAD study design is staggered, where after the 6 patients in Cohort 1 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 2 begins dosing (after a data monitoring committee [DMC] evaluates the safety and tolerability data from Cohort 1). Similarly, after 8 of the 12 patients in Cohort 2 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 3 begins dosing (based on the dose level determined after DMC evaluation of the safety and tolerability data from Cohort 2 and Cohort 1). Two weeks after the last patient in Cohort 3 receives the second dose, the DMC will conduct a data review for the first interim analysis (IA1) to determine which dose will be carried forward into the POC Phase 2 study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2 and 3; this dose will not exceed doses tested during the MAD study. The DMC will be reviewing all relevant data from Cohorts 1, 2, and 3 that is available when the last patient in Cohort 3 reaches 60 days (dose 2). Once the POC dose decision has been made, screening for the POC study can begin.

For the POC study, 156 patients will be randomized to active or placebo groups in a 2:1 ratio. As in the MAD study, each patient in the POC study may receive a total of 7 SC monthly doses on Days 1, 30, 60, 90, 120, 150, and 180. A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 1 (randomization day). One oral CS “burst” for increased SLE disease activity may occur during the study either between Weeks 1 and 8 or between Weeks 16 and 20. Tapering of steroids during the course of the study will be encouraged and should be evaluated at all visits. Tapering may occur after randomization except within 8 weeks of the primary (Week 28) and secondary (Week 16) endpoint assessments. Between Week 8 and Week 16, and between Week 20 and Week 28, oral corticosteroid (OCS) doses must be held constant otherwise the patient will be declared a

non-responder in efficacy assessments.

Data from 60 patients, including the 12 from the MAD study, or 6 fewer if the low dose is chosen, who are in the cohort of the chosen dose for the POC study who complete 3 months of treatment will be used in a second IA (IA2) at Week 16 to assess if the trial could stop for an early futility conclusion. If futility is not claimed in the IA2, the POC study will continue to 156 patients.

Following the 6-month treatment period, primary and secondary efficacy endpoints will be assessed for each patient, after providing their 24-week disease activity assessments. DMC monitoring will be conducted periodically throughout the study as described in the DMC charter.

Main Criteria for Inclusion and Exclusion

Inclusion Criteria:

1. Men and women, ages 18 to 70 years, inclusive.

2. Patients must be mentally capable of giving consent and there must be evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

3. Patients must have SLE as defined by meeting 4 of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE (with at least 1 clinical and 1 immunologic criterion OR Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies), either sequentially or simultaneously.

4. At screening, patients must have at least 1 of the following:

    a. Elevated ANA ≥ 1:80 via immunofluorescent assay at the central laboratory;

    b. Positive anti-dsDNA or anti-Sm above the normal level as determined by the central laboratory;

    c. C3 or C4 below normal as determined by the central lab.

5. At screening, the SLEDAI-2K must be ≥ 6, including points from at least 1 of the following clinical components:

    a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis

        i. Excluding parameters which require central laboratory

results: (hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia);

ii. Points from lupus headache and organic brain syndrome will also be excluded.

6. On Day 1, the SLEDAI-2K must be ≥ 6, including points from at least 1 of the following clinical components:

   a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis.

      i. Excluding parameters which require central laboratory results: hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia and leukopenia;

      ii. Points from lupus headache and organic brain syndrome are also excluded.

7. Patients must have at least 1 of the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer:

   a. BILAG A or B score in the mucocutaneous body system;

   b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis as defined in the protocol Section 5.4;

   c. If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in the other body systems for a total of 2 "B" BILAG body system scores.

8. Patients must be currently receiving at least 1 of the following:

   a. Administration for a minimum of 12 weeks, and a stable dose for at least 56 days (8 weeks prior to signing consent) of the following permitted steroid-sparing agents:

      i. Azathioprine (AZA), mycophenolate mofetil or mycophenolic acid, chloroquine, hydroxychloroquine, or methotrexate (MTX).

   b. Prednisone (or prednisone-equivalent) cannot exceed 30 mg/day at screening for a patient to be eligible and must

be stable at a maximum of 10 mg/day for at least 5 days prior to Day 1 (randomization).

9. Women of childbearing potential (WOCBP; see Section 5.7 for full information regarding WOCBP, definition of menopause, and contraception):

    a. Must have a negative serum pregnancy test at screening. Urine pregnancy test must be negative prior to first dose.

    b. Must not be breastfeeding;

    c. Must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS1617219 plus 30 days (duration of ovulatory cycle) for a total of 36 weeks after treatment completion;

10. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of BOS161721 plus 90 days (duration of sperm turnover) for a total of 44 weeks after treatment completion.

11. Patients must demonstrate willingness and ability to comply with the scheduled study visits, treatment plans, laboratory tests, and other procedures.

Exclusion Criteria

Patients presenting with any of the following will not be included in this study:

1. Drug-induced SLE, rather than “idiopathic” SLE;
2. Other systemic autoimmune disease (eg, erosive arthritis, rheumatoid arthritis [RA], multiple sclerosis [MS], systemic scleroderma, or vasculitis not related to SLE);
    a. RA-Lupus overlap (Rupus), and secondary Sjögren syndrome are allowed.
3. Any major surgery within 6 weeks of study drug administration, (Day 1), or any elective surgery planned during the course of the study;
4. Any history or risk for tuberculosis (TB), specifically those with:
    a. Current clinical, radiographic, or laboratory evidence of active TB;

   b. History of active TB;

   c. Latent TB defined as positive QuantiFERON-TB Gold In-Tube (QFT-G) or other diagnostic test in the absence of clinical manifestations. Latent TB is not excluded if the patient has documented completion of adequate course of prophylactic treatment with regimen recommended by local health authority guideline, or the patient has started treatment with isoniazid, or other regimen recommended by local health authority guidelines for at least 1 month before Day 1 and continues to receive the prophylactic treatment during study until the treatment course is completed.

5. Active or unstable lupus neuropsychiatric manifestations, including but not limited to any condition defined by BILAG A criteria, with the exception of mononeuritis multiplex and polyneuropathy, which are allowed;
6. Severe proliferative lupus nephritis, (WHO Class III, IV), which requires or may require induction treatment with cytotoxic agents or high dose CS;
7. Concomitant illness that, in the opinion of the investigator, is likely to require additional systemic glucocorticosteroid therapy during the study, (eg, asthma), is exclusionary
   a. However, treatment for asthma with inhalational CS therapy is allowed.
8. Use or planned use of concomitant medication outside of standard of baseline treatment for SLE from Day -1 or for any time during the study;
9. Active and clinically significant infection (bacterial, fungal, viral, or other) within 60 days prior to first dose of study drug. Clinically significant is defined as requiring systemic antibiotics or hospitalization;
10. A history of opportunistic infection, or a history of recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years;
11. Chronic viral hepatitis including hepatitis B (HBV) and hepatitis C (HCV), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness;
12. Cryptosporidium in the stool sample at screening;
13. White blood cells (WBC) < 1,200/mm^3 (1.2×10^9/L) at screening;
14. Absolute neutrophil count (ANC) < 500/mm^3 at screening;

15. CD4+ count < 500/μL at screening;
16. Platelets < 50,000/mm^3 (50 × 10^9/L) or < 35,000/ mm^3 (35 × 10^9/L) if related to SLE, at screening;
17. Hemoglobin < 8 g/dL or < 7 g/dL at screening if due to anemia related to SLE.
18. Proteinuria > 3.0 g/day (3000 mg/day) at screening or equivalent level of proteinuria as assessed by protein/creatinine ratio (3 mg/mg or 339 mg/mmol);
19. Serum creatinine > 2.0 mg/dL at screening or creatinine clearance (CrCL) < 40 ml/minute based on Cockcroft-Gault calculation;
20. Serum alanine aminotransferase (ALT) and/or serum aspartate aminotransferase (AST) > 2 × the upper limit of normal (ULN) at screening, unless explicitly related to lupus based on the investigator's judgment;
21. Creatinine kinase (CK) > 3.0 × ULN at screening unless related to lupus myositis.
22. Direct bilirubin > 1.5 × ULN at screening (unless related to Gilbert's syndrome);
23. Any other laboratory test results that, in the opinion of the Investigator, might place a patient at unacceptable risk for participating in this study;
24. History of allergic or anaphylactic reaction to any therapeutic or diagnostic mAb (eg, IgG protein) or molecules made of components of mAbs;
25. History substance and/or alcohol abuse, or dependence within the past 1 year, at the investigator's judgement;
26. History of cancer within the last 5 years (except for cutaneous basal cell or squamous cell cancer, or cervical cancer in situ resolved by excision;
27. Any other severe acute or chronic medical or psychiatric condition, including recent (within the past year) medical conditions (eg, cardiovascular conditions, respiratory illnesses) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study;
28. Investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or patients who are

employees of the sponsor or directly involved in the conduct of the trial;

29. Currently participating in, or who have participated in other interventional (drug or device) clinical study within 30 days or 5 half-lives of baseline, whichever is longer;
30. Recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4, or 5 on the Columbia Suicide severity Rating Scale (C-SSRS);
31. Current or pending incarceration;
32. Current or pending compulsory detainment for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Statistical Considerations

Below is a summary of the statistical methods. Further details can be found in Section 9.

Baseline and patient characteristics will be summarized via appropriate summary statistics by treatment group and overall, for each phase of the trial.

Binary efficacy endpoints will be compared between treatments via Cochran-Mantel-Haenszel (CMH) analysis. Continuous efficacy endpoints will be assessed via analysis of covariance (ANCOVA) repeated measures mixed model analysis with factors including treatment, time, treatment-by-time interaction, baseline covariate, and covariate-by-time interaction. Summary statistics will be provided by dose/treatment for all safety endpoints. Details will be provided in the statistical analysis plan (SAP).

Two IAs are planned for this study. The initial IA (IA1) will be conducted at the time of the POC decision for dose selection. The second IA (IA2) will be performed for futility. IA2 is planned to be conducted when SRI-4 response is determined for approximately 60 patients (including all patients at the same dose level/matching placebo from the MAD study) after completing 3 months of treatment. The purpose of IA2 is to assess if the trial could stop for an early futility conclusion, or continue. Since there is no plan to stop the trial for an early efficacy conclusion, there is no impact on the type 1 error level.

AEs will be summarized by counts and percentages of patients by treatment group. Laboratory data and vital signs will be summarized by treatment group as summary statistics for value and change from baseline at each individual time point. Summary statistics will include n, arithmetic mean, median, arithmetic SD, minimum, and maximum.

The PK parameter data will be listed and summarized descriptively in tabular format. Binary PD endpoints will be assessed for the full analysis set (FAS) population via CMH analysis. Continuous PD endpoints will be assessed via ANCOVA repeated measures mixed model analysis with multiple factors. PK and PD relationships will be explored graphically and where appropriate model based methods of analysis will used.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADA	anti-drug antibody
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANC	absolute neutrophil count
APL	antiphospholipid
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AZA	azathioprine
BICLA	BILAG-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BP	blood pressure
BUN	blood urea nitrogen
BW	body weight
CD	cluster of differentiation
CK	creatine kinase
C	complement
C_L	systematic clearance
CLASI	Cutaneous Lupus Erythematosus Area and Severity Index
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CS	corticosteroids
CSR	clinical study report
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
dsDNA	double-stranded deoxyribonucleic acid
ECG	electrocardiogram
EOT	end of treatment
eCRF	electronic case report form
F	female
Fc	fragment crystallizable
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
eGFR	estimated glomerular filtration rate
GLP	Good Laboratory Practice

GWAS	genome-wide association studies
γc	gamma chain
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCl	hydrochloride
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IL	interleukin
IL-21R	interleukin 21 receptor
IM	intramuscular
INFγ	interferon gamma
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
IVRS	interactive voice response system
JAK	Janus kinase
kg	kilogram
KLH	keyhole limpet hemocyanin
LOCF	last observation carried forward
M	male
mAb	monoclonal antibody
MAD	multiple ascending dose
MAPK	mitogen-activated protein kinase
MS	multiple sclerosis
MTX	methotrexate
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIAID/FAAN	National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network
NK	natural killer
NOAEL	no observed adverse event level
NO	nitric oxide
OCS	oral corticosteroid

OTC	over-the-counter
PD	pharmacodynamics
PEF	peak expiratory flow
PGA	Physician's Global Assessment
PK	pharmacokinetics
POC	proof of concept
PR	(interval) from onset of the p-wave to the end of the r-wave
pSS	primary Sjögren's syndrome
pSTAT3	phosphorylated signal transducer and activator of transcription 3
PT	preferred term
QRS	(interval) from the onset of the q-wave to the end of the s-wave
QT	(interval) from onset of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
QFT-G	QuantiFERON-TB Gold In-Tube
RA	rheumatoid arthritis
RNP	ribonucleoprotein
RR	(interval) from the onset of the r-wave to the onset of the next consecutive r-wave
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SDMT	safety data monitoring board
CCI	[redacted]
SLE	systemic lupus erythematosus
SLEDAI-2K	SLE Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
Sm	Smith
SOC	system organ class
SRI-4	SLE Responder Index 4
SRI-5	SLE Responder Index 5
SRI-6	SLE Responder Index 6
SSA	Sjögren syndrome-A (Ro)
SSB	Sjögren syndrome-B (La)
STAT3	signal transducer and activator of transcription 3
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
TB	tuberculosis
TDAR	T-cell dependent antibody response
Tfh	T-follicular helper
Th	T-helper
TK	toxicokinetics

T_{max}	first time to maximum concentration
Treg	regulatory T-cell
TT	tetanus toxoid
ULN	upper limit of normal
US	United States
Vd	volume of distribution
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
YTE	triple mutation

1 INTRODUCTION AND RATIONALE

1.1 Indication

BOS161721 is a humanized monoclonal antibody (mAb), which binds to and inhibits interleukin-21 (IL-21) bioactivity, and is being developed for the treatment of moderately to severely active systemic lupus erythematosus (SLE) in adults.

1.2 Background and Rationale

1.2.1 Overview of the Disease State

SLE is a chronic inflammatory autoimmune disease that has variable manifestations in multiple organ systems and follows a relapsing and remitting course. The disease process includes abnormal immune responses mediated by tissue-binding autoantibodies and immune complex deposition, giving rise to tissue damage often resulting in end organ disease and even mortality. Survival of SLE has improved due to earlier detection, improved overall medical care, and standardized SLE treatment with corticosteroids, immunosuppressants, and cytotoxic agents.[1] However, some of the morbidity in patients with SLE is related to its treatment. Comparison of early and late outcomes in patients with SLE demonstrate that death in early disease is most commonly due to infections and active SLE causing multi-system organ damage, while thromboses were the most common cause of death during later disease.[2]

The reported prevalence of SLE in the United States (US) is 20 to 70 cases per 100,000 people.[3] More than 90% of cases of SLE occur in women, frequently starting at childbearing age. Women of color are disproportionately affected by SLE. This suggests multiple genetic and environmental factors are at play. Accordingly, a multifactorial view of the immunopathogenesis of SLE suggests more than 1 area of interest, including breach in central tolerance in the adaptive arm of the immune system, peripheral amplification of the autoimmune response by the innate immune system, and local processes in the target organ that facilitate end-organ disease.[4]

1.2.2 BOS161721 Development

Boston Pharmaceuticals is developing BOS161721 for the treatment of SLE. BOS161721 is a humanized immunoglobulin G1 (IgG1) mAb directed against human IL-21.

Murine mAb 19E3, the progenitor of BOS161721, was generated using mouse hybridoma technology. 19E3 has subpicomolar (pM) affinity to human IL-21 and was selected for its potent neutralization of IL-21 bioactivity. BOS161721 was generated by the humanization of mAb 19E3 where its complementarity-determining regions were grafted onto a human IgG1 kappa backbone. The fragment crystallizable (Fc) portion of BOS161721 contains a YTE (M252Y/S254T/T256E triple mutation) in the constant domain of the IgG1 heavy chain that was introduced into the parental molecule, 19E3, intended to prolong the in vivo terminal elimination half-life ($t_{1/2}$) of the mAb.[5] Thus, BOS161721 retains sub-pM binding to IL-21 and prevents IL-21 from binding to the IL-21 receptor (IL-21R), inhibiting IL-21 bioactivity.

BOS161721 binds to human IL-21 and Cynomolgus monkey IL-21, which are highly homologous, and neutralizes the bioactivity of both. BOS161721 is specific for IL-21 as it does not bind to or inhibit the other gamma-chain (γc) family of cytokines, and acts to specifically neutralize the IL-21 pathway. In *in vitro* studies, BOS161721 inhibited downstream IL-21-induced signaling, IL-21-induced plasma cell differentiation, and IL-21-induced natural killer (NK) cell activation. In *in vivo* studies, BOS161721 significantly inhibited the T-cell dependent antibody response (TDAR) to immunization with a protein antigen as well as B-cell expansion following a second protein antigen immunization in Cynomolgus monkeys.

1.2.2.1 Interleukin-21

IL-21 is an inflammatory cytokine, which belongs to a family of cytokines that also includes IL-2, IL-4, IL-7, IL-9, and IL-15, all of which bind to private receptors in complex with the common cytokine receptor γc.[6] Most cytokines in this family are critically important for both the maintenance and function of T-cell and B-cell responses. IL-21 signals through a receptor complex consisting of its own private receptor, the IL-21R and γc.[6,7] Engagement of the IL-21R/γc complex leads to the activation of several signaling pathways, including the Janus kinase/signal transducer and activator of transcription, mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase pathways.[8] IL-21 is produced mainly by T-cells and NK T-cells, but neutrophils have also been reported to produce IL-21.[9,10] The IL-21R is expressed on a broad array of cell types, including B-cells, T-cells, NK-cells, macrophages and dendritic cells, as well as other hematopoietic and nonhematopoietic cells such as fibroblasts, keratinocytes, and intestinal epithelial cells.[9,11] Activation of signal transducer and activator of transcription 3 (STAT3) via phosphorylation is critical in regulating human B-cell responses to IL-21[12]; phosphorylated STAT3 (pSTAT3) forms a homodimer, which translocates to the nucleus where it initiates transcription of the IL-21 gene, forming an autocrine loop for IL-21 production via STAT3 phosphorylation.[13] In addition, IL-21 has been shown to upregulate expression of its own receptor[14] and induces an autocrine feedback loop.[15]

IL-21 modulates various aspects of immune function. It promotes cluster of differentiation 4 (CD4+) T-cell differentiation and promotes the generation of T-helper (Th)17[16] and T-follicular helper (Tfh) cells.[15,17] In mice, IL-21 has been shown to regulate the balance between Th17 and regulatory T-cell (Treg), in that it increases Th17, while inhibiting Treg differentiation.[18] Less is understood with regards to human Tregs, although IL-21 has been reported to counteract Treg suppression of human effector T-cells[19] and blockade of IL-21 promotes Treg generation in a murine model of graft versus host disease induced by human T-cells.[20] IL-21 upregulates CD8+ T-cell and NK-cell expansion and cytolytic activity by increasing granzyme B and perforin.[21,22] IL-21 also has been reported to increase granzyme B in plasmacytoid dendritic cells and B-cells resulting in inhibition of T-cell responses.[23,24] IL-21 also has a variety of effects on nonhematopoietic cells, such as stromal cells and induces inflammation through matrix metalloproteinase release by gut intestinal fibroblasts.[25]

One principal non-redundant role of IL-21 is the promotion of B-cell activation, differentiation, or death during humoral immune responses.[14] Furthermore, increased IL-21 production is characteristic of several autoimmune diseases and is likely to contribute to autoantibody production as well as pathologic features of autoimmune disease.[26] The critical role of IL-21 in promoting humoral and other immune responses makes it an important focus of potential

therapeutic interventions in conditions characterized by overproduction of pathogenic autoantibodies. IL-21 production by Tfh cells in humans is believed to play a major role in driving the autoantibody production through its role in plasma cell differentiation. Importantly, Tfh cell populations are expanded in patients with autoimmune diseases such as lupus, bullous pemphigoid, rheumatoid arthritis (RA) and primary Sjögren's syndrome (pSS) and have been reported to correlate with IL-21 levels, autoantibodies, and disease severity.[26,27,28,29] Furthermore, loss of number and functionality of Tregs has been associated with autoimmune diseases such as SLE and giant cell arteritis, which IL-21 is expected to modulate.[30,31] Thus, neutralization of IL-21 in settings of autoimmunity is expected to impact several cell populations believed to be involved in the pathogenesis of autoimmune disorders including SLE.

BOS161721 selectively binds IL-21 with high affinity to neutralize IL-21, and due to its pleiotropic nature, neutralization of IL-21 is expected to impact several cell populations believed to be involved in the pathogenesis of SLE. Importantly, patients with SLE have elevated IL-21 plasma levels that correlate with the severity of the disease. Recently, genome-wide association studies (GWAS) have provided convincing evidence that the chromosomal 4q 27 region harbors the IL-21 genes and is associated with chronic inflammatory disorders, including SLE.[29]

1.2.2.2 Preclinical Studies

The pharmacokinetics (PK) of BOS161721 were characterized following single-dose intravenous (IV) administration of BOS161721 (0.01 to 30 mg/kg) in male Cynomolgus monkeys or repeat, every 2 weeks IV administration (15 to 100 mg/kg) and subcutaneous (SC) administration (50 mg/kg) in male and female Cynomolgus monkeys. Systemic exposure was approximately dose-proportional within the tested dose range. SC bioavailability was determined to be 64.3%. CCI [redacted]

Two single-dose (IV) non-good laboratory practice (GLP) studies conducted in Cynomolgus monkeys evaluated the toxicity, pharmacodynamics (PD), toxicokinetics (TK), and immunogenicity of BOS161721. Following a single IV administration (slow bolus), there were no BOS161721-related adverse changes, resulting in a no-observed-adverse-effect-level (NOAEL) value of 30 mg/kg, the highest dose tested among 2 studies. CCI [redacted]

In a repeat-dose GLP toxicology study in Cynomolgus monkeys, BOS161721 was administered every 2 weeks by IV or SC (50 mg/kg) administration for 3 months (a total of 7 doses). CCI [redacted]

CCI [redacted] The NOAELs were determined to be 100 mg/kg IV and 50 mg/kg SC, the highest doses tested.

1.2.2.3 Clinical Studies

BOS161721-01 was a double-blind, Phase 1, single ascending dose (SAD) study to assess the safety, PK, and PD of BOS161721 in healthy subjects. The primary objective of the study was to characterize the safety and tolerability of IV and SC SADs of BOS161721 in an otherwise healthy subject population without concomitant illnesses, immune abnormalities, or concomitant medications. Secondary objectives included characterization of the PK and immunogenicity of BOS161721, and exploratory objectives included the evaluation of the effect of BOS161721 on TDAR to keyhole limpet hemocyanin (KLH) (primary and secondary immunizations) in healthy subjects, the effects of BOS161721 on plasma levels of IL-21 (free and bound), and the evaluation of the effect of BOS161721 on IL-21 gene expression (via gene signature) in blood. This study consisted of 8 cohorts. Subjects were randomized in a 3:1 ratio (BOS161721: placebo) and received either a single dose of BOS161721 (1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg) or placebo, with safety follow-up. For the first cohort, after the first 2 subjects were dosed (1 active and 1 placebo), there was a minimum gap of 48 hours before the remaining subjects from that cohort were dosed, to allow for an initial review of any emerging safety and tolerability data. For all cohorts, escalation to the next dose was not sooner than 8 days after all the subjects in the prior cohort had been dosed and were based on a review of at least 7 days of safety and tolerability data by the Safety Data Monitoring Team (SDMT).

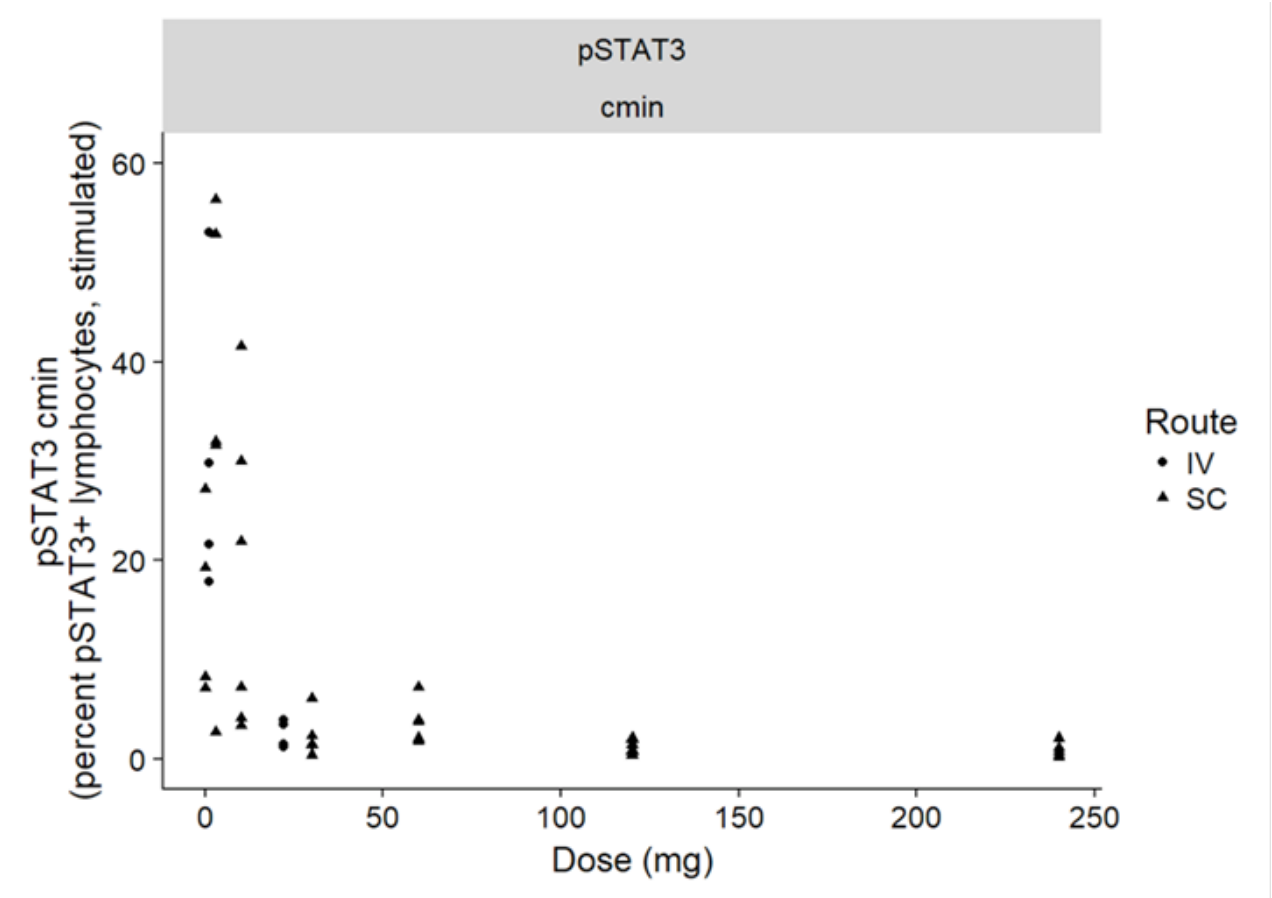
Blood samples were collected at every in-house study visit for BOS161721 concentration determinations. Blood samples were also collected for determination of IL-21 plasma levels (free and total). Safety was assessed based on the occurrence of treatment-emergent AEs, hepatic function abnormality, and acute and delayed hypersensitivity reactions. Other safety variables included electrocardiograms (ECGs), vital signs (blood pressure, heart rate, and temperature), safety laboratory assessments, blood sampling for ADAs, total IgG and IgM levels, CD4+ count, and full and targeted physical examinations. Overall, there were no clinically significant findings from this study; there were no serious adverse events (SAEs), deaths, or discontinuations due to AEs during the study, AEs reported as related to the study drug, particularly infections (flu-like symptoms, etc), were expected for the compound, and there were no clinically relevant changes in laboratory and ECG results or vital signs. PK data from the SAD study demonstrates BOS161721 has an extended $t_{1/2}$ (provisional single dose data indicates this to be approximately 42-46 days) which supports evaluation of monthly dosing.

1.2.3 Study Dose Selection

Doses have been selected for the multiple ascending dose (MAD) Phase 1 study based on a 90-day safety, tolerability, PK, and PD data review from the Phase 1 SAD study (BOS161721-01); the SDMT reviewed the blinded safety data from subjects for each dose cohort (8 cohorts, evaluating 1 [IV], 3 [SC], 10 [SC], 22 [IV], 30 [SC], 60 [SC], 120 [SC], or 240 [SC] mg), along with the accumulated safety and available PK/PD data from all subjects in the previous dose cohorts, to make a decision on whether to proceed to the next higher dose level, repeat a dose level, or stop dose escalation. Overall, there were no clinically significant safety or tolerability findings from this study.

Based on the Day-90 interim cut of the PK and biomarker data in the BOS161721-01 study, the recommended doses for evaluation in the MAD phase of this study are 20, 60, and 120 mg SC monthly. This dose recommendation is supported by evidence of linear PK with BOS161721 resulting in a median T_{max} of 6 days and an apparent terminal half-life of 44 days. Furthermore, pSTAT3 suppression, a marker of IL-21 target engagement, follows a similar time course of the mAb levels, with maximal and sustained suppression apparent with doses greater than 30 mg SC (Figure 1).

Figure 1. Individual pSTAT3 C_{min} Levels Versus Dose



IV = intravenous, pSTAT3 = phosphorylated signal transducer and activator of transcription 3; SC = subcutaneous

All doses selected for the MAD study are projected not to exceed peak levels or exposure of that achieved following the highest single dose of 240 mg SC administered in the Phase 1 SAD study. Cohort 1 will include randomized treatment to the 20 mg dose. Based on the staggered study design, the data monitoring committee (DMC) will perform a scheduled review of safety data and sequentially consider dose escalation for Cohorts 2 and 3. In addition, the DMC will conduct a data review for the first interim analysis (IA1) to determine which dose will be carried forward into the proof of concept (POC) Phase 2 study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2 and 3 from the MAD study (see Section 4.1.1.1).

1.2.4 Risk-Benefit Assessment

The available preclinical data on BOS161721, the findings in clinical study BOS161721-01, and existing clinical information on IL-21 inhibitors suggest that the present clinical study has an acceptable risk-benefit ratio. In this study, the risk-benefit assessment of BOS161721 in adult patients with moderately to severely active SLE will be ongoing, with step-wise evaluations during the staggered MAD study. The DMC used in this study is charged with assessing such actions in light of an acceptable benefit-risk profile for BOS161721 as an anti-IL-21 mAb. Formal DMC monitoring meetings will occur as described in the DMC Charter. Two weeks after Cohort 1 has received a second dose of study drug, the DMC will evaluate the safety and tolerability data from Cohort 1 to determine the recommended dose for Cohort 2. Two weeks after 8 patients in Cohort 2 receive a second dose, the DMC will determine if dose escalation to Cohort 3 can proceed. Two weeks after the last patient in Cohort 3 receives the second dose, the DMC will conduct a data review for the IA1 to determine which dose will be carried forward into the POC Phase 2 study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2 and 3 during the MAD study. Thereafter, DMC monitoring will be conducted periodically throughout the study as described in the DMC charter. With the agreement of the DMC and sponsor, this schedule may be modified depending on the rate of patient accrual. Additional details can be found in the DMC Charter.

The benefit of participation for all patients in this study is close monitoring of their medical condition and safety of their treatment. Those randomized to the active treatment arm may potentially experience improvement in their SLE disease. Those randomized to the placebo (in combination with standard of care) arm are not expected to obtain any additional benefit, beyond those of their background treatment, though close monitoring of their medical condition and safety may itself be associated with improving their SLE.

1.2.5 Potential Risks

Potential risks based on the mechanism of action of BOS161721 include infections, risks associated with the administration of any foreign protein or biologic agent, including injection site reaction, anaphylaxis, serious allergic reaction, and development of ADAs. ADAs could result in immune complex disease (with manifestations such as arthralgias, serum-sickness, and vasculitis), autoimmunity, or altered BOS161721 levels or activity. Further details can be found

in the current Investigator's Brochure (IB) for BOS161721, which contains comprehensive toxicology, preclinical and clinical information on BOS161721.

Two investigational drug products are considered to be in the same pharmacological class as BOS161721 based on interruption of signaling through the IL-21 signaling pathway. No potential risk generalizable across the class has been observed with these investigational products. Based on the clinical Phase 1 SAD study (BOS161721-01), AEs reported as related to the study drug, particularly infections (flu-like symptoms, etc), were expected for the compound, and there were no clinically relevant changes in laboratory and ECG results or vital signs.

The majority of IgG elimination occurs via intracellular catabolism, following fluid-phase or receptor-mediated endocytosis. This type of endocytosis and elimination is a form of target-mediated disposition where the interaction of the drug and its pharmacological target (eg, a target receptor) serves as a significant contributor to the kinetics of antibody distribution and elimination. Renal elimination, which is a primary pathway of clearance of small-molecule drugs, is relatively unimportant for IgG, as its large size prevents efficient filtration through the glomerulus. Secretion into the bile is an important pathway of elimination of IgA antibodies, but this route is not a significant contributor to the elimination of IgG antibodies. Thus, risk to renal and hepatic systems due to metabolism of BOS161721 is low.[33]

1.2.5.1 Anaphylaxis and Serious Allergic Reactions

As with the administration of any foreign protein and/or other biological agents, acute hypersensitivity reactions, including acute anaphylactic/hypersensitivity, severe allergic, and anaphylactoid reactions may follow infusion of mAbs and can be caused by various mechanisms. These acute hypersensitivity reactions may be severe and result in death.

Anaphylaxis will be defined according to the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria,[34] and are discussed in Section 7.2.2.6.1.

Based on the limited Phase 1 SAD study (BOS161721-01), anaphylaxis and serious allergic reactions in subjects who received BOS161721 was not observed.

Patients with a known history of allergy or severe hypersensitivity reaction to any component of BOS161721 formulation or patients with a history of anaphylaxis to any other biological therapy such as mAbs will be excluded from studies with BOS161721. In addition, appropriate drugs and medical equipment to treat acute hypotensive, bronchoconstrictive, or anaphylactic reactions will be immediately available at the unit and study personnel will be trained to recognize and treat these reactions.

1.2.5.2 Injection Site Reactions

In a repeat-dose GLP toxicology study in Cynomolgus monkeys, BOS161721 was administered every 2 weeks by IV or SC (50 mg/kg) for 3 months (a total of 7 doses); no SC animals had injection reactions.

Based on the Phase 1 SAD study (BOS161721-01), incidence of injection site reactions in subjects who received BOS161721 was similar to placebo.

Patients will be monitored for local injection site reactions in this study. See Section 7.2.7.

1.2.5.3 Immune Complex Disease

The potential risk of immune complex disease for BOS161721 is theoretical, based on the known risks associated with mAbs. The administration of a mAb can result in the formation of ADAs. Administration of the mAb in the presence of ADA may result in the formation of circulating antibody-antigen complexes potentially resulting in altered BOS161721 levels or activity or deposition of the complexes in microvasculature. Complement is frequently involved in the latter setting, and the breakdown products of complement attract polymorphonuclear leukocytes to the site of deposition where they can provoke local tissue damage through specific or nonspecific release of enzymes. Two of the more common end-organ targets are the blood vessels (vasculitis) and kidney (nephritis). These clinical manifestations represent immune complex disease or Type III hypersensitivity. Although BOS161721 is a humanized mAb, ADAs may develop; however, the likelihood of occurrence of immune complex disease with BOS161721 is low. The findings of immune complex disease are typically reversible when mAb administration stops and the antibody-antigen complexes are cleared from the body.

Based on the limited Phase 1 SAD study (BOS161721-01), immune complex disease in subjects who received BOS161721 was not observed.

1.2.5.4 Infections

BOS161721 is expected to diminish the activity of T-cell, B-cell and NK-cell lines. Like other medications modulating immune response, BOS161721 may increase the potential risk for infection, including serious infections. IL-21 produced by CD4+ Th cells is required to sustain the anti-viral function of CD8+ T-cells against chronic viral infections. Nonclinical evidence suggests that the risk of chronic viral infection recurrence or increased severity may occur with IL-21 inhibition.[35]

These conditions will be fully characterized with clinical descriptions and routine laboratory and/or specialty testing and treated where indicated with appropriate local standard of care.

Patients with a history of opportunistic infection, including recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years, or any other underlying pathology predisposing to serious infection, are excluded from studies with BOS161721 (for further details please refer to the current IB for BOS161721).

Patients will be assessed for hepatitis B, and C, and HIV-1/2 combination, at screening.

<u>Cryptosporidium Infection</u>

Cryptosporidium infection was noted in patients with an IL-21 receptor loss-of-function gene mutation and similar findings of cryptosporidium infection have been observed in immunosuppressed liver transplant and human immunodeficiency virus patients.[36,37] Since

BOS161721 is expected to diminish the immunosurveillance activity of T-cell, B-cell, and NK-cell lines, a similar risk is biologically plausible with prolonged exposure to BOS161721.

Since the risk of opportunistic cryptosporidium infection increases with low levels of CD4+ T-cells,[37] patients with a CD4+ count < 500 cell/mm^3 were excluded from the Phase 1 SAD study (BOS161721-01), and will be excluded from the proposed MAD/POC studies. Patients exposed to investigational product who develop diarrhea during the course of the study should immediately undergo an assessment for opportunistic infection including stool for ova and parasites and stool examination for cryptosporidium. Positive cryptosporidium in stool sample at screening is an exclusion. Treatment by the investigator where indicated should be guided by findings and be consistent with local standard of care.

Based on the limited Phase 1 SAD study (BOS161721-01), infections in subjects who received BOS161721 was not observed.

1.2.5.5 Malignancy

The stimulatory effect of IL-21 on NK cells and CD8+ T-cells suggests the cytokine may have anti-tumor activity. Nonclinical studies have demonstrated significant anti-tumor effects of IL-21 in a number of tumor models. IL-21 therapy of human metastatic melanoma and renal cell carcinoma has demonstrated POC with significant increases in levels of perforin, granzyme B, and interferon gamma (IFNγ) expression in CD8+ T-cells and NK T-cells. Clinical response has been limited in these generally unmanageable diseases.

The impact of treatment with anti-IL-21 therapy on the development or growth of malignancies is not known; however, as with other immunomodulatory biologic agents, treatment with BOS161721 may result in an increase in the risk of malignancies. NK cell suppression by IL-21 neutralization may represent a biological mechanism for a potential risk for malignancy. Patients with a history or current diagnosis of cancer within the past 5 years, with the exception of non-melanoma skin cancer or cervical cancer in situ treated with apparent success with curative therapy, are excluded from the study.

Based on the limited Phase 1 SAD study (BOS161721-01), malignancy in subjects who received BOS161721 was not observed.

1.2.5.6 Hepatic Function Abnormality

There is no substantial evidence suggesting BOS161721 is associated with liver function abnormality. However as a precaution, patients with a history of abnormal alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), or bilirubin at screening (ALT/AST > 2 × upper limit of normal [ULN]; total bilirubin > 1.5 × [ULN] and judged by the investigator to be clinically significant) were excluded from the Phase 1 SAD study (BOS161721-01), and will be excluded from the MAD study. Patients with a positive hepatitis B or C test or a history of alcohol dependence will also be excluded.

Based on the limited Phase 1 SAD study (BOS161721-01), hepatic function abnormality in subjects who received BOS161721 was not observed.

1.2.5.7 Failure of Vaccination

IL-21 is a key cytokine in development of B-cells into immunoglobulin-secreting plasma cells. Abnormal signaling through the IL-21R/Janus Kinase (JAK)3/signal transducer and activator of transcription (STAT3) pathway leads to defective humoral immune responses to both T-dependent and T-independent antigens and impairs the establishment of long-lasting B-cell memory. Abnormal signaling through the pathway has been related to decreased specific antibody responses following vaccination, and to increased susceptibility to encapsulated bacterial infections.[38]

The effect of BOS161721 was evaluated in in vivo single dose studies in Cynomolgus monkey in which the animals received vaccination to T-cell dependent KLH antigen to stimulate a TDAR. These in vivo studies demonstrated that BOS161721 significantly inhibited B-cell proliferation and IgG antibody responses to the KLH protein antigen; however, it is worth noting that BOS161721 administration did not produce any remarkable changes in anti-KLH antibody data for IgM, IgG1, IgG3, and IgG4 or anti-tetanus toxoid (TT) antibody data for IgM, IgG, IgG1, or IgE during the dosing phase in the same study.

1.2.5.8 Potential for Drug-Drug Interactions

Drug-drug interactions were not evaluated in the Phase 1 SAD study (BOS161721-01), which included only healthy adult subjects. Use of prescription medications (with the exceptions of oral contraceptives), and over-the-counter (OTC) treatments including herbal supplements such as St John's Wort (except multivitamins), in the 2 weeks prior to screening was prohibited in the SAD study.

See Section 5.5 for other specific exclusion criteria which support lowered risk of interactions, and Section 5.6.1 for corticosteroid (CS) dosing. In addition, Section 1.2.5.6 describes considerations for hepatic function for this study.

1.2.5.9 Potential Risk to Fetal Development

No data on preclinical reproductive toxicity are available at the time of this study.

2 STUDY OBJECTIVES

This trial has separate primary and secondary objectives for the MAD Phase 1b and POC Phase 2 studies.

2.1 Phase 1b Multiple Ascending Dose

2.1.1 Primary Objective

To assess safety, tolerability, and immunogenicity of repeat doses of BOS161721 (20 mg, 60 mg, and 120 mg) administered SC in adult patients with moderately to severely active SLE on limited background standard of care treatment, in order to estimate the optimal dose.

2.2 Phase 2 Proof of Concept

2.2.1 Primary Objective

To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on the SLE Responder Index 4 (SRI-4), with sustained reduction of oral CS, in adult patients with moderately to severely active SLE on limited background standard of care treatment.

2.2.2 Secondary Objectives

To demonstrate a superior effect of BOS161721 at the chosen dose compared with placebo for response on clinical indicators of SLE activity, in adult patients with moderately to severely active SLE on limited background standard of care treatment, including:

- Changes in SLE-specific autoantibody titers;
- Changes in complement 3 and 4 (C3 and C4) levels;
- Responses on SRI-4, SRI-5, and SRI-6, with sustained reduction of oral CS;
- Response on the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA);
- Response on the Cutaneous Lupus Erythematosus Area and Severity Index (CLASI);
- Changes in the SLEDAI-2K;
- Changes in American College of Rheumatology (ACR)-28 joint count.

3 STUDY ENDPOINTS

This trial has separate primary and secondary endpoints for the MAD Phase 1b and POC Phase 2 studies.

3.1 Phase 1b MAD Study

3.1.1 Primary Endpoints

Evaluation of safety, tolerability, and immunogenicity at each dose level, to determine the optimal dose, will include the recording of the following parameters:

- Incidence and severity of AEs, AEs of special interest, and SAEs;
- 12-lead ECGs;
- Vital signs (blood pressure [BP], heart rate, and temperature);
- Clinical laboratory assessments;
- Physical examinations;
- Evaluation for ADAs.

3.1.2 Exploratory Endpoints

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

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

3.1.3 Other Endpoints

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

3.1.4 PRO Endpoints

- CCI [redacted]
- CCI [redacted]

3.2 Phase 2 POC Study

3.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients who achieve treatment response as measured by the SRI-4 at Week 28, along with a sustained reduction of oral CS (≤ 10 mg/day and ≤ Day 1 dose) between Week 16 and Week 28.

3.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The proportion of patients who achieve treatment response for the SRI-5 and SRI-6 at Week 28, along with a sustained reduction of oral CS (≤ 10 mg/day and ≤ Day 1 dose) between Week 16 and Week 28;
- Changes from baseline in dsDNA, ANA, SSA, SSB, RNP, Sm, APL autoantibodies, at Week 16 and Week 28;
- Changes from baseline in C3 and C4 levels at Week 16 and Week 28;
- Changes from baseline in the SLEDAI-2K at Week 28;

- Time to BILAG A or B flare;
- Changes from baseline in the CLASI at Week 28;
- The proportion of patients with a BICLA response at Week 28;
- The proportion of patients with CLASI response at Week 28;
- Changes from baseline (percentage) in swollen joints and tender joints ACR-28 joint count;
- Incidence and severity of AEs, AEs of special interest, and SAEs;
- 12-lead ECGs;
- Vital signs (BP, heart rate, and temperature);
- Clinical laboratory assessments;
- Physical examinations and targeted physical examinations;
- Evaluation for ADAs.

3.2.3 Exploratory Endpoints

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted];
- CCI [redacted]
- CCI [redacted]

3.2.4 Other Endpoints

- CCI [redacted]

- CCI [redacted]
- CCI [redacted]

3.2.5 PRO Endpoints

- CCI [redacted]
- CCI [redacted]

4 STUDY PLAN

4.1 Study Design

This is a Phase 1b/2 combined, randomized, multicenter, double-blind, placebo-controlled trial to study the clinical efficacy, safety, and PK of SC doses of BOS161721 in adult patients with moderately to severely active SLE. After successfully completing a screening phase, patients will be randomized to a specified dose of BOS161721 or placebo. The dosing schedule will be monthly.

The trial will consist of 2 studies: MAD Phase 1b, and POC Phase 2. Both studies will be double-blinded, and patients will have the same number of visits. Patients may receive a total of 7 SC monthly doses of study drug on Days 1, 30, 60, 90, 120, 150, and 180, followed by a 90-day safety follow-up visit.

SLE disease activity assessment data will be centrally reviewed by medical monitor and sponsor to ensure the scores are clinically meaningful and compliant with specific definition. The scope of responsibility includes, but is not limited to, review and confirmation of "A" and "B" BILAG system organ disease, confirmation of clinical components of the SLEDAI-2K score at screening and during the study, and cross-validation of the instruments used in this study to assess the disease being studied. Further details on the content and methods of data reports by the medical monitor and sponsor will be outlined in the Medical Data Review Plan along with the processes and procedures that will be followed.

4.1.1 Multiple Ascending Dose Phase 1b Study

The MAD study will consist of 3 cohorts:

- Cohort 1 (20 mg SC) will include 6 patients
    - 5 patients will receive BOS161721 (active group) and 1 patient will receive placebo (placebo group)

- Cohorts 2 (60 mg SC) and 3 (120 mg SC) will include 12 patients each
    - 9 patients in the active group and 3 in the placebo group

Doses selected for each of the 3 cohorts is based on a 90-day safety, tolerability, PK and PD data review from the Phase 1 SAD study (BOS161721-01) in healthy subjects. All doses selected for the MAD study are projected not to exceed the mean peak levels or exposures of that achieved in the SAD study.

4.1.1.1 Dose Escalation for the MAD Study

The MAD study design is staggered, where after the 6 patients in Cohort 1 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 2 begins dosing (after DMC evaluation of the safety and tolerability data from Cohort 1). Similarly, after 8 of the 12 patients in Cohort 2 have received 2 doses and have completed 2 weeks of follow-up after the second dose, Cohort 3 begins dosing (based on the dose level determined after DMC evaluation of the safety and tolerability data from Cohorts 1 and 2). Two weeks after the last patient in Cohort 3 receives the second dose, the DMC will conduct a data review for the IA1 to determine which dose will be carried forward into the POC Phase 2 study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2, and 3; this dose will not exceed doses tested during the MAD study. The DMC will be reviewing all relevant data from Cohorts 1, 2, and 3 that is available when the last patient in Cohort 3 reaches 60 days (dose 2). Each cohort will continue at their assigned dose level through their respective 6-month treatment periods (See Study Schematic, Section 4.1). If > 3 patients discontinue the study in a cohort, he/she will be replaced.

Criteria for dose escalation are further described in the DMC Charter. See Section 4.1.1.2 for additional details about DLTs.

4.1.1.2 Dose Limiting Toxicity (DLT)

Severity of adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. For the purpose of dose escalation, any of the following AEs occurring after study drug administration, which are attributable to the study drug, will be considered DLTs:

Hematologic:

- Grade 4 neutropenia;
- Grade 3 neutropenic infection;
- Grade 3 thrombocytopenia with bleeding;
- Grade 4 thrombocytopenia.

Non-Hematologic:

- Grade 3 or above toxicities, persisting after optimal treatment with standard medical therapy (eg, anti-emetics, anti-diarrheals);
- Drug-induced liver injury ([DILI], Hy's Law), as defined in Section 7.2.2.6.3.

Investigators should always manage their patients according to their medical judgment which may include interruption of study drug based on the particular clinical circumstances. All dose modifications/adjustments must be clearly documented in the patient's source notes and electronic Case Report Form (eCRF).

4.1.1.3 DMC Recommendations

During scheduled meetings, the DMC will review relevant study data for safety or benefit-risk concern. During the MAD study, the DMC may provide the following recommendations to the sponsor:

- Expanding a cohort at a specific dosing level, or repeating a lower dose in a subsequent cohort;
- Continuing a dose level for a given cohort;
- Escalating a dose level for a subsequent cohort;
- Termination of current or previous cohort(s).

Further dosing in a given cohort will be halted if 2 or more DLTs are identified intra- and inter-patients dosed. For the POC study, the DMC will conduct a data review for the IA1 to determine which dose will be carried forward into the POC Phase 2 study. This POC dose decision will be based on evaluation of the PK, safety (inclusive of dose-limiting toxicity [DLT]), and tolerability data (and available PD/biomarker data) from Cohorts 1, 2, and 3; this dose will not exceed doses tested during the MAD study. The DMC will be reviewing all relevant data from Cohorts 1, 2, and 3 that is available when the last patient in Cohort 3 reaches 60 days (dose 2). Details are provided in the DMC Charter.

4.1.2 POC Phase 2 Study

4.1.2.1 BOS161721 Dose

The optimal dose evaluation is chosen based on MAD Phase 1b safety results. The dose will be communicated by a letter to site investigators participating in the POC Phase 2 study, and to the IRB/IEC. Once the POC dose decision has been made, screening for the POC study can begin.

4.1.2.2 POC Study Design

For the POC study, 156 patients will be randomized to active or placebo groups in a 2:1 ratio.

As in the MAD study, each patient in the POC study may receive a total of 7 SC monthly doses of study drug on Days 1, 30, 60, 90, 120, 150, and 180. Assessments will be completed according to the Schedule of Assessments (Section 4.3). Dose selection will be based on the sponsor's assessment of safety, tolerability, immunogenicity, and PK and PD data from the MAD study of 30 patients treated with BOS161721/placebo.

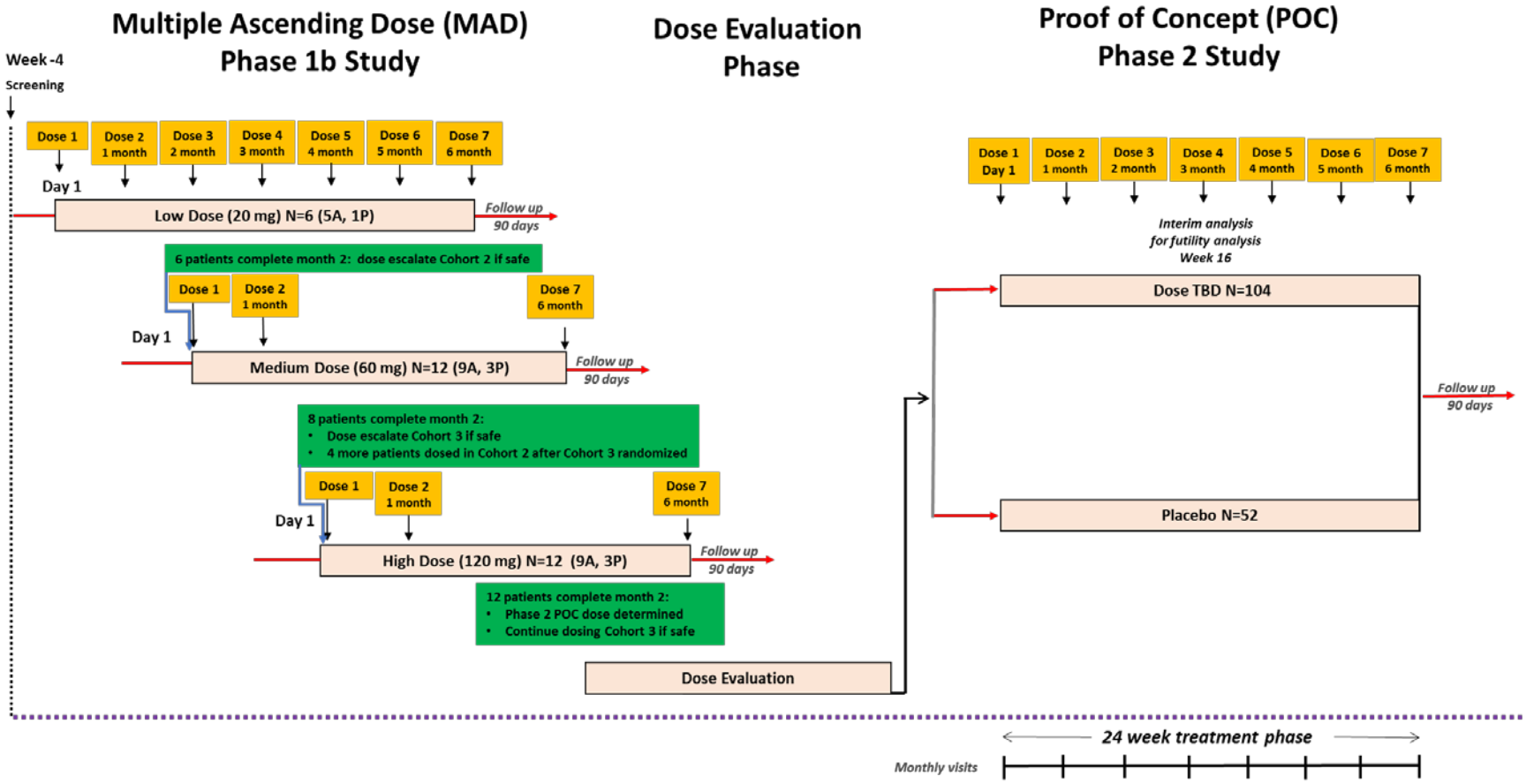
Data from approximately 60 patients (including the 12 from the MAD study, or 6 fewer if the low dose is chosen who are in the cohort of the chosen dose for the POC study) who complete 3 months of treatment will be used in the IA2 at Week 16 to assess if the trial could stop for an early futility conclusion (see Section 9.3 for details regarding the IA). If futility is not claimed in the IA2, the POC study will continue to 156 patients.

Following the 6-month treatment period, primary and secondary efficacy endpoints will be assessed for each patient after providing their 24-week disease activity assessments.

DMC monitoring will be conducted periodically throughout the study as described in the DMC charter.

4.2 Study Schematic

Figure 2. Study Diagram for MAD Phase 1b and POC Phase 2 Studies



A = active drug (BOS161721); P = placebo

4.3 Schedule of Assessments

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Months					1	1.5	2	3	4	5	6			7	8	9
Weeks			1	2	4	6	8	12	16	20	24	25	26	28	32	36
Days	-28 to -1	1	7 (± 1)	15 (± 3)	30 (± 3)	44 (± 3)	60 (± 3)	90 (± 3)	120 (± 3)	150 (± 3)	180 (± 3)	187 (± 3)	195 (± 3)	210 (± 3)	240 (± 3)	270 (± 3)
Visit Number	1	2		3	4	5	6	7	8	9	10			11	12	13
Informed consent	X															
Inclusion/Exclusion criteria	X															
Medical history	X															
Demographics	X															
Full physical exam	X	X														
Serum pregnancy test (women)	X															
FSH and estradiol (postmenopausal women)	X															
TB test (QuantiFERON-TB Gold In-Tube)[b]	X															
Chest x-ray[b]	X															
Serology (hepatitis B and C, HIV-1/2 combination)	X															
SLICC Criteria for SLE	X															
Stool sample[c]	X															
C-SSRS	X	X						X			X					
Randomization[d]		X														

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Months					1	1.5	2	3	4	5	6			7	8	9
Weeks			1	2	4	6	8	12	16	20	24	25	26	28	32	36
Days	-28 to -1	1	7 (± 1)	15 (± 3)	30 (± 3)	44 (± 3)	60 (± 3)	90 (± 3)	120 (± 3)	150 (± 3)	180 (± 3)	187 (± 3)	195 (± 3)	210 (± 3)	240 (± 3)	270 (± 3)
Visit Number	1	2		3	4	5	6	7	8	9	10			11	12	13
General																
BOS161721 or placebo dosing		X			X		X	X	X	X	X					
Injection site reaction assessment[e]		X			X		X	X	X	X	X			X	X	X
Targeted physical examination				X	X	X	X	X	X	X	X			X	X	X
Vital signs (BP, HR, and temperature)[f]	X	X		X	X	X	X	X	X	X	X			X	X	X
Urine pregnancy test (women)[g]		X			X		X	X	X	X	X					
Spot urine for protein/creatinine ratio	X	X			X		X	X	X	X	X			X	X	X
Urinalysis	X	X			X		X	X	X	X	X			X	X	X
Concomitant medication[h]	X	X		X	X	X	X	X	X	X	X			X	X	X
AEs and SAEs		X		X	X	X	X	X	X	X	X			X	X	X
BILAG-2004 Index	X	X			X		X	X	X	X	X			X	X	X
SLEDAI-2K	X	X			X		X	X	X	X	X			X	X	X
PGA of disease activity	X	X			X		X	X	X	X	X			X	X	X
ACR-28 joint count	X	X			X		X	X	X	X	X			X	X	X
CLASI	X	X			X		X	X	X	X	X			X	X	X
CCI		X			X		X	X	X	X	X			X	X	X
SLICC/ACR Damage		X									X					

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Months					1	1.5	2	3	4	5	6			7	8	9
Weeks			1	2	4	6	8	12	16	20	24	25	26	28	32	36
Days	-28 to -1	1	7 (± 1)	15 (± 3)	30 (± 3)	44 (± 3)	60 (± 3)	90 (± 3)	120 (± 3)	150 (± 3)	180 (± 3)	187 (± 3)	195 (± 3)	210 (± 3)	240 (± 3)	270 (± 3)
Visit Number	1	2		3	4	5	6	7	8	9	10			11	12	13
Index																
CCI		X			X		X	X	X	X	X			X	X	X
12-lead ECG[i]	X	X			X			X								X
Laboratory																
CD4+ count	X	X		X	X	X		X			X					
Clinical laboratory assessments (hematology and clinical chemistry)	X[j]	X			X	X	X	X	X	X	X			X[j]	X	X
Coomb's test direct[k]	X	X			X		X	X	X	X	X			X	X	X
Total IgG and IgM	X	X		X	X	X		X			X					
Plasma CCI	X	X			X		X	X	X	X	X			X	X	X
Plasma CCI & CCI	X	X		X	X		X	X			X					
Whole blood for leukocyte immunophenotype	X	X		X	X		X	X			X					
ADA[l]		X		X	X		X	X			X					X
nAb[m]								X			X					
pSTAT3		X			X	X	X	X			X					X
CCI		X									X					
Whole blood RNA collection		X		X	X			X								X
CCI	X	X			X		X	X	X	X	X			X[n]	X[n]	X[n]

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Months					1	1.5	2	3	4	5	6			7	8	9
Weeks			1	2	4	6	8	12	16	20	24	25	26	28	32	36
Days	-28 to -1	1	7 (± 1)	15 (± 3)	30 (± 3)	44 (± 3)	60 (± 3)	90 (± 3)	120 (± 3)	150 (± 3)	180 (± 3)	187 (± 3)	195 (± 3)	210 (± 3)	240 (± 3)	270 (± 3)
Visit Number	1	2		3	4	5	6	7	8	9	10			11	12	13
CRP	X							X								X
PK Labs																
Predose[o]		X			X		X	X	X	X	X					
Postdose		X[p]	X	X	X[p]						X[p]	X	X	X	X	X

Abbreviations: ACR = American College of Rheumatology; ADA= anti-drug antibody; AE = adverse event; CCI [redacted]; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; C = complement; CD4+ = cluster of differentiation 4; CLASI = Cutaneous Lupus Area and Severity Index; CRP = C-reactive protein; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; CCI [redacted]; FSH = follicle stimulating hormone; HR = heart rate; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IL-21 = interleukin 21; IV = intravenous; nAb = neutralizing antibody; PGA = Physician's Global Assessment; PK = pharmacokinetic; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; RNA = ribonucleic acid; RNP = ribonucleoprotein; SAE = serious adverse event; SC = subcutaneous; CCI [redacted]; SLEDAI-2K = SLE Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; CCI [redacted]; TB = tuberculosis; TDAR = T-cell dependent antigen response.

[a] Screening assessments will be performed over more than 1 visit.

[b] If patients have had a TB test and chest x ray within 3 months prior to screening, then these assessments do not need to be repeated during screening. The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 1).

[c] Cryptosporidium test is required at screening. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

[d] Randomization should occur after patient eligibility has been confirmed by central eligibility review.

[e] Injection site reaction assessments to be performed predose and at 2 hours postdose.

[f] Vital signs will be assessed after the patient has been supine and at rest ≥ 5 minutes. Vital signs will be assessed on Day 1 at predose and at 1 and 2 hours postdose as well as on each of the scheduled outpatient days in the table above. When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

[g] Urine pregnancy test will be collected on WOCBP prior to study drug administration on dosing visits.

[h] Concomitant use of oral corticosteroids: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 1 (randomization day). See Section 5.6.1 for further details.

[i] ECG will be performed after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws.

Table 1. Schedule of Assessments - Phase 1b - Multiple Ascending Dose

	Screen[a]	Enroll	Treatment Period Follow-Up											Safety Follow-Up		
Months					1	1.5	2	3	4	5	6			7	8	9
Weeks			1	2	4	6	8	12	16	20	24	25	26	28	32	36
Days	-28 to -1	1	7 (± 1)	15 (± 3)	30 (± 3)	44 (± 3)	60 (± 3)	90 (± 3)	120 (± 3)	150 (± 3)	180 (± 3)	187 (± 3)	195 (± 3)	210 (± 3)	240 (± 3)	270 (± 3)
Visit Number	1	2		3	4	5	6	7	8	9	10			11	12	13

[j] Clinical laboratory assessments will include a fasting glucose and lipid panel during screening and Week 28.
[k] When clinically indicated.
[l] Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only assayed if the patient had a positive ADA on Day 90.
[m] nAb is assessed if patient is positive for ADA.
[n] Only dsDNA collected during safety follow-up visits.
[o] Predose samples occur on study drug administration visit days.
[p] Postdose samples will be collected at 4, 8, and 24 hours after study drug administration on Days 1, 30, and 180.

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC) Study

	Screen[a]	Enroll	Treatment Period Follow-up											Safety Follow-Up		
Months					1	1.5	2	3	4	5	6			7	8	9
Weeks			1	2	4	6	8	12	16	20	24	25	26	28	32	36
Days	-28 to -1	1	7 (± 1)	15 (± 3)	30 (± 3)	44 (± 3)	60 (± 3)	90 (± 3)	120 (± 3)	150 (± 3)	180 (± 3)	187 (± 3)	195 (± 3)	210 (± 3)	240 (± 3)	270 (± 3)
Visit Number	1	2		3	4	5	6	7	8	9	10			11	12	13
Informed consent	X															
Inclusion/Exclusion criteria	X															
Medical history	X															
Demographics	X															
Full physical exam	X	X														
Serum pregnancy test (women)	X															
FSH and estradiol (postmenopausal women)	X															
TB test (QuantiFERON-TB Gold In-Tube)[b]	X															
Chest x-ray[b]	X															
Serology (Hepatitis B and C; HIV-1/2 combination)	X															
SLICC Criteria for SLE	X															
Stool sample[c]	X															
C-SSRS	X	X						X			X					
Randomization[d]		X														

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC) Study

	Screen[a]	Enroll	Treatment Period Follow-up											Safety Follow-Up		
Months					1	1.5	2	3	4	5	6			7	8	9
Weeks			1	2	4	6	8	12	16	20	24	25	26	28	32	36
Days	-28 to -1	1	7 (± 1)	15 (± 3)	30 (± 3)	44 (± 3)	60 (± 3)	90 (± 3)	120 (± 3)	150 (± 3)	180 (± 3)	187 (± 3)	195 (± 3)	210 (± 3)	240 (± 3)	270 (± 3)
Visit Number	1	2		3	4	5	6	7	8	9	10			11	12	13
General																
BOS161721 or placebo dosing		X			X		X	X	X	X	X					
Injection site reaction assessment[e]		X			X		X	X	X	X	X			X	X	X
Targeted physical examination				X	X	X	X	X	X	X	X			X	X	X
Vital signs (BP, HR, and temperature)[f]	X	X		X	X	X	X	X	X	X	X			X	X	X
Urine pregnancy test (women)[g]		X			X		X	X	X	X	X					
Spot urine for protein/creatinine ratio	X	X			X		X	X	X	X	X			X	X	X
Urinalysis	X	X			X		X	X	X	X	X			X	X	X
Concomitant medication[h]	X	X		X	X	X	X	X	X	X	X			X	X	X
AEs and SAEs		X		X	X	X	X	X	X	X	X			X	X	X
BILAG-2004 Index	X	X			X		X	X	X	X	X			X	X	X
SLEDAI-2K	X	X			X		X	X	X	X	X			X	X	X
PGA	X	X			X		X	X	X	X	X			X	X	X
ACR-28 joint count	X	X			X		X	X	X	X	X			X	X	X
CLASI	X	X			X		X	X	X	X	X			X	X	X
CCI		X			X		X	X	X	X	X			X	X	X
SLICC/ACR Damage Index		X									X					

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC) Study

	Screen[a]	Enroll	Treatment Period Follow-up											Safety Follow-Up		
Months					1	1.5	2	3	4	5	6			7	8	9
Weeks			1	2	4	6	8	12	16	20	24	25	26	28	32	36
Days	-28 to -1	1	7 (± 1)	15 (± 3)	30 (± 3)	44 (± 3)	60 (± 3)	90 (± 3)	120 (± 3)	150 (± 3)	180 (± 3)	187 (± 3)	195 (± 3)	210 (± 3)	240 (± 3)	270 (± 3)
Visit Number	1	2		3	4	5	6	7	8	9	10			11	12	13
CCI		X			X		X	X	X	X	X			X	X	X
12-lead ECG[i]	X	X			X			X								X
Laboratory																
CD4+ count	X	X		X	X	X		X			X					
Clinical laboratory assessments (hematology and clinical chemistry)	X[j]	X			X		X	X	X	X	X			X[j]	X	X
Coomb's test direct[k]	X	X			X		X	X	X	X	X			X	X	X
Total IgG and IgM	X	X		X	X	X		X			X					
Plasma CCI	X	X			X		X	X	X	X	X			X	X	X
Plasma CCI & CCI	X	X		X	X		X	X			X					
Whole blood for leukocyte immunophenotype	X	X		X	X		X	X			X					
ADA[l]		X		X	X		X	X			X					X
nAb[m]								X			X					
pSTAT3[n]		X			X	X	X	X			X					
CCI		X									X					
Whole blood RNA collection		X		X	X			X								X
CCI	X	X			X		X	X	X	X	X			X[o]	X[o]	X[o]

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC) Study

	Screen[a]	Enroll	Treatment Period Follow-up											Safety Follow-Up		
Months					1	1.5	2	3	4	5	6			7	8	9
Weeks			1	2	4	6	8	12	16	20	24	25	26	28	32	36
Days	-28 to -1	1	7 (± 1)	15 (± 3)	30 (± 3)	44 (± 3)	60 (± 3)	90 (± 3)	120 (± 3)	150 (± 3)	180 (± 3)	187 (± 3)	195 (± 3)	210 (± 3)	240 (± 3)	270 (± 3)
Visit Number	1	2		3	4	5	6	7	8	9	10			11	12	13
CRP	X							X								X
PK Labs[p]																
Predose[q]		X			X		X	X	X	X	X					
Postdose				X								X	X	X	X	X

Abbreviations: ACR = American College of Rheumatology; ADA= anti-drug antibody; AE = adverse event; CCI [redacted]; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; C = complement; CD4+ = cluster of differentiation 4; CLASI = Cutaneous Lupus Area and Severity Index; CRP = C-reactive protein; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; CCI [redacted]; FSH = follicle stimulating hormone; HR = heart rate; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IL-21 = interleukin 21; IV = intravenous; nAb = neutralizing antibody; PGA = Physician's Global Assessment; PK = pharmacokinetic; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; RNA = ribonucleic acid; RNP = ribonucleoprotein; SAE = serious adverse event; SC = subcutaneous; CCI [redacted]; SLEDAI-2K = SLE Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; CCI [redacted]; TB = tuberculosis; TDAR = T-cell dependent antigen response.

[a] Screening assessments will be performed over more than 1 visit.

[b] If patients have had a TB test and chest x ray within 3 months prior to screening, then these assessments do not need to be repeated during screening. The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 1).

[c] Cryptosporidium test is required at screening. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

[d] Randomization should occur after patient eligibility has been confirmed. The actual randomization procedure can be completed on Day -1 after eligibility confirmation or the morning of Day 1 prior to dosing for logistical purposes.

[e] Injection site reaction assessments to be performed predose and at 2 hours postdose.

[f] Vital signs will be assessed after the patient has been supine and at rest ≥ 5 minutes. Vital signs will be assessed on Day 1 at predose and at 1 and 2 hours postdose as well as on each of the scheduled outpatient days in the table above. When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

[g] Urine pregnancy test will be collected on WOCBP prior to study drug administration on dosing visits.

[h] Concomitant use of oral corticosteroids: A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 1 (randomization day). See Section 5.6.1 for further details.

[i] ECGs will be performed after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK

Table 2. Schedule of Assessments - Phase 2 Proof of Concept (POC) Study

	Screen[a]	Enroll	Treatment Period Follow-up											Safety Follow-Up		
Months					1	1.5	2	3	4	5	6			7	8	9
Weeks			1	2	4	6	8	12	16	20	24	25	26	28	32	36
Days	-28 to -1	1	7 (± 1)	15 (± 3)	30 (± 3)	44 (± 3)	60 (± 3)	90 (± 3)	120 (± 3)	150 (± 3)	180 (± 3)	187 (± 3)	195 (± 3)	210 (± 3)	240 (± 3)	270 (± 3)
Visit Number	1	2		3	4	5	6	7	8	9	10			11	12	13

blood draws (Section 7.5).

[j] Clinical laboratory assessments will include a fasting glucose and lipid panel during screening and Week 28

[k] When clinically indicated.

[l] Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only assayed if the patient had a positive ADA on Day 90.

[m] nAb is assessed if patient is positive for ADA.

[n] Predose (trough) samples only.

[o] Only CCI collected during safety follow-up visits.

[p] PK samples will only be collected at the investigational sites that will be participating in the PK portion of the study.

[q] Predose samples occur on study drug administration visit days.

5 POPULATION

5.1 Participant Recruitment

Advertisements approved by the IRB, and investigator databases, may be used as recruitment procedures for adult men and women with moderately to severely active SLE.

5.2 Number of Patients

Approximately 186 male and female patients are planned for enrollment, but may be adjusted upward according to the dropout (noncompliance) rate, which will be monitored in a blinded fashion in an ongoing basis. Approximately 30 patients will be randomized for the MAD Phase 1b study, and approximately 156 patients will be randomized in the POC Phase 2 study. Note that approximately 30 dropouts are assumed.

5.3 Patient Screening

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular individual. Patient eligibility will be reviewed and confirmed by the medical monitor or designee prior to randomization. Screening assessments (see the Schedule of Assessments [Section 4.3]) for this study must be performed between Day -28 and Day -1.

5.4 Inclusion Criteria

Patients who meet the following criteria will be considered eligible to participate in this clinical study:

1. Men and women, ages 18 to 70 years, inclusive;
2. Patients must be mentally capable of giving consent and there must be evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study;
3. Patients must have SLE as defined by meeting 4 of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE (with at least 1 clinical and 1 immunologic criterion or Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies), either sequentially or simultaneously.
4. At screening, patients must have at least 1 of the following:
    a. Elevated antinuclear antibodies (ANA) ≥ 1:80 via immunofluorescent assay at the central laboratory;
    b. Positive anti-dsDNA or anti-Smith (Sm) above the normal level as determined by the central laboratory;
    c. C3 or C4 below normal as determined by central lab.

5. At screening, the SLE Disease Activity Index 2000 (SLEDAI-2K) must be ≥ 6, including points from at least 1 of the following clinical components:
   a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis
      i. Excluding parameters which require central laboratory results: (hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia)
      ii. Points from lupus headache and organic brain syndrome will also be excluded.
6. On Day 1, the SLEDAI-2K must be ≥ 6, including points from at least 1 of the following clinical components:
   a. Arthritis, rash, myositis, mucosal ulcers, pleurisy, pericarditis, and vasculitis.
      i. Excluding parameters which require central laboratory results: (hematuria, pyuria, urinary casts, proteinuria, positive anti-dsDNA, decreased complement, thrombocytopenia, and leukopenia);
      ii. Points from lupus headache and organic brain syndrome are also excluded.
7. Patients must have at least 1 of the following manifestations of SLE, as defined by the BILAG criteria as modified for use in this study, which must be confirmed by the central data reviewer:
   a. BILAG A or B score in the mucocutaneous body system;
   b. BILAG A or B score in the musculoskeletal body system due to active polyarthritis defined as follows:
      i. "BILAG A:" Severe Arthritis, (BILAG item number 41), manifested by observed active synovitis in ≥ 2 joints with marked loss of functional range of movements and significant impairment of basic activities of daily living that has been present on several days cumulatively over the past 4 weeks, including at the time of the screening visit. See APPENDIX 5 for additional detailed specifications.
         - Basic ADLs are defined as the following activities which require assistance or assistive devices, (at least 1 must be present and documented in source):
            - Ambulation, toileting, grooming- including bathing and dressing; feeding oneself, (and not responsive to steroids up to 10 mg/day, antimalarials, NSAIDs).
      ii. "BILAG B:" Moderate Arthritis, Tendonitis or Tenosynovitis, (BILAG item number 42), defined as tendonitis/tenosynovitis, or active synovitis in ≥ 1 joint, (observed or throughout history), with some loss of functional range of movements which lead to some loss of functional range of motion as manifested by effects on instrumental ADLs such as:

- Cooking, driving, using the telephone or computer, shopping, cleaning, etc, and has been present on several days over the last 4 weeks, and is present at the time of the screening visit.

c. If only one "B" and no "A" score is present in the mucocutaneous body system or in the musculoskeletal body system due to arthritis, then at least 1 "B" must be present in the other body systems for a total of 2 "B" BILAG body system scores.

8. Patients must be currently receiving at least 1 of the following:
   a. Administration for a minimum of 12 weeks, and a stable dose for at least 56 days (8 weeks prior to signing consent) of the following permitted steroid-sparing agents:
      i. Azathioprine (AZA), mycophenolate mofetil or mycophenolic acid, chloroquine, hydroxychloroquine, or methotrexate (MTX).
   b. Prednisone (or prednisone-equivalent) cannot exceed 30 mg/day at screening for a patient to be eligible and must be stable at a maximum of 10 mg/day for at least 5 days prior to Day 1 (randomization) (see APPENDIX 3).
9. Women of childbearing potential (WOCBP; see Section 5.7 for full information regarding WOCBP, definition of menopause, and contraception):
   a. Must have a negative serum pregnancy test at screening. Urine pregnancy test must be negative prior to first dose;
   b. Must not be breastfeeding;
   c. Must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS161721 plus 30 days (duration of ovulatory cycle) for a total of 36 weeks after treatment completion;
10. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of BOS161721 plus 90 days (duration of sperm turnover) for a total of 44 weeks after treatment completion.
11. Patients must demonstrate willingness and ability to comply with the scheduled study visits, treatment plans, laboratory tests, and other procedures.

5.5 Exclusion Criteria

Patients presenting with any of the following will not be included in this study:

1. Drug-induced SLE, rather than "idiopathic" SLE;
2. Other systemic autoimmune disease (eg, erosive arthritis, rheumatoid arthritis [RA], multiple sclerosis [MS], systemic scleroderma, or vasculitis not related to SLE);
   a. RA-Lupus overlap (Rupus), and secondary Sjögren syndrome are allowed.
3. Any major surgery within 6 weeks of study drug administration, (Day 1), or any elective surgery planned during the course of the study;

4. Any history or risk for tuberculosis (TB), specifically those with:
    a. Current clinical, radiographic, or laboratory evidence of active TB;
    b. History of active TB;
    c. Latent TB defined as positive QuantiFERON-TB Gold In-Tube (QFT-G) or other diagnostic test in the absence of clinical manifestations. Latent TB is not excluded if the patient has documented completion of adequate course of prophylactic treatment with regimen recommended by local health authority guideline, or the patient has started treatment with isoniazid, or other regimen recommended by local health authority guidelines for at least 1 month before Day 1 and continues to receive the prophylactic treatment during study until the treatment course is completed.
5. Active or unstable lupus neuropsychiatric manifestations, including but not limited to any condition defined by BILAG A criteria, with the exception of mononeuritis multiplex and polyneuropathy, which are allowed;
6. Severe proliferative lupus nephritis, (WHO Class III, IV), which requires or may require induction treatment with cytotoxic agents or high dose CS;
7. Concomitant illness that, in the opinion of the investigator, is likely to require additional systemic glucocorticosteroid therapy during the study, (eg, asthma), is exclusionary;
    a. However, treatment for asthma with inhalational CS therapy is allowed.
8. Use or planned use of concomitant medication outside of standard of baseline treatment for SLE from Day -1 or for any time during the study. (See Section 5.6 for prohibited concomitant medication);
9. Active and clinically significant infection (bacterial, fungal, viral, or other) within 60 days prior to first dose of study drug. Clinically significant is defined as requiring systemic antibiotics or hospitalization;
10. A history of opportunistic infection, or a history of recurrent or severe disseminated herpes zoster or disseminated herpes simplex within the last 3 years;
11. Chronic viral hepatitis including hepatitis B (HBV) and hepatitis C (HCV), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness;
12. Cryptosporidium in the stool sample at screening;
13. White blood cells (WBC) < 1,200/mm^3 (1.2×10^9/L) at screening;
14. Absolute neutrophil count (ANC) < 500/mm^3 at screening;
15. CD4+ count < 500/µL at screening;
16. Platelets < 50,000/mm^3 (50×10^9/L) or < 35,000/ mm^3 (35×10^9/L) if related to SLE, at screening;
17. Hemoglobin < 8 g/dL or < 7 g/dL at screening if due to anemia related to SLE;
18. Proteinuria > 3.0 g/day (3000 mg/day) at screening or equivalent level of proteinuria as assessed by protein/creatinine ratio (3 mg/mg or 339 mg/mmol);

19. Serum creatinine > 2.0 mg/dL at screening or creatinine clearance (CrCL) < 40 ml/minute based on Cockcroft-Gault calculation[39]:

    GFR = ([1 for male] or [0.85 for female]) × (140 – Age) × BW / (72 × Creatinine)

20. Serum alanine aminotransferase (ALT) and/or serum aspartate aminotransferase (AST) > 2 × ULN at screening, unless explicitly related to lupus based on the investigator's judgment;
21. Creatinine kinase (CK) > 3.0 × ULN at screening, unless it is related to lupus myositis
22. Direct bilirubin > 1.5 × ULN at screening (unless related to Gilbert's syndrome);
23. Any other laboratory test results that, in the opinion of the Investigator, might place a patient at unacceptable risk for participating in this study;
24. History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody (eg, IgG protein) or molecules made of components of monoclonal antibodies;
25. History substance and/or alcohol abuse or dependence within the past 1 year, at the investigator's judgement;
26. History of cancer within the last 5 years (except for cutaneous basal cell or squamous cell cancer, or cervical cancer in situ resolved by excision);
27. Any other severe acute or chronic medical or psychiatric condition, including recent (within the past year) medical conditions (eg, cardiovascular conditions, respiratory illnesses) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study;
28. Investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or patients who are employees of the sponsor or directly involved in the conduct of the trial;
29. Currently participating in, or who have participated in other interventional (drug or device) clinical study within 30 days or 5 half-lives of baseline, whichever is longer;
30. Recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4 or 5 on the Columbia Suicide severity Rating Scale (C-SSRS);
31. Current or pending incarceration;
32. Current or pending compulsory detainment for treatment of either a psychiatric or physical (eg, infectious disease) illness.

5.6 Concomitant Medications

Any medicinal product, prescribed or OTC, including herbal and other nontraditional remedies, is considered a concomitant medication. Patients should stay on stable regimen of other

concomitant medications for the treatment of SLE (eg, analgesics, NSAIDs, statins, ACE inhibitors/ARBs and other antihypertensive drugs), unless changes in these treatments are clinically indicated. Use of any other drugs for non-SLE conditions, including over-the-counter medications and herbal preparations, should remain stable unless change or addition is clinically necessary. Discussion with the medical monitor prior to initiation of new medication is strongly recommended. Any concomitant therapies must be recorded on the eCRF. Prior and concomitant medication use will be recorded for the 30 days prior to screening until the last follow-up visit. In addition, historical treatment for SLE (including immunosuppressant, anti-malarial, corticosteroid, and/or biologic agent) will be recorded for the 48 weeks prior to screening in the eCRF.

5.6.1 Oral Corticosteroid Dose

Prior to randomization, oral CSs (prednisone or prednisone equivalent), may be used in accordance with the investigator's clinical judgment and best standard of care. See APPENDIX 3 for examples of equivalents.

A maximum daily dose of 30 mg/day of oral CS will be acceptable for eligibility for the study, however, the daily dose must be tapered down to a maximum of 10 mg/day for at least 5 days prior to Day 1 (randomization day).

After Day 1 (after initiation of study therapy), no up-titration above 10 mg/day is allowed except for up to 1 CS burst for increased disease activity.

Tapering of steroids during the course of the study will be encouraged and should be evaluated at all visits.

- Once a patient has received the first dose of study drug, prednisone (or prednisone equivalent) may be tapered down at the discretion of the investigator;
    - Tapering is allowed after randomization except within 8 weeks of the primary (Week 28) and secondary (Week 16) endpoint assessments. Between Week 8 and Week 16, and between Week 20 and Week 28, oral corticosteroid (OCS) doses must be held constant otherwise the patient will be declared a non-responder in efficacy assessments.

A maximum of 1 oral CS "burst" for increased SLE disease activity will be allowed during the study either between Weeks 1 and 8 or between Weeks 16 and 20, according to the following:

- An oral CS "burst" between Week 1 and Week 8; (an increase of ≤ 40 mg/day of prednisone or equivalent), which must be tapered down to a maximum of 10 mg/day within 2 weeks of initiation of the "burst."
    - Alternatively, a single intramuscular (IM) dose of methylprednisolone (40 mg or equivalent) is permitted;
    - The course of the oral CS "burst" is not permitted to extend beyond Week 8.

- An oral CS "burst" between Week 16 and Week 20 (an increase of ≤ 20 mg/day prednisone or equivalent), which must be tapered down to a maximum of 10 mg/day within 2 weeks of initiation of the "burst".
    - Alternatively, a single IM dose of methylprednisolone (40 mg or equivalent) is permitted.

Treatment with inhalational CS therapy (eg, for asthma), or by any other route, is allowed. Other concomitant medications for SLE need to be taken at stable doses as per the inclusion criteria (Section 5.4).

5.6.2 Other Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study drug administration in the study are described below, and washout requirements are provided in APPENDIX 4. Medications taken within 30 days prior to screening must be recorded on the eCRF.

1. Prior exposure to BOS161721;
2. Patients who have received treatment with anti-CD20 monoclonal antibodies within 6 months of screening; recovery of B cells (CD19+) must be documented (record absolute number of CD19+ B cells);
3. Patients who have received treatment with cyclophosphamide within the 1 year prior to screening;
4. Patients who have received treatment with cyclosporine (with exception of ophthalmic use), any other calcineurin inhibitor or other immunosuppressive medication not specified in the inclusion criteria (oral or topical) within 3 months of screening;
5. Patients who are currently receiving or are scheduled to receive plasmapheresis or lymphapheresis therapy, or have received such therapy within 8 weeks prior to screening;
6. Patients who have received any live vaccines within 30 days of screening. Note: Furthermore, live vaccines should not be used during the course of the study and within the 2 months following last dose. Other inactivated vaccines such as tetanus, etc, may be used according to local guidelines during treatment period;
7. Patients who are scheduled or anticipated to have elective surgery during the course of the study;
8. Initiation of new immunosuppressant or anti-malarial agent is not permitted. Note: Dose reduction or replacement may be allowed due to intolerability or shortage for patients on a stable dose prior to study initiation.

5.7 Women of Childbearing Potential

WOCBP is defined as any woman who has experienced menarche and who has not undergone surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) and is not postmenopausal.

See Section 5.7.2 for detailed information regarding contraceptive requirements for WOCBP.

5.7.1 Determination of Menopause

Menopause is defined as at least 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. Women under the age of 55 years must have a documented serum FSH level > 40 mIU/mL at screening to confirm menopause.

5.7.2 Contraception

WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS161721 plus 30 days (duration of ovulatory cycle) for a total of 36 weeks after treatment completion.

Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug BOS161721 plus 90 days (duration of sperm turnover) for a total of 44 weeks after treatment completion.

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

At a minimum, patients must agree to the use of 1 method of highly effective contraception from the following:

- Male condoms with spermicide;
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by patients who are WOCBP or a male patient's WOCBP partner. Women who are partner of men who are patients participating in the study may use hormone-based contraceptives as 1 of the acceptable methods of contraception since they will not be receiving study drug.
- IUDs, such as ParaGard®;
- Vasectomy;
- Complete abstinence, defined as complete avoidance of heterosexual intercourse, is an acceptable form of contraception. Women who are abstinent while participating in the study must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the patient chooses to forego complete abstinence.

Azoospermic men and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing.

5.8 Deviation from Inclusion/Exclusion Criteria

Deviation from the inclusion or exclusion criteria will not be allowed. If deviation of inclusion/exclusion criteria is discovered after randomization, the investigator should contact the medical monitor for discussion. A decision will be made whether to allow a patient continue or withdrawal from the study medication.

See Section 7.8 for additional details.

5.8.1 Patient Withdrawal and Replacement

See Section 6.5 for reasons for removal from the trial. Withdrawn patients may be replaced during the MAD study after discussion between the principal investigator or designee and sponsor.

5.8.2 Exception for Non-Responders

Patients will be classified as non-responders if they (1) receive a second rescue medication at any time in the study or (2) take rescue medications between Week 8 and Week 16 or between Week 20 and Week 28 (as described in Section 5.6.1). If a patient has been deemed a non-responder, they will discontinue from treatment and all End of Treatment assessments will be performed. The patient will then enter the safety follow-up period. The use of rescue medications in the case of non-responders is not to be considered a protocol violation (exclusion criteria 8). Protocol violations will be identified based on blinded data prior to unblinding the final analysis dataset.

6 STUDY PROCEDURES

Refer to the eCRF completion guidelines for data collection requirements and documentation of study assessments/procedures.

6.1 Screening

Screening will be the same for both the MAD and POC studies. Screening for the POC study cannot begin until the POC dose decision has been made.

Screening will take place from Day -28 to Day -1, and assessments may be performed over more than 1 visit. Confirmation that the most current IRB/IEC approved informed consent form (ICF) has been signed must occur before any study-specific screening procedures are performed. Procedures that are part of standard of care are not considered study-specific procedures and may be performed prior to informed consent and used to determine eligibility.

All screened patients will be assigned a unique screening number. The screening number will include a 3-digit site number and a 4-digit sequential number to identify patients from the time of screening. Only eligible patients who are confirmed by central review as meeting the inclusion/exclusion criteria listed in Section 5.4 and Section 5.5 will be enrolled in the study. Screened patients who drop out of the clinical study before randomization will be recorded as screen failures. If rescreening occurs, the site will assign a new screening number.

Specific procedures at the screening visit will include:

- Medical history documentation;
- Review of inclusion and exclusion criteria;
    - Patient medical records must contain documentation of SLE diagnosis;
    - C-SSRS.
- Concomitant medication documentation;
- Demographics;
- Full physical examination;
- Vital signs;
- Laboratory evaluations:
    - Hematology and clinical chemistry;
    - Serology (Hepatitis B and C; HIV-1/2 combination);
    - TB test

- CRP
- Direct Coomb's test (if indicated)
- CD4+ count, total IgG and IgM levels, plasma [redacted], plasma [redacted] and [redacted], whole blood for leukocyte immunophenotype; [redacted];
- Serum pregnancy test (WOCBP);
- FSH and estradiol (postmenopausal women)
- Spot urine for protein/creatinine ratio;
- Urinalysis.
- Stool sample

- 12-lead ECG;
- SLE-related indices (BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, Physician's Global Assessment (PGA) of disease activity.

Screening procedures are listed in the Schedule of Assessments (Section 4.3), and details are provided in Section 7.

6.1.1 Retesting During Screening Period

A single retesting of laboratory parameters and/or other assessments during the screening period is permitted (in addition to any parameters that require a confirmatory value) only if:

- medically indicated;
- there is evidence a laboratory sample was mislabeled, inadequately processed, and/or deteriorated in transit to the central laboratory.

Any new result will override the previous result (ie, the most current result prior to randomization) and is the value by which study inclusion/exclusion will be assessed, as it represents the patient's most current clinical state. This will also apply to patients who are being rescreened.

6.2 Enrollment/Randomization and Day 1 Treatment

Randomization should occur after patient eligibility for enrollment has been confirmed by the central eligibility review.

The study site will obtain a randomization number when registering the patient in IWRS. All patients will receive BOS161721 or placebo according to the kit number assigned by the IWRS randomization scheme.

After randomization, procedures include:

- PROs: CCI ;
- C-SSRS;
- Laboratory evaluations:
  - Hematology and clinical chemistry
  - Direct Coomb's test (if indicated)
  - CD4+ count, total IgG and IgM levels, plasma CCI , plasma CCI and CCI , whole blood for leukocyte immunophenotype;
  - ADA;
  - pSTAT3 (predose [trough] samples only in Phase 2);
  - CCI ;
  - Whole blood RNA collection;
  - CCI ;
  - See Table 1 and Table 2 for details of PK sampling in the MAD and POC studies;
  - Urine pregnancy test will be collected on WOCBP prior to study drug administration;
  - Spot urine for protein/creatinine ratio;
  - Urinalysis.
- Concomitant medication documentation;
- Documentation of AEs and SAEs (see Section 7.2.2.5 on SAE reporting requirements);
- Full physical examination;
- Vital signs (prior to PK blood draw, predose, and at 1 and 2 hours postdose on Day 1);
- 12-lead ECG (prior to PK blood draw);
- SLE-related indices (BILAG-2004 Index, SLEDAI-2K , ACR-28 joint count, CLASI, PGA);
- SLICC/ACR damage index;
- Study drug administration;

- Administration of BOS161721 or placebo will take place on-site, and is discussed in Section 8.3.

- Injection site reaction assessment, predose and 2 hours postdose.

Procedures on Day 1 are listed in the Schedule of Assessments (Section 4.3), and details are provided in Section 7.

All patients who are enrolled, randomized, and receive study drug, or undergo study-specific procedures should reconsent with any updated versions of IRB/IEC approved informed consents during study participation as applicable and per institutional guidelines.

6.3 Treatment Period/Follow-Up Visits

See Section 4.3 for allowable windows for each visit. The following procedures will be performed at every study drug administration visit (Weeks 4, 8, 12, 16, 20, and 24) and follow-up visits during the treatment period (Weeks 2 and 6):

- Targeted physical examination;
- Vital signs (prior to PK blood draw);
- Concomitant medication documentation;
- Documentation of AEs and SAEs (see Section 7.2.2.5 on SAE reporting requirements).

The following assessments will be performed only at Weeks 4, 8, 12, 16, 20, and 24:

- PROs: CCI [redacted];
- Urine pregnancy tests will be collected on WOCBP prior to study drug administration;
- Injection site reaction assessments will be performed predose and 2 hours postdose;
- Direct Coomb's test (if indicated);
- Spot urine for protein to creatinine ratio;
- Urinalysis;
- CCI [redacted];
- Plasma CCI [redacted];
- PGA, BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, and the CLASI will be completed.
- In addition the following assessments will be completed:

- SLICC/ACR Damage Index will be completed at Week 24 (Visit 10).
- C-SSRS will be completed at Weeks 12 and 24 (Visits 7 and 10);
- ECGs will be performed at Weeks 4 and 12 (Visits 4 and 7) prior to PK blood draw.
- See Table 1 and Table 2 for details of PK sampling in the MAD and POC studies, respectively.
- Hematology and chemistry assessments will be performed at Weeks 4 and 6 (Visits 4 and 5) for the MAD study, only, and at Weeks 8, 12, 16, 20, and 24 (Visits 6 through 10) for both studies.
- The CD4+ count and total IgG and IgM levels will be assessed at Weeks 2, 4, 6, 12, and 24 (Visits 3, 4, 5, 7, and 10).
- Plasma CCI & CCI, ADA, and whole blood for leukocyte immunophenotype will be assessed at Weeks 2, 4, 8, 12, and 24 (Visits 3, 4, 6, 7, and 10).
- pSTAT3 will be assessed at Weeks 4, 6, 8, 12, and 24 (Visits 4, 5, 6, 7, and 10).
- Whole blood RNA will be collected at Weeks 2, 4, and 12 (Visits 3, 4, and 7).
- CRP will be measured at Week 12 (Visit 7), and nAb will be assessed if patient is positive for ADA at Weeks 12 and 24 (Visits 7 and 10).
- CCI will be assessed at Week 24 (Visit 10).

6.4 Safety Follow-Up Visits

Safety follow-up visits will take place at Weeks 28, 32, and 36 (Visits 11, 12, and 13). These visits will include the following:

- PROs: CCI;
- Documentation of AEs and SAEs (see Section 7.2.2.5 on SAE reporting requirements);
- Injection site reactions;
- Targeted physical examination;
- Vital signs (prior to PK blood draw);
- Spot urine for protein/creatinine ratio and urinalysis;
- Concomitant medication documentation;
- BILAG-2004 Index, SLEDAI-2K, ACR-28 joint count, CLASI, and PGA;

- Clinical laboratory assessments (hematology and clinical chemistry);
- Direct Coomb's test (if indicated);
- Plasma CCI ;
- CCI ;
- pSTAT3 (Week 36 only for MAD study);
- 12-lead ECG (Week 36 only, prior to PK blood draw);
- CRP (Week 36 only);
- ADA (Week 36 only);
- Whole blood RNA collection (Week 36 only);
- See Table 1 and Table 2 for details of PK sampling in the MAD and POC studies, respectively.

6.5 Premature Discontinuation

While patients are encouraged to complete all study evaluations, they may withdraw from the study at any time and for any reason. Every effort will be made to determine why any patient withdraws from the study prematurely. If the patient is unreachable by telephone, a registered letter, at the minimum, should be sent to the patient requesting him/her to contact the clinic.

All patients who withdraw from the study with an ongoing AE or SAE must be followed until the end of study or until the event is resolved or deemed stable, respectively.

If a patient withdraws prematurely after dosing, an end of treatment (EOT) visit should be performed (Visit 10) and a last follow-up visit 90 days after dosing should be scheduled (Visit 13). Safety follow-up visit procedures based on the Schedule of Assessments (see Section 6.4).

Patient participation may be terminated prior to completing the study and the reason recorded as follows:

- AE/SAE;
- Protocol deviation;
- Lost to follow-up;
- Patient withdraws consent at their own request;
- Investigator decision;

- Decision by sponsor (other than AE/SAE, protocol deviation, or lost to follow-up).

Withdrawn patients may be replaced after discussion between the investigator or designee and sponsor.

7 ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, which may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and wellbeing of the patient. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. All protocol violations are entered directly into the eCRFs.

7.1 Medical History, Demographic and Other Baseline Information

The medical history comprises:

- General medical history;
- Documentation of SLE diagnosis;
- Historical medication therapy for SLE.

The following demographic information will be recorded:

- Age;
- Ethnic origin (Hispanic/Latino or not Hispanic/not Latino);
- Race (White, American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black/African American);
- Height (without shoes, in cm);
- Body weight, without shoes (kg);
- Body mass index (BMI [kg/m^2]).

Other baseline characteristics will be recorded as follows:

- Concomitant medication documentation (see Section 5.6);
- Status of child bearing potential and contraception.

7.2 Safety Assessments

7.2.1 Laboratory Assessments

Laboratory tests will be performed at times defined in the Schedule of Assessments (Section 4.3). Patient eligibility will be determined based on these tests at screening. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

A central laboratory will be used (with the exception of urine pregnancy tests and stool analysis) to ensure accuracy and consistency in test results. The central laboratory will transmit all results for protocol tests, scheduled and unscheduled, to the clinical data base. Laboratory/analyte results that could unblind the study (ie, biomarker results) will not be reported to investigative sites or other blinded personnel until the study has been unblinded. Urinalysis will be performed on midstream, clean catch specimens. Some biomarkers listed above will not be drawn at some sites due to geographical logistical challenges. See the laboratory manual for details.

Table 3. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other Safety Tests
Hemoglobin	BUN	pH	Spot urine for protein/creatinine ratio
Hematocrit	Creatinine	Glucose (qual)	FSH[b]
RBC count	Glucose (fasting)	Protein (qual)	Estradiol[b]
RDW	Calcium	Blood (qual)	Urine pregnancy test[c]
MCV	Sodium	Ketones	QuantiFERON®-TB Gold In-Tube test (QFT-G)
MCH	Potassium	Nitrites	
MCHC	Chloride	Leukocyte esterase	Serology[d] (Hepatitis B and C; HIV-1/2 combination)
Platelet count	Total CO_2 (bicarbonate)	Urobilinogen	
WBC count	AST, ALT	Urine bilirubin	Stool sample[e]
CD4+ count	Total bilirubin	Microscopy[a]	
Total neutrophils (Abs)	Alkaline phosphatase		
Eosinophils (Abs)	Creatine kinase		
Monocytes (Abs)	Uric acid		
Basophils (Abs)	Albumin		
Lymphocytes (Abs)	Total cholesterol (fasting)		
Reticulocytes (%)	LDL-C (fasting)		
	HDL-C (fasting)		
	Triglycerides (fasting)		
	Total protein		
	PT/INR		

	Additional Tests[f] (potential Hy's Law)	Immunogenicity, PD and other Biomarker Tests
	AST, ALT (repeat)	ADA
	Total bilirubin (repeat)	nAb[g]
	Albumin (repeat)	pSTAT3 (predose [trough] samples only, in Phase 2)
	Alkaline phosphatase (repeat)	Total IgG & IgM
	Direct bilirubin	Plasma CCI
	Indirect bilirubin	Plasma CCI & CCI
	GGT	Whole blood for leukocyte immunophenotype and RNA
		CCI
		Antibodies CCI
		CRP
		Direct Coomb's test[h]

Abbreviations: Abs = absolute; ADA = anti-drug antibody; ALT = alanine aminotransferase; CCI; CCI; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C = complement; CD4+ = cluster of differentiation 4; CRP = C-reactive protein; dsDNA = double-stranded deoxyribonucleic acid;; FSH = follicle stimulating hormone; GGT = gamma-glutamyltransferase; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ration; IL-21 = interleukin 21; LDL-C = low-density lipoprotein cholesterol; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = Mean corpuscular volume; nAb = neutralizing antibody; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; PT = prothrombin time; qual = qualitative; RBC = red blood cell; RDW = RBC distribution width; RNA = ribonucleic acid; RNP = ribonucleoprotein; SAE = serious adverse event; SC = subcutaneous; CCI CCI; TB = tuberculosis.

Table 3. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other Safety Tests

[a] On all urine samples.
[b] At screening only, in women who are amenorrheic for at least 12 consecutive months and under 55 years old.
[c] For WOCBP.
[d] Screening only.
[e] At screening, and if a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.
[f] Additional testing for potential Hy's Law cases only (See Section 7.2.2.6.3).
[g] If patient is positive for ADA.
[h] If clinically indicated.

7.2.1.1 Pregnancy testing

For WOCBP, a serum pregnancy test will be performed at screening. Following a negative serum pregnancy result at screening, appropriate contraception must be commenced or continued and a further negative urine pregnancy test results will then be required at the baseline visit before the patient may receive the investigational product. Urine pregnancy tests will also be routinely repeated at study drug administration visits (Visits 2, 4, 6, 7, 8, 9, and 10) prior to study drug administration, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive pregnancy test or confirmed pregnancy, the patient will be withdrawn from study drug but may remain in the study for safety monitoring.

See Section 7.2.2.7.1 for information on reporting of pregnancies as AEs/SAEs during the study.

7.2.1.2 Tuberculosis Screening

During the screening period, it must be determined and documented that a patient does not have evidence of active or latent or inadequately treated TB per the exclusion criteria (Section 5.5). The results of TB screening, which includes the QuantiFERON®-TB Gold In-Tube (QFT-G) test and a chest x-ray, conducted in the 3 months prior to screening or during the screening period must be documented in study records prior to randomization (Day 1).

7.2.1.2.1 Mycobacterium Tuberculosis Testing Using QuantiFERON Test[40]

QuantiFERON®-TB Gold In-Tube (QFT-G) is an in vitro diagnostic test using a peptide cocktail simulating ESAT-6, CFP-10, and TB 7.7 proteins to stimulate cells in heparinized whole blood. Detection of INFγ performed by enzyme-linked immunosorbent assay (ELISA) is used to identify in vitro responses to these peptide antigens that are associated with Mycobacterium tuberculosis infection. QFT-G is an indirect test for M. tuberculosis infection (including disease) and is intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.

Test results will be reported as positive, negative, or indeterminate. A negative QFT-G test result is required to meet the inclusion criterion. In the case of an indeterminate result, repeat tests should be permitted for the purpose of determining eligibility of patients to enroll in this

study. If a repeat test is indeterminate again, the patient is a screen failure. The procedure for using this test and interpreting the results will be described fully in the laboratory manual, which will be provided to investigators.

7.2.2 Adverse Events

7.2.2.1 Definitions

An AE is defined as any untoward medical occurrence experienced by a study patient, whether or not considered drug related by the principal investigator.

AEs are unfavorable changes in a general condition, subjective or objective signs or symptoms, worsening of pre-existing concomitant disease, and clinically significant abnormality in laboratory parameters observed in a patient in the course of a clinical study.

Non-serious SLE manifestations or abnormal laboratory results related to SLE disease activity would not be recorded as AEs unless they meet the definition for SAEs (Section 7.2.2.5).

7.2.2.2 Recording of Adverse Events

AEs should be collected and recorded for each patient from the date of the first dose of study drug until the end of their participation in the study, including the safety follow up period.

AEs may be volunteered spontaneously by the study patient, or discovered by the study staff during physical examinations or by asking an open, nonleading question such as 'How have you been feeling since you were last asked?' All AEs and any required remedial action will be recorded on the Adverse Events eCRF and Safety Adverse Event Form. The details of the AE, date of AE onset (and time, if known), date of AE outcome (and time, if known), and action taken for the AE will be documented together with the principal investigator's assessment of the seriousness of the AE and causal relationship to the study drug and/or the study procedure.

All AEs should be recorded individually, using diagnostic terms where possible. If the diagnosis is not established, individual symptoms may be reported. The AEs will subsequently be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

7.2.2.3 Severity of Adverse Events

Each AE will be assessed by the principal investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03 criteria. [41] When changes in the severity (grade) of an AE occur more frequently than once a day, the maximum severity for the event should be noted for that day. Any change in severity of signs and symptoms over a number of days will be captured by recording a new AE, with the amended severity grade and the date (and time, if known) of the change.

7.2.2.4 Causality of Adverse Events

The principal investigator will assess the causal relationship between BOS161721 or placebo and the AE. One of the following categories (Table 4) should be selected based on medical judgment, considering the definitions below and all contributing factors.

Table 4.	Causality Definitions
Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment (dechallenge[a]) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge[b] procedure if necessary.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (eg, concomitant disease, environmental factors, or other drugs or chemicals).

[a] Dechallenge: Upon discontinuation of a drug suspected of causing an AE, the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation (positive dechallenge), or the symptoms continue despite withdrawal of the drug (negative dechallenge). Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists (for example, as in bone marrow suppression, fixed drug eruptions, or tardive dyskinesia).

[b] Rechallenge: Upon re-administration of a drug suspected of causing an AE in a specific patient in the past, the AE recurs upon exposure (positive rechallenge), or the AE does not recur (negative rechallenge).

An unexpected adverse drug event is any adverse drug event for which the specificity or severity is not consistent with the current IP.

7.2.2.5 Seriousness of Adverse Events

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

- Results in death;
- Is life threatening; this means that the patient was at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe;
- Requires hospitalization or prolongation in existing hospitalization;
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Is a congenital anomaly or birth defect;
- Is another important medical event (see below).

Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm;

- Blood dyscrasias or convulsions that do not result in inpatient hospitalization;
- Development of drug dependency or drug abuse.

Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (eg, elective surgery for a pre-existing condition that has not worsened) need not be considered SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'nonserious' according to the usual criteria.

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are associated with the use of the drug and are serious and unexpected.

7.2.2.6 Adverse Events of Special Interest

AEs of special interest in this study include the following:

1. Anaphylaxis and serious allergic reactions;
2. Injection site reaction, including erythema, pain, and induration;
3. Drug Induced Liver Injury (DILI) assessed following Hy's Law;
4. Malignancy;
5. Opportunistic infections such as disseminated histoplasmosis, cryptococcosis, and disseminated tuberculosis;
6. Cryptosporidiasis.

7.2.2.6.1 Anaphylaxis and Serious Allergic Reactions

Anaphylaxis will be defined according to the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria.[42] In the event of anaphylactic reaction or severe/serious hypersensitivity/allergic reaction, the patient must discontinue IP and emergency resuscitation measures implemented. In case of other mild to moderate hypersensitivity reaction, depending on the severity, the investigator may manage in accordance with the standard-of-care.

Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus, or flushing, swollen lips-tongue-uvula) and at least 1 of the following:
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):

   a. Systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from the patient's baseline.

7.2.2.6.2 Injection Site Reactions

Injection site reactions are to be captured and reported as AEs. These may include injection site erythema, pain, and induration. The investigator should provide a clear description of the observed or reported AE including location and severity. All concomitant treatments used to treat injection site reactions should be recorded and captured in the eCRF, together with the AE of injection site reactions.

7.2.2.6.3 Potential Drug-Induced Liver Injury

Abnormal values in AST and/or ALT levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of DILI, and as potential Hy's Law cases, and should always be considered important medical events. If symptoms compatible with DILI precede knowledge of serum chemical test abnormalities, liver enzyme measurements should be made immediately, regardless of when the next visit or monitoring interval is scheduled. In some cases, symptoms may be an early sign of injury and although typically less sensitive than serum enzyme elevations, they may indicate a need for prompt serum testing. An increase in liver enzymes should be confirmed by a repeated test within 48 to 72 hours following the initial test, prior to reporting of a potential DILI event. Patients will continue to have weekly or biweekly liver enzyme measurements until resolution or levels return to baseline.

All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 7.2.2.7.2 for reporting details).

Potential DILI is defined as:

1. ALT or AST elevation > 3 × ULN

AND

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

AND

3. No other immediately apparent possible causes of Alt or AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

The patient should return to the investigational site and be evaluated as soon as possible, include laboratory tests, detailed history, and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, CK, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/International Normalized Ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

Study drug discontinuation is considered if there is marked serum AST or ALT elevation or evidence of functional impairment (as indicated by rising bilirubin or INR, which represent substantial liver injury) that is related to study drug. Discontinuation of treatment should be considered if:

- ALT or AST > 8 × ULN;
- ALT or AST > 5× ULN for more than 2 weeks;

Discontinuation of treatment must occur if:

- ALT or AST >3 × ULN and (total bilirubin > 2 × ULN or INR > 1.5);
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

7.2.2.6.4 Malignancy

The identification of a malignancy event will be made by the study site and communicated to the sponsor or designee. AEs should be reported as serious per the criteria in Section 7.2.2.5.

After the first dose of study drug, when there is a decision to biopsy a potentially malignant tumor, lymph node, or other tissue, the investigator and/or consultant(s) should contact the sponsor clinicians or designee to discuss the issue and any decisions as soon as possible.

7.2.2.6.5 Specific Infections

Any diagnosis or suggested diagnosis of opportunistic infections such as disseminated histoplasmosis, cryptococcosis, shingles, disseminated herpes simplex, or disseminated tuberculosis will be recorded as AEs of special interest.

Cryptosporidiosis is also considered an AE of special interest. Patients will be evaluated for cryptosporidium in the stool at screening, and as clinically indicated (eg, watery diarrhea) during the study. If a patient develops diarrhea during the study a stool sample must be provided to test for ova, parasites, and cryptosporidium.

7.2.2.7 Reporting of Adverse Events

AE reporting will be carried out in accordance with applicable local regulations, including regulatory agency and IRB reporting requirements.

Each AE is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate, and is further outlined in Section 7.2.2.7.2.

7.2.2.7.1 Reporting of Pregnancy

As information is available, a pregnancy diagnosed during the study will be reported within 24 hours to the sponsor via the Pregnancy Notification and Outcome Form, including pregnancy in female patients who received study drug and female partners of male study patients who received study drug. The pregnancy should be followed to term and/or outcome and this outcome should also be reported to the sponsor via the Pregnancy Notification and Outcome Form. Pregnancy itself is not regarded as an AE or SAE unless there is complication.

In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an AE or SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the neonatal death as related or possibly related to exposure to investigational product.

7.2.2.7.2 Reporting of Serious Adverse Events

The principal investigator is responsible for providing notification to the sponsor of any SAE via the Safety Adverse Event Form, whether deemed study drug related or not, that a patient experiences during their participation in this study within 24 hours of becoming aware of the event.

If an SAE is fatal or life threatening, notification to the sponsor must be made aware immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding cases. In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

The principal investigator will review each SAE and evaluate the intensity and the causal relationship of the event to the study drug. All SAEs will be recorded from the time of first dose of study drug through the safety follow-up period (up to Week 36). SAEs occurring after the final follow-up visit and coming to the attention of the principal investigator must be reported only if there is (in the opinion of the principal investigator) reasonable causal relationship with the study drug.

As a minimum requirement, the initial notification should provide the following information:

- Study number;
- Patient number;
- Details of the SAE (verbatim details are sufficient for immediate notification);
- Criterion for classification as ‘serious’;
- Causality assessment (which may be updated in a follow-up report when sufficient information is available to make this classification).

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (eg, hospital reports, consultant reports, autopsy reports, etc), with the study patient’s personal identifiers removed. All relevant information obtained by the principal investigator through review of these documents will be recorded and submitted to the sponsor within 24 hours of receipt of the information. If a new Safety Adverse Event Form is submitted, then the principal investigator must sign and date the form. The sponsor may also request additional information on the SAE, or clarification of omitted or discrepant information from the initial notification, which the principal investigator or an authorized delegate should submit to the sponsor within 24 hours of the request as possible.

7.2.2.7.3 Reporting of Adverse Events of Special Interest

AEs of special interest will be reported to safety immediately or within 24 hours of the site becomes aware of the event and recorded as such on the Adverse Events eCRF and Safety Adverse Event Form.

Potential DILI will be reported based on specifications mentioned in Section 7.2.2.6.3.

Each AE of special interest is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate, and is further outlined in Section 7.2.2.7.2.

7.2.2.8 Follow Up of Adverse Events

All AEs will be followed up through the safety follow-up visits. All SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the event has resolved, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the principal investigator and medical monitor, until there is a satisfactory explanation for the changes observed, or until the patient is lost to follow-up.

See Section 7.2.2.7.1 for details related to follow-up of pregnancy. See Section 7.2.2.6.3 for details related to follow-up of potential DILI. See Section 7.2.2.6.4 for details related to follow-up of malignancy.

7.2.3 Vital Signs

Vital signs (blood pressure, heart rate, and body temperature) will be assessed as specified in the Schedule of Assessments (Section 4.3). Vital signs will be assessed on Day 1 at predose and at 1 and 2 hours postdose, as well as on each of the scheduled visit days during the study. Supine BP and heart rate recordings will be made after the patient has been recumbent and at rest ≥ 5 minutes. When the timing of these measurements coincides with a blood collection, vital signs should be obtained prior to the time of the blood collection.

7.2.4 12-Lead Electrocardiograms

ECG will be performed at screening, and Visits 2, 4, and 7, and 13. ECG recording will initiate after the patient has been supine for at least 5 minutes. On days of PK blood draws, the ECG will be collected before scheduled PK blood draws, though timing will be such that PK draws are collected on their scheduled times where possible.

The ECG will include all 12 standard leads and a Lead II rhythm strip on the bottom of the tracing. The ECG will be recorded at a paper speed of 25 mm/second. The following ECG parameters will be collected: PR interval, QRS interval, RR interval, QT interval, and QT interval corrected for heart rate using Fridericia's formula (QTcF).

All ECGs must be evaluated by a qualified physician or qualified designee for the presence of abnormalities and will be captured electronically and retained for future evaluation if required, up to the time of the clinical study report (CSR) completion.

7.2.5 Physical Examinations

The full physical examination will be completed at screening and Visit 2. It includes an assessment of general appearance and evaluation of head, eyes, ears, nose, mouth, throat, neck, thyroid, lymph nodes, and extremities, and dermatologic, respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurologic, and psychiatric systems.

The targeted (limited) physical examination will be completed at Visits 3 through 13. It includes evaluation of patient complaints and SLE disease-related issues, and will exclude the genitourinary system.

7.2.6 C-SSRS

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed by Columbia University researchers for the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment. It is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS can also be used during treatment to monitor for clinical worsening.[43]

The C-SSRS evaluation will be performed at screening, Visit 2 (Day 1) and at Visits 7 and 10 (Weeks 12 and 24, respectively). Patients with recent (within the past 12 months) or active suicidal ideation or behavior based on patient responding "yes" to question 3, 4, or 5 is exclusionary at screening will be excluded from the study. Patients with recent or active suicidal ideation or behavior at subsequent study visits will have responses to the C-SSRS reviewed in detail to assess patient risk, and appropriate consultative mental health services will be provided.

7.2.7 Injection Site Reactions

Patients will be monitored for local injection site reactions at dosing administration visits, Visits 2 (Day 1), Visit 4 (Week 4), and Visits 6 through 10 (Weeks 8, 12, 16, 20, and 24). Patients will also be monitored for local injection site reactions at the safety follow-up visits, Visits 11, 12, and 13 (Weeks 28, 32, and 36, respectively). Local injection site reactions will be assessed predose and at 2 hours postdose. Injection site reactions should be managed according to the standard of care. Injection site reactions are to be reported as AEs of special interest (see Section 7.2.2.7.3).

7.2.8 Immunogenicity

The serum samples to measure the presence of ADA will be collected as Visits 2, 3, 4, 6, 7, 10, and 13 (Week 0, 2, 4, 8, 12, 24, and 36, respectively). Blood samples (4 mL) to provide approximately 1.5 mL of plasma for anti BOS161721 antibody analysis will be collected into appropriately labeled tubes containing K_2EDTA. The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods. Blood samples for ADA analysis will be collected up to Day 90 from all patients. Subsequent ADA samples will be collected from all patients but only assayed if the patient had a positive ADA on Day 90.

After the first dose, if a patient tests positive in the validated confirmatory ADA assay, the sample from this patient will be further analyzed in the neutralizing antibody (nAb) assay.

7.3 Efficacy Assessments

7.3.1 SLEDAI-2K

The SLEDAI-2K is a validated instrument that measures disease activity in SLE patients at the time of the visit and in the previous 30 days. It is a global index and includes 24 clinical and laboratory variables that are weighted by the type of manifestation, but not by severity. The total score falls between 0 and 105, with higher scores representing increased disease activity. The SLEDAI-2K has been shown to be a valid and reliable disease activity measure in multiple patient groups. A SLEDAI -2K of 6 or more generally represents moderately to severely active disease.[44]

The SLEDAI-2K is completed at screening, at Visit 2, Visit 4, and Visits 6 through 13.

7.3.2 BILAG 2004

The BILAG-2004 index is an organ-specific 97-question assessment based on the principle of the doctor's intent to treat. Only clinical features attributable to SLE disease activity are to be recorded and based on the patient's condition in the last 4 weeks compared with the previous 4 weeks. It will be scored as not present (0), improved (1), the same (2), worse (3), or new (4). Disease activity is graded separately for 9 body systems to 5 different grades (A to E) as follows: A ("Active") is very active disease, B ("Beware") is moderate activity, C ("Contentment") is mild stable disease, D ("Discount") is inactive now but previously active, and E ("Excluded") indicates the organ was never involved.[44] A shift from BILAG-2004 Grade A or B to a lower grade indicates a clinically relevant change in disease activity as the BILAG-2004 grades mirror the decision points for treatment interventions.

Only investigators that complete BILAG-2004 training will be allowed to perform the BILAG-2004 assessments. Preferably, the same investigator should evaluate the patient at each BILAG-2004 assessment from screening to study completion. The investigator must maintain documentation with descriptive details supporting the BILAG-2004 scoring (eg, chart, worksheet, clinic notes, and labs) at each visit.

The BILAG-2004 is completed at screening, Visit 2, 4, and 6 through 13. See APPENDIX 5 for detailed specifications.

7.3.3 PGA of Disease Activity

The PGA is used to assess investigator's general impression on the patient's overall status of SLE disease activity via visual analogue scale (100 mm) with 0 being "very good, asymptomatic and no limitation of normal activities" with 100 mm being "most severe possible disease ever seen in all SLE patients".

The PGA is completed at screening, Visit 2, 4, and Visits 6 through 13. When scoring the PGA, the assessor should always look back at the score from the previous visit.

7.3.4 Composite Endpoints: SRI-4, SRI-5, SRI-6, and BICLA Response

7.3.4.1 SRI-4 Response

Patients will be evaluated for SRI-4 scores at Week 28, with evaluation for sustained reduction of oral CS (≤ 10 mg/day and ≤ Day 1 dose) between Week 16 and Week 28.

The SRI-4 is a composite index of SLE disease improvement that consists of scores derived from the SLEDAI-2K and the BILAG 2004 Index. Response based on the SRI-4 is defined by:

1) ≥ 4-point reduction in SLEDAI-2K global score, 2) no new severe disease activity (BILAG A organ score) or more than 1 new moderate organ score (BILAG B), and 3) no deterioration from baseline in the PGA by ≥ 0.3 points. The SRI-4 response in patients with moderate to severe SLE is associated with broad improvements in clinical and patient-reported outcomes.[45]

Each patient, after providing their 28-week SRI-4 response, will be evaluated as either a responder or non-responder.

7.3.4.2 SRI-5 and SRI-6 Response

Like the SRI-4, the SRI-5 and SRI-6 are composite indices of SLE disease improvement that consists of scores derived from the SLEDAI-2K and the BILAG 2004 Index. However, the SRI-5 and SRI-6 are computed with a minimal three-point or five-point improvement in SLEDAI-2K being required, respectively.[46]

The SRI-5 and SRI-6 are evaluated for response at Week 24, along with a sustained reduction of oral CS (≤ 10 mg/day and ≤ Day 1 dose) between Week 16 and Week 28.

7.3.4.3 BICLA Response

The BICLA is a responder index developed to measure response to therapy, and it includes scores from the BILAG, SLEDAI-2K, and PGA. BICLA response is defined as 1) at least 1 gradation of improvement in baseline BILAG 2004 scores in all body systems with moderate disease activity at entry (eg, all B [moderate disease] scores falling to C [mild], or D [no activity]); 2) no new BILAG A or more than 1 new BILAG B scores; 3) no worsening of total SLEDAI-2K score from baseline; 4) ≤ 10% deterioration in PGA score and 5) no treatment failure.[44] It is driven primarily by the BILAG, and has been used in Phase 2 and 3 mAb studies.[47]

For the endpoints of BICLA response at Week 28, Week 32, and Week 36, patient scores will be completed and response determined.

7.3.5 CLASI Response

The CLASI is a comprehensive tool for assessment of disease activity and damage in cutaneous lupus, shown to be valid, reliable, and sensitive to changes in disease activity.[48] Response is defined as 50% improvement from baseline in “A” or “B” scores. This assessment will be applied to all patients as all are required to have cutaneous disease activity.

For the secondary efficacy endpoint of CLASI response at Week 28, patient scores on MAD and POC studies will be compared with baseline for 50% improvement.

7.3.6 ACR-28 Joint Count

The ACR-28 joint count will evaluate the number of tender and swollen joints in the shoulder, elbow, wrist, hand, knee joints. Joints of the feet are excluded. The ACR-28 joint count will be performed at screening, Visit 2, 4, and 6 through 13.

7.3.7 Laboratory Assessments

Patients will be evaluated for laboratory parameters as specified in the Schedule of Assessments (Section 4.3), including: Fasting glucose and lipid panels, pSTAT3 (predose samples in Phase 2), total IgG & IgM, complement: CCI, Plasma CCI & CCI, whole blood for leukocyte immunophenotype and RNA, CCI, and antibodies: (CCI).

Endpoint analyses will be based on changes from baseline assessments at Week 16 and Week 28.

7.4 Other Variables

7.4.1 SLICC/ACR Damage Index

The SLICC/ACR damage index is a validated instrument to assess damage, defined as irreversible impairment, continuously persistent for 6 months (ascertained by clinical assessment), occurring since the onset of lupus, and it is based on a weighted scoring system. This index records damage occurring in patients with SLE regardless of cause, with demonstrated content, face, criterion, and discriminant validity.[49] It will be performed on Day 1 (Visit 2), and Day 180 (Visit 10).

7.4.2 PROs

Patients should be encouraged to complete the PROs at the clinic at the beginning of the study visit prior to any clinical assessments. A member of the staff should be available if a patient requires further instruction and to review the PRO questionnaires for completeness prior to leaving the clinic. The PROs include the CCI and the CCI.

CCI

CCI

7.5 Pharmacokinetic Assessments

During the MAD Phase 1b (all sites) and POC Phase 2 (select sites only) studies, blood samples for PK analysis of BOS161721 or placebo concentration will be collected according to Table 1 and Table 2.

PK parameters include the following:

- C_{max}, T_{max}, AUC, $t_{½}$, CL, V_d.

In addition to samples collected at the scheduled times, an additional blood sample should be collected from patients experiencing unexpected AEs and/or SAEs and the date and time documented in the eCRF.

Plasma concentrations of BOS161721 will be measured using a validated immunoassay. The PK parameters will be calculated from the plasma concentration-nominal time profiles for the IA2 and actual time profiles for the final analysis. The non-compartmental analysis will be performed using appropriately validated PK/PD software.

7.6 Pharmacodynamic Assessments

Blood samples for PD parameters (plasma) will be collected at times indicated for each of the following parameters:

- pSTAT3 at Visits 2, 4, 7, 10 (predose samples in POC study), and at Visit 13 (MAD study);
- Antibodies: CCI at Visits 1, 2, 4, and 6 through 13;
- Plasma complement (CCI) at Visits 1, 2, 4 and 6 through 13.
- Plasma CCI, and CCI at Visits 1 through 4, 6, 7, and 10;
- Whole blood for leukocyte immunophenotype at Visits 1 through 4, 6, 7, and 10;
- Whole blood RNA collection at Visits 2 through 4, 7, and 13;
- IgG and IgM and CD4+ count at Visits 1 through 5, 7, and 10.

7.7 Pharmacokinetic/Pharmacodynamic Relationship

Evidence of any PK/PD relationships will be evaluated between BOS161721 plasma concentrations and the available PD endpoints and biomarkers.

7.8 Protocol Deviations

Protocol deviations will be documented during the study. Per the statistical analysis plan (SAP), these will be listed by patient and summarized by deviation category by treatment group.

8 STUDY DRUG MANAGEMENT

8.1 Description

8.1.1 Formulation

CCI [redacted]

CCI [redacted]

Additional information regarding dose preparation will be provided in a separate Pharmacy Manual.

8.1.2 Storage

All supplies of BOS161721 or placebo must be stored in accordance with the manufacturer's instructions. BOS161721 or placebo will be stored in a securely locked area, accessible to authorized persons only, until needed for dosing.

Information regarding storage and dose preparation will be provided in a separate Pharmacy Manual.

8.2 Packaging and Shipment

Investigational medicinal products will be supplied by Boston Pharmaceuticals, Inc. Investigational medicinal products will be packaged and labeled according to applicable local and regulatory requirements.

8.3 Dose and Administration

Details of dosing are provided in Section 4.1.

Each unit dose will be prepared by a qualified staff member. The vials of investigational product (IP) will appear identical and will have a "blinded" label on the vials that will state CCI [redacted] mg or placebo. When the site goes into the IWRS to request the patient kit(s), the IWRS will assign the appropriate number of kits (regardless of assignment to placebo or active treatment) per the dose (ie, CCI [redacted]). If a patient is randomized to the placebo arm, they will receive the matching number of kits.

The designated staff member (or designee under the direction of the designated staff member) will dispense BOS161721 or placebo for each patient according to the protocol, randomization list, and Pharmacy Manual, if applicable.

After receiving sponsor approval in writing, the investigational site is responsible for returning all unused or partially used BOS161721 or placebo to the sponsor or designated third party or for preparing BOS161721 or placebo for destruction via incineration.

Further details are found in a separate Pharmacy Manual.

8.4 Accountability

The Principal Investigator or designee is responsible for maintaining accurate accountability records of BOS161721 or placebo throughout the clinical study. The drug accountability log includes information such as, randomization number, amount dispensed and amount returned to the pharmacy (if any). Products returned to the pharmacy will be stored under the same conditions as products not yet dispensed. The returned products should be marked as 'returned' and kept separate from the products not yet dispensed.

All dispensing and accountability records will be available for sponsor review after database lock procedures are completed. During safety monitoring, the drug accountability log will be reconciled with the products stored in the pharmacy.

8.5 Prohibited Concomitant Therapy

Prohibited concomitant medications are discussed in Section 5.6 and APPENDIX 4.

8.6 Compliance

Dosing will be performed by trained, qualified personnel designated by the principal investigator. The date and time of dosing will be documented on each dosing day. Comments will be recorded if there are any deviations from the planned dosing procedures.

9 STATISTICS

There are 2 IAs planned for the study. The first IA will be conducted at the time of the POC decision for dose selection. The second IA will be performed for futility (see Section 9.3). Before the first IA, a SAP will be finalized, providing detailed methods for the analyses outlined below. Any deviations from the planned analyses will be described and justified in the final integrated CSR.

The following standards will be applied for the analysis unless otherwise specified. Continuous data will be summarized by treatment group using descriptive statistics (number, mean, standard deviation [SD], minimum, median, and maximum). Categorical data will be summarized by treatment group using frequency tables (number and percentage).

9.1 Sample Size

Sample size in the Phase 1b study is based on operational consideration.

A summary of the power in the trial for the chosen sample size is provided in Table 5, with N = 132 randomized 89:43 to the chosen dose for the POC study and placebo, respectively; this includes 12 patients from the MAD study who were in the cohort of the mid or high dose if chosen for the POC study.

Table 5. Sample Size

Type 1 Error (1-Sided)	TRUE Underlying Response Rate (%)		Overall Power	Minimum OBSERVED Response Rates Yielding Statistical Significance	
	Placebo	Treatment		Placebo	Treatment
0.025	40	60	0.54	40	60
	40	65	0.75		
	40	70	0.9		
0.05	40	60	0.63	40	58
	40	65	0.81		
	40	70	0.93		

Total sample size of 156 patients is planned for analysis, but may be adjusted upward according to the dropout (noncompliance) rate, which will be monitored in a blinded fashion in an ongoing basis. Note that approximately 36 dropouts are assumed.

9.2 Statistical Methods

9.2.1 Analysis Populations

The primary efficacy analysis will be based on the full analysis set (FAS), defined to be all patients with at least 1 baseline and post-baseline efficacy evaluation. A per protocol (PP) analysis set may be defined to exclude major protocol violations from the efficacy analysis. The PP Population will include all patients from the FAS except those with major violations to the protocol deemed to impact the analysis of the primary endpoint. These violations will be

identified based on blinded data prior to unblinding the final analysis dataset. Safety analyses will be based on all patients who receive test treatment. Pharmacokinetic analysis will be conducted on the PK analysis set (PK), defined as the FAS with sufficient concentration data for the calculation of PK parameters. All analyses will combine data from the MAD and POC studies and focus on the active treatment dose chosen for the POC study versus placebo. The 0.05 1-sided type 1 error level is included for POC, and the 0.025 1-sided type 1 error level for potential use of this trial to support regulatory filing.

9.2.2 Demographics and Baseline Characteristics

Baseline and patient characteristics will be summarized via appropriate summary statistics by treatment group and overall, for each phase of the trial.

9.2.3 Primary Endpoint(s)

The proportion of patients who achieve treatment response (measured by SRI-4 at Week 28 along with a sustained reduction of oral CS) will be analyzed via Cochran-Mantel-Haenszel (CMH) analysis. The primary endpoint will be analyzed on the FAS and if needed the PP analysis set. In addition, missing values will be addressed by employing a last observation carried forward (LOCF) analysis and/or other appropriate analytic approaches as a sensitivity analysis. Details will be available in the SAP.

9.2.4 Secondary Endpoint(s)

Binary efficacy endpoints will be assessed via CMH analysis. Continuous efficacy endpoints will be assessed via analysis of covariance (ANCOVA) repeated measures mixed model analysis with factors including treatment, time, treatment-by-time interaction, baseline covariate, and covariate-by-time interaction. The secondary efficacy endpoint will be analyzed on the FAS and if needed the PP analysis set. Details will be available in the SAP.

9.2.5 Analysis of Safety

9.2.5.1 Safety Analysis

Safety analyses will be performed on the Safety Analysis Set. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Incidences (number and percent) of AEs will be presented by treatment group. Incidences of AEs will also be presented by maximum severity and relationship to study medication. For the MAD study, the placebo patients from each cohort will be combined for the summaries. If there is a clear increase in AE rates for placebo patients across the cohorts, the AEs will also be summarized by cohort.

AEs will be summarized by counts and percentages of patients by treatment group. Laboratory data and vital signs will be summarized by treatment group as summary statistics for value and change from baseline at each individual time point. Summary statistics will include n, arithmetic mean, median, arithmetic SD, minimum, and maximum.

Additional safety parameters will be analyzed descriptively by treatment group. Descriptive statistics (n, mean, standard deviation (SD), median, minimum, maximum) will be calculated by

treatment group and time point for continuous variables. Frequencies and percentages will be presented by treatment group for categorical and ordinal variables.

9.2.5.2 Data Monitoring Committee

This study will use an external DMC. The DMC is an independent committee established to provide oversight of safety considerations in study and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of enrolled patients and those yet to be recruited to the trial as well as for the continuing validity and scientific merit of the study results. The DMC is charged with assessing such actions in light of an acceptable benefit/risk profile for anti-IL-21 mAb. The recommendations made by the DMC (ie, dose escalation, etc.) will be forwarded to the sponsor for final decision. The sponsor will forward such decisions, which may include summaries of safety data which are not endpoints, to regulatory authorities, as appropriate.

The DMC will have access to unblinded treatment information during the clinical trial. To prevent inadvertent unblinding of sponsor staff, reports to the DMC will describe each treatment group by a coded identifier rather than actual treatment group assignment. Details regarding management and process of this committee are found in the DMC Charter.

The DMC may recommend termination of an anti-IL-21 mAb treatment arm or the entire BOS161721 MAD/POC trial for any safety concern that is felt to outweigh potential benefits. The recommendation must be supported by the sponsor as indicated in the DMC Charter.

9.2.6 Pharmacokinetic and Pharmacodynamic Data

9.2.6.1 Analysis of Pharmacokinetic Data

The PK parameter data will be listed and summarized descriptively in tabular format.

If data permit, the following analyses will be performed for plasma BOS161721 concentration data:

- A listing of all plasma BOS161721 concentrations by patient at actual times post dose;
- A descriptive summary of plasma BOS161721 concentrations. Summary statistics of geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum will be tabulated by study days with PK assessments.

Details will be available in the SAP.

9.2.6.2 Analysis of Pharmacodynamic Data

The PD parameter data will be listed and summarized descriptively in tabular format.

Binary PD endpoints will be assessed for the FAS population. Binary PD endpoints will be assessed via CMH analysis. Continuous PD endpoints will be assessed via analysis of covariance (ANCOVA) repeated measures mixed model analysis with factors including treatment, time, treatment-by-time interaction, baseline covariate, and covariate-by-time

interaction. Normality will be assessed via diagnostic residual plots and Shapiro-Wilk statistic, but not as a formal statistical test of normality. If substantial departures from normality are observed, transformation will be used (eg, log and/or rank).

Details will be available in the SAP.

9.2.6.3 Population Pharmacokinetic Analysis or PK/PD Modeling

Plots of individual patient values for each relevant PD parameter on Y-axis and each relevant PK parameter on X-axis will be examined for relationship. If relationships are revealed by these diagnostic plots, PK and PD data from this study may be analyzed using modeling approaches to describe the relationship and may also be pooled with data from other studies to investigate any association between BOS161721 exposure and biomarkers or significant safety endpoints.

Details will be available in the SAP.

9.3 Interim Analysis and Power

Two IAs are planned for this study. The initial IA will be conducted at the time of the POC decision for dose selection. The DMC will review safety and tolerability, and PK/PD/biomarkers for dose selection. Efficacy data will not be reviewed for dose selection so there should be no impact on the type 1 error.

The second IA will be performed for futility. IA2 is planned to be conducted at Week 16 when SRI-4 response is determined for approximately 60 patients (including all patients at the same dose level/matching placebo from the MAD study) after completing 3 months of treatment. The purpose of the IA2 is to assess if the trial could stop for an early futility conclusion, or continue. Since there is no plan to stop the trial for an early efficacy conclusion, there is no impact on the type 1 error. If that intention changes, then $p < 0.0001$ is required for an early efficacy conclusion at the IA2 in order to not impact the planned type 1 error level.

Nominal time profiles will be used for calculating PK parameters in the IA2.

10 ETHICS AND RESPONSIBILITIES

10.1 Good Clinical Practice

The procedures set out in this protocol are designed to ensure that the sponsor and the principal investigator abide by the principles of the International Council for Harmonisation (ICH) guidelines on GCP and the Declaration of Helsinki (Version 2013). The clinical study also will be carried out in the keeping with national and local legal requirements (in accordance with US IND regulations [21 CFR 56]).

10.2 DMC

The sponsor will appoint a DMC for the periodic review of available study data. The DMC is an independent group of experts that advises the sponsor and the study investigators. The members of the DMC serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DMC are to (1) periodically review and evaluate the accumulated study data for participant safety, study conduct, and progress, (2) make recommendations to the sponsor concerning the continuation, modification, or termination of the study and (3) make a dose recommendation for POC portion of the study.

The DMC considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. The DMC is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking (unblinding), and voting procedures prior to initiating any data review. The DMC is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

10.3 Institutional Review Board/Independent Ethics Committee

Independent Ethics Committees (IEC)/Institutional Review Boards (IRB) must meet the guidelines set out by the U.S. Food and Drug Administration (FDA) and conform to local laws and customs where appropriate. Written IRB/IEC approval for the protocol and the signed ICF must be obtained and transmitted to Boston Pharmaceuticals or representative before the study can be initiated. The IRB/IEC must be informed of and approve all protocol amendments. The investigator will ensure that this study is conducted in full conformance with all applicable local and regional laws and regulations. The complete text of the World Medical Association Declaration of Helsinki is given in APPENDIX 2.

10.4 Informed Consent

Before each patient is enrolled in the clinical study, written informed consent will be obtained from the patient according to the regulatory and legal requirements of the participating country. As part of this procedure, the principal investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study patient should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. The

principal investigator or designee will provide the sponsor with a copy of the IRB-approved ICF prior to the start of the study.

The informed consent document must be signed and dated; 1 copy will be handed to the patient and the principal investigator will retain a copy as part of the clinical study records. The principal investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

If the informed consent document is revised, it must be reviewed and approved by the responsible IRB/IEC. Patients currently enrolled may need to sign this revision (based on IRB/IEC requirements) and all future subjects enrolled in the clinical study will be required to sign this revised ICF.

10.5 Records Management

The principal investigator will ensure the accuracy, completeness, and timeliness of the data reported to the sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The principal investigator or designee will cooperate with the sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The principal investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each patient receiving BOS161721 or placebo.

The principal investigator will allow sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB to have direct access to all documents pertaining to the study.

Electronic case report forms are required and should be completed for each randomized patient. It is the principal investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported on the patients' eCRF. Electronic case report forms should be completed in a timely fashion to support the study timelines. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status. The principal investigator or designated representative should complete and the principal investigator should verify the source documents as the information is collected. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The principal investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and

validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes.

10.6 Source Documentation

The documents that will form the source data for the clinical study (eg, patient charts, laboratory reports) must be defined and documented in the in-house study master file prior to the start of the study. Data on the eCRFs which will be checked against source data during monitoring visits must also be defined and documented in the in-house study master file including the percentage of each of the source data to be verified and the percentage of patients' eCRFs to be monitored.

10.7 Study Files and Record Retention

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of BOS161721. However, these documents should be retained for a longer period if required by the applicable legal requirements.

11 AUDITING AND MONITORING

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and on-site visits. The study will be routinely monitored to ensure compliance with the study protocol and the overall quality of data collected. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor may periodically request review of the investigator study file to assure the completeness of documentation in all respects of clinical study conduct. The study monitor will verify that each patient has proper consent documentation from the patient and/or patient's authorized representative for study procedures and for the release of medical records to the sponsor, FDA, other regulatory authorities, and the IRB. The study monitor will also verify that assent was obtained for patients not capable of providing informed consent or that documentation is provided by the investigator explaining why the patient was unable to provide assent. The investigator or appointed delegate will receive the study monitor during these on-site visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies. On completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

Throughout the course of the study, the medical monitor will determine eligibility of all screened patients, will address any medical issues that might arise, clarify medical questions, review patient safety data (eg, AE/SAE, laboratory, and ECG), and partner with the study team in the overall study management. The study medical monitoring plan will document additional details of the study medical oversight and monitoring.

12 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by Boston Pharmaceuticals. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. Boston Pharmaceuticals will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, and/or Boston Pharmaceuticals, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the patient and/or has an impact on the patient's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for patients enrolled in the study before continued participation.

13 STUDY REPORT AND PUBLICATIONS

Boston Pharmaceuticals is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

By signing the protocol, the principal investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the competent authorities will be notified of the principal investigator's name, address, qualifications, and extent of involvement.

The principal investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted and obtained approval from the sponsor in advance.

14 STUDY DISCONTINUATION

Both Boston Pharmaceuticals and the principal investigator reserve the right to terminate the study at the investigator's site at any time. Should this be necessary, Boston Pharmaceuticals or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the principal investigator will inform the IRB/IEC of the same. In terminating the study Boston Pharmaceuticals and the principal investigator will assure that adequate consideration is given to the protection of the patients' interests.

15 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Boston Pharmaceuticals, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial or to comply with regulatory requirements. However, authorized regulatory officials, IRB/IEC personnel, Boston Pharmaceuticals, and its authorized representatives are allowed full access to the records.

Identification of patients and eCRFs shall be by initials, birthdate, or patient number. Documents that identify the patient (eg, the signed informed consent document) must be maintained in confidence by the principal investigator. If required, the patient's full name may be made known to an authorized regulatory agency or other authorized official.

16 REFERENCES

1 Urowitz MB, Gladman DD. How to improve morbidity and mortality in systemic lupus erythematosus. Rheumatology 2000;39:238-44.

2 Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Morbidity and Mortality in Systemic Lupus Erythematosus During a 10-Year Period. Medicine 2003;82(5):299-308.

3 Pons-Estel GJ, Alarcón GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. Semin Arthritis Rheum. 2010;39(4):257. Epub 2009 Jan 10.

4 Kanta H, Mohan C. Three Checkpoints in lupus development: central tolerance in adaptive immunity, peripheral amplification by innate immunity, and end-organ inflammation. Genes and Immunity 2009;10:390-6.

5 Dall'Aqua WF, Kiener PA, Wu H. Properties of Human IgG1s Engineered for Enhanced Binding to the Neonatal Fc Receptor (FcRn). J Biol Chem. 2006 Aug 18, 281(33):23514-24.

6 Spolski R, Leonard WJ. The Yin and Yang of interleukin-21 in allergy, autoimmunity and cancer. Curr Opin Immunol. 2008a;20:295-301.

7 Asao H, Okuyama C, Kumaki S, Ishii N, Tsuchiya S, Foster D, et al. Cutting edge: the common gamma-chain is an indispensable subunit of the IL-21 receptor complex. J Immunol. 2001;167:1-5.

8 Habib T, Senadheera S, Weinberg K, Kaushansky K. The common gamma chain (gamma c) is a required signaling component of the IL-21 receptor and supports IL-21-induced cell proliferation via JAK3. Biochemistry. 2002;41:8725-31.

9 Spolski R, Leonard WJ. Interleukin-21: basic biology and implications for cancer and autoimmunity. Annu Rev Immunol. 2008b;26:57-79.

10 Puga I, Cols M, Barra CM, He B, Cassis L, Gentile M, et al. B-cell-helper neutrophils stimulate the diversification and production of immunoglobulin in the marginal zone of the spleen. Nat Immunol. 2011;13(2):170-80.

11 Costanzo A, Chimenti MS, Botti E, Caruso R, Sarra M, Monteleone G. IL-21 in the pathogenesis and treatment of skin diseases. J Dermatol Sci. 2010;60(2):61-6.

12 Avery DT, Bryant VL, Ma CS, de Waal Malefy R, Tangye SG. IL-21-induced isotype switching to IgG and IgA by human naive B cells is differentially regulated by IL-4. J Immunol. 2008;181:1767-79.

13 Rasmussen TK, Andersen T, Bak, RO, Yiu G, Sorensen CM, Stengaard-Pedersen K, et al. Overexpression of microRNA-155 increases IL-21 mediated STAT3 signaling and IL-21 production in systemic lupus erythematosus. Arthritis Research & Therapy 2015;17(154)

14 Ettinger R, Kuchen S, Lipsky PE. The role of IL-21 in regulating B-cell function in health and disease. Immunol Rev. 2008;223:60-86.

15 Caprioli F, Sarra M, Caruso R, Stolfi C, Fina D, Sica G, et al. Autocrine regulation of IL-21 production in human T lymphocytes. J Immunol. 2008;180(3):1800-7.

16 Yang L, Anderson DE, Baecher-Allan C, Hastings WD, Bettelli E, Oukka M, et al. IL-21 and TGF-beta are required for differentiation of human T(H)17 cells. Nature. 2008;454(7202):350-2.

17 Tangye SG, Ma CS, Brink R, Deenick EK. The good, the bad and the ugly - TFH cells in human health and disease. Nat Rev Immunol. 2013;13(6):412-26.

18 Fantini MC, Rizzo A, Fina D, Caruso R, Becker C, Neurath MF, et al. IL-21 regulates experimental colitis by modulating the balance between Treg and Th17 cells. Eur J Immunol. 2007;37(11):3155-63.

19 Peluso I, Fantini MC, Fina D, Caruso R, Boirivant M, MacDonald TT, et al. IL-21 counteracts the regulatory T-cell-mediated suppression of human CD4+ T lymphocytes. J Immunol. 2007;178(2):732-9.

20 Hippen KL, Bucher C, Schirm DK, Bearl AM, Brender T, Mink KA, et al. Blocking IL-21 signaling ameliorates xenogeneic GVHD induced by human lymphocytes. Blood. 2012;119(2):619-28.

21 Davis ID, Skrumsager BK, Cebon J, Nicholaou T, Barlow JW, Moller NP, et al. An open-label, two-arm, phase I trial of recombinant human interleukin-21 in patients with metastatic melanoma. Clin Cancer Res. 2007;13:3630-6.

22 Frederiksen KS, Lundsgaard D, Freeman JA, Hughes SD, Holm TL, Skrumsager BK, et al. IL-21 induces in vivo immune activation of NK cells and CD8(+) T-cells in patients with metastatic melanoma and renal cell carcinoma. Cancer Immunol Immunother. 2008;57(10):1439-49.

23 Karrich JJ, Jachimowski LC, Nagasawa M, Kamp A, Balzarolo M, Wolkers MC, et al. IL-21- stimulated human plasmacytoid dendritic cells secrete granzyme B, which impairs their capacity to induce T-cell proliferation. Blood. 2013;121(16):3103-11.

24 Lindner S, Dahlke K, Sontheimer K, Hagn M, Kaltenmeier C, Barth TF, et al. Interleukin-21-induced granzyme B-expressing B-cells infiltrate tumors and regulate T-cells. Cancer Res. 2013;73(8):2468-79.

25 Monteleone G, Caruso R, Fina D, Peluso I, Gioia V, Stolfi C, et al. Control of matrix metalloproteinase production in human intestinal fibroblasts by interleukin 21. Gut. 2006;55(12):1774-80.

26 Nakou M, Papadimitraki ED, Fanouriakis A, Bertsias GK, Choulaki C, Goulidaki N, et al. Interleukin-21 is increased in active systemic lupus erythematosus patients and contributes to the generation of plasma B-cells. Clin Exp Rheumatol. 2013;31(2):172-9.

27 Li Q, Liu Z, Dang E, Jin L, He Z, Yang L, et al. Follicular helper T-cells (Tfh) and IL-21 involvement in the pathogenesis of bullous pemphigoid. PLoS One. 2013;8(7):e68145.

28 Liu R, Wu Q, Su D, Che N, Chen H, Geng L, et al. A regulatory effect of IL-21 on T follicular helper-like cell and B-cell in rheumatoid arthritis. Arthritis Res Ther. 2012;14(6):R255.

29 Kang KY, Kim HO, Kwok SK, Ju JH, Park KS, Sun DI, et al. Impact of interleukin-21 in the pathogenesis of primary Sjögren's syndrome: increased serum levels of interleukin-21 and its expression in the labial salivary glands. Arthritis Res Ther. 2011;13(5):R179.

30 Terrier B, Geri G, Chaara W, Allenbach Y, Rosenzwajg M, Costedoat-Chalumeau N, et al. Interleukin-21 modulates Th1 and Th17 responses in gianT-cell arteritis. Arthritis Rheum. 2012a;64(6):2001-11.

31 Terrier B, Costedoat-Chalumeau N, Garrido M, Geri G, Rosenzwajg M, Musset L, et al. Interleukin 21 correlates with T-cell and B-cell subset alterations in systemic lupus erythematosus. J Rheumatol. 2012b;39(9):1819-28.

32 International Conference on Harmonisation. Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6 (R1). 2011.

33 Wang W, Wang EQ, Balthasar JP. Monoclonal Antibody Pharmacokinetics and Pharmacodynamics. Clin Pharm & Ther 2008; 84(5):548-58.

34 Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. Journal of Allergy and Clinical Immunology 2006;117:391–7.

35 Elsaesser H, Sauer K, Brooks DG. IL-21 is required to control chronic viral infection. Science. 2009;324(5934):1569-72

36 Kotlarz D, Zietara N, Uzel G, Weidemann T, Braun CJ, Diestelhorst J, et al. Loss-of-function mutations in the IL-21 receptor gene cause a primary immunodeficiency syndrome. J Exp Med. 2013;210(3):433-43.

37 Hunter PR, Nichols G. Epidemiology and clinical features of Cryptosporidium infection in immunocompromised patients. Clinical microbiology reviews. 2002;15(1):145-54.

38 Desjardins M, Mazer BD. B-cell memory and primary immune deficiencies: interleukin-21 related defects. Curr Opin Allergy Clin Immunol. 2013;13(6):639-45.

39 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.

40 Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, US: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a4.htm.

41 NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, available at https://evs.nci.nih.gov/ftp1/CTCAE/About.html.

42 Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report –

Second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. Journal of Allergy and Clinical Immunology 2006;117:391–7.

43 Posner K, Melvin G a, Stanley B, Oquendo M a, Gould M. Factors in the assessment of suicidality in youth. *CNS Spectr*. 2007;12(2):156-162.

44 Castrejon I, Tani C, Jolly M, Huang A, Mosca M. Indices to assess patients with systemic lupus erythematosus in clinical trials, long-term observational studies, and clinical care. Clin Exp Rheumatol 2014; 32(85):S85-95.

45 Furie R, Wang L, Drappa J, Illei G. Systemic Lupus Erythematosus (SLE) Responder Index [SRI(4)] Response Is Associated with Global Benefit in Patients with Moderate to Severe SLE [abstract]. *Arthritis Rheumatol.* 2016; 68 (suppl 10).

46 Thanou A, Chakravarty E, James JA, Merrill JT. Which outcome measures in SLE clinical trials best reflect medical judgment? Lupus Science & Medicine 2014;1:e000005. doi:10.1136/lupus-2013-000005.

47 Wallace DJ, Kalunian K, Petri MA, Strand V, Houssiau FA, Pike M,*et al.* Efficacy and safety of epratuzumab in patients with moderate/severe active systemic lupus erythematosus: results from EMBLEM, a phase IIb, randomised, double-blind, placebo-controlled, multicentre study. *Ann Rheum Dis* 2014;73:183-90.

48 Albrecht J, Taylor L, Berlin JA, Dulay S, Ang G, Fakharzadeh S. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): An Outcome Instrument for Cutaneous Lupus Erythematosus. J Invest Derm. 2005;125(5):889-94.

49 Stoll T, Seifert B, Isenberg DA. SLICC/ACR Damage Index is Valid, and Renal and Pulmonary Organ Scores are Predictors of Sever Outcome in Patients with Systemic Lupus Erythematosus. Br J Rheumatol. 1996;35:248-54.

50 CCI [redacted].

17 APPENDICES

APPENDIX 1 NAMES OF STUDY PERSONNEL

Sponsor:	Boston Pharmaceuticals 55 Cambridge Parkway Suite 401 Cambridge, MA 02142, USA
Medical Monitor:	PPD
	PPD
Clinical Research Organizations:	PPD
	PPD
	PPD
Bioanalytical Laboratory:	PPD
Central Laboratory:	PPD

APPENDIX 2 DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles
For
Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subject."

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic, and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility, and quality.

In current medical practice and in medical research, most prophylactic, diagnostic, and therapeutic procedures involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Research investigators should be aware of the ethical, legal, and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal, or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any SAEs. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a subject of the research, even though the subject has given consent.

Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the

subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

The subjects must be volunteers and informed participants in the research project.

The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the subject's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining

informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic, or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the subjects who are research subjects.

The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists.

At the conclusion of the study, every subject entered into the study should be assured of access to the best-proven prophylactic, diagnostic, and therapeutic methods identified by the study.

The physician should fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study must never interfere with the subject-physician relationship.

In the treatment of a subject, where proven prophylactic, diagnostic, and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the subject, must be free to use unproven or new prophylactic, diagnostic, and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health, or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

APPENDIX 3 COMMONLY USED CORTICOSTEROID EQUIVALENTS

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

APPENDIX 4 MEDICATION WASHOUT PERIODS

WASHOUT TIMES OF MEDICATIONS BASED ON 5 HALF-LIVES

Medication	Discontinuing Prior to Signing Consent
Abatacept (CTLA4Ig)	24 weeks
Alefacept	12 weeks
AMG 623 (blisibimod)	24 weeks
Anifrolumab	12 weeks
Atacicept (TACI-Ig)	12 weeks
Belimumab	48 weeks
Cyclophosphamide	24 weeks
Cyclosporine (except for CSA eye drops)	4 weeks
Danazol	4 weeks
Dapsone	4 weeks
Eculizumab	12 weeks
Efalizumab	12 weeks
Epratuzumab	24 weeks
Intravenous globulin	4 weeks
Leflunomide	8 weeks (4 weeks for washout with cholestyramine)
Lenalidomide with cholestiramine	8 weeks
Lupuzor	12 weeks
Memantine	4 weeks
Natalizumab	24 weeks
Ocrelizumab	48 weeks (or 24 weeks with recovery of B cell)
Pimecrolimus	4 weeks
Plasmapheresis	24 weeks
Retinoids (oral or topical)	4 weeks
Rituximab	48 weeks (or 24 weeks with recovery of B cell)
Sirolimus	4 weeks
Tacrolimus	4 weeks
Thalidomide	8 weeks
Tocilizumab	12 weeks

APPENDIX 5 BILAG-2004 (STUDY-SPECIFIC MODIFIED CRITERIA)

CCI