Protocol I4V-MC-JAHH

A Randomized, Double-Blind, Placebo-Controlled, Parallel- Group, Phase 2 Study of Baricitinib in Patients with Systemic Lupus Erythematosus (SLE)

NCT02708095

Approval Date: 11-Dec-2015

Protocol I4V-MC-JAHH
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2 Study of Baricitinib in Patients with Systemic Lupus Erythematosus (SLE)

Confidential Information

Baricitinib (LY3009104)

Study I4V-MC-JAHH is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient, 24-week study designed to evaluate the efficacy and safety of baricitinib 4-mg and 2-mg in patients with SLE receiving standard therapy.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 11-Dec-2015 GMT

Table of Contents

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Appendices

Appendix **Page**

1. Protocol Synopsis

Title of Study:
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2 Study of Baricitinib in Patients with Systemic Lupus Erythematosus (SLE)

Rationale:
Systemic lupus erythematosus (SLE) is a chronic, debilitating autoimmune disease that is characterized by the presence of autoreactive B cells and elevated levels of autoantibodies, which directly damage the body's cells and tissues. SLE can affect multiple organ systems simultaneously or sequentially, and follows an unpredictable clinical course where periods of relatively stable disease are followed by flares and/or periods of active disease that can ultimately lead to irreversible damage to tissues and organ systems.

Baricitinib is an orally available, selective Janus kinase (JAK) inhibitor with excellent potency and selectivity for JAK1 and JAK2 and less potency for JAK3 or Tyrosine kinase 2 (TYK2; Fridman et al. 2010). This activity profile suggests that baricitinib may inhibit cytokines implicated in SLE such as type I interferon (IFN; JAK1/TYK2), type II IFN-γ, interleukin (IL)-6 (JAK1/JAK2/TYK2), and IL-23 (JAK2/TYK2) as well as other cytokines that may have a role in SLE, including granulocyte-macrophage colony stimulating factor (JAK2/JAK2) and IL-12 (JAK2/TYK2). The potential impact of baricitinib on the IFN pathway is highly relevant to SLE, as clinical and preclinical studies have established that this pathway is involved in the pathogenesis of SLE.

Clinical studies have established that baricitinib is effective in autoimmune/autoinflammatory diseases involving the joints, skin, and kidneys. Baricitinib was effective at reducing swollen and tender joints in patients with rheumatoid arthritis (RA; I4V-MC-JADA [Phase 2] and I4V-MC-JADW and I4V-MC-JADX [Phase 3]), was effective at reducing disease severity in patients with moderate to severe plaque psoriasis (Menter et al. 2014), and was effective at reducing the urinary albumin-to-creatinine ratio (UACR) in patients with diabetic kidney disease (Tuttle et al. 2015). The mechanism of action, combined with demonstration of clinical benefit in inflammatory diseases involving joints, skin and kidneys, provides the rationale for evaluating baricitinib in SLE.

Objectives/Endpoints:

Objectives	Endpoints
Primary	
To evaluate the effect of baricitinib 4-mg daily (QD) or 2-mg QD compared to placebo on remission of SLE arthritis and/or rash in patients with SLE receiving concomitant standard therapy over 24 weeks.	Change in the proportion of patients who achieve remission of arthritis and/or rash as defined by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) at Week 24 compared to baseline.
Secondary	
To evaluate the effect of baricitinib 4-mg QD or 2-mg QD compared to placebo on overall SLE disease activity in patients with SLE receiving concomitant standard therapy over 24 weeks.	• Change in the proportion of patients achieving SLE Responder Index (SRI)-4 response at Week 24 compared to baseline. SRI-4 response is defined as: o Reduction of ≥4 points from baseline in SLEDAI-2K score; o No new British Isles Lupus Assessment Group (BILAG) A or no more than 1 new BILAG B disease activity scores; and o No worsening (defined as an increase of ≥0.3 points [10 mm] from baseline) in the Physician's Global Assessment of Disease Activity.

Objectives	Endpoints
	• Change in the proportion of patients achieving a reduction of ≥4 points from baseline in SLEDAI-2K score at Week 24 compared to baseline. • Change in SLEDAI-2K total score at Week 24 compared to baseline.
To evaluate the effect of baricitinib 4-mg QD or 2-mg QD compared to placebo on the Patient's Global Assessment of Disease Activity in patients with SLE receiving concomitant standard therapy over 24 weeks.	• Change in Patient's Global Assessment of Disease Activity at Week 24 compared to baseline.
To characterize the pharmacokinetics (PK) of baricitinib 4-mg QD or 2-mg QD in patients with SLE receiving concomitant standard therapy over 24 weeks.	• Plasma baricitinib concentrations will be analyzed using a population PK (popPK) approach.

Summary of Study Design:
Study I4V-MC-JAHH (JAHH) is a Phase 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient, 24-week study evaluating the efficacy and safety of baricitinib 4-mg and 2-mg in patients with SLE receiving standard therapy.

Treatment Groups and Duration:
Patients will be randomized at Week 0 to 1 of 3 treatment groups, baricitinib 4-mg daily, baricitinib 2-mg daily, or placebo. The maximum total study duration will be up to 34 weeks over 3 periods (Screening Period: up to 6 weeks prior to randomization; Double-Blinded Treatment Period: 24 weeks; Follow-up Period: 4 weeks after the last dose of investigational product).

Number of Patients:
This study will include approximately 300 patients with SLE who will be randomized 1:1:1 to 1 of 2 dose groups of baricitinib or placebo (100 patients per treatment group).

Statistical Analysis:
Unless otherwise specified, the efficacy, health outcomes, and safety analyses will be conducted on the modified intent-to-treat (mITT) population.

Comparisons between baricitinib 4-mg or 2-mg and placebo will be performed for all analyses in the treatment period. Baseline will be defined as the last available value before the first dose of investigational product for both efficacy and safety analyses.

Treatment comparisons of categorical efficacy variables will be made using a logistic regression analysis with treatment, baseline disease activity (SLEDAI-2K <10 versus SLEDAI-2K ≥10), baseline anti double-stranded deoxyribonucleic acid (anti-dsDNA) status (positive; negative), and region in the model. The proportions and 95% confidence interval (CI) will be reported. Missing data will be imputed using the nonresponder imputation (NRI) method.

Treatment comparisons of continuous efficacy and health outcome variables will be made using mixed-effects models for repeated measures (MMRM) model with treatment, baseline score, baseline disease activity (SLEDAI-2K <10 versus SLEDAI-2K ≥10), baseline anti-dsDNA status (positive; negative), region, visit, and the interaction of treatment-by-visit as fixed factors. An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. Type III sums of squares for the least squares (LS) means will be used for the statistical comparison; the 95% CI will also be reported. Treatment group comparisons with placebo at Week 24 and other visits will be tested.

Fisher exact test will be used for all adverse events (AEs), baseline, discontinuation, and other categorical safety data. Continuous vital signs and laboratory values will be analyzed by an analysis of covariance (ANCOVA) with treatment and baseline values in the model. Other continuous safety variables will be analyzed by t-tests, unless otherwise stated.

2. Introduction

2.1. Background

Systemic lupus erythematosus (SLE) is a chronic, debilitating autoimmune disease that is characterized by the presence of autoreactive B cells and elevated levels of autoantibodies, which directly damage the body's cells and tissues. SLE can affect multiple organ systems simultaneously or sequentially, and follows an unpredictable clinical course where periods of relatively stable disease are followed by flares and/or periods of active disease that can ultimately lead to irreversible damage to tissues and organ systems.

SLE is predominately a disease of women (~9:1, female to male), often beginning in adolescence or early adulthood. It affects approximately 1 in 1000 people in the United States (US) and is more common in African-Americans, with as many as 1 in 330 African-American women afflicted with SLE (Lim et al. 2014; Somers et al. 2014). Additionally, SLE appears to be more severe in African-Americans, Asian-Americans, and Latinos compared to Caucasians (Pons-Estel et al. 2004).

Clinically, SLE presents with varying signs and symptoms, including arthralgia/arthritis, skin rash, alopecia, pleuritis, pericarditis, nephritis, vasculitis, stroke, seizure, thrombocytopenia, anemia, photosensitivity, and the presence of autoantibodies directed to nuclear antigens. Skin and joint disease are the most frequent features at diagnosis. Age, USA African race/ethnicity, Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score, steroid use, and hypertension were associated with transition from no damage to damage, and increase(s) in preexisting damage (Bruce et al. 2015). Over 60% of patients with SLE will develop clinically detectable organ damage within 2 to 7 years of diagnosis, as measured by the Systemic Lupus Erythematosus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) damage index (Cooper et al. 2007).

Improvements in earlier diagnosis, treatment regimens, and medical care over the past several decades have reduced mortality in SLE; however, patients continue to experience premature death, with cardiovascular disease being the leading cause. A recent meta-analysis of published data involving over 27,000 patients with SLE observed a 3-fold increase in risk of death in patients with SLE compared to the general population (Yurkovich et al. 2014). Thus, there remains substantial unmet medical need for individuals who suffer from SLE.

Standard of care for SLE includes corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), antimalarial agents, immunosuppressive agents, and cytotoxic agents; however, there are relatively few drugs approved for treatment of SLE. For example, in the US, approved therapies for SLE include aspirin, antimalarials, corticosteroids, and belimumab. In general, treatment regimens are similar around the world and are tailored to the severity of disease. Mild disease is often treated with low-dose corticosteroids, NSAIDs, and antimalarials; while serious, organ-threatening or life-threatening disease is typically treated with high-dose corticosteroids and immunosuppressive agents. In addition to their direct impact on disease, immunosuppressive agents are also utilized as corticosteroid sparing agents to reduce chronic exposure to corticosteroids.

The current standard of care (SoC) therapies have broad effects on immune and inflammatory pathways and have been associated with short-term and long-term morbidity. For example, long-term use of corticosteroids is associated with cataracts, osteoporosis, avascular necrosis, increased infection, hyperglycemia, and weight gain, while cyclophosphamide increases the risk of premature ovarian failure, serious infection, and cancer.

Although recent improvements in treatment regimens and medical care have reduced mortality and morbidity, many patients still have incompletely controlled disease and progress to end-stage organ involvement. In addition, the disease increases mortality and negatively impacts health-related quality of life. New treatment options with an acceptable safety profile that reduce disease activity, reduce flares, delay organ damage, and reduce the requirement for corticosteroids and cytotoxic agents are urgently needed for patients with SLE.

Accordingly, pharmacologic interventions that target specific pathways associated with the pathology of SLE may provide novel therapeutic approaches to disease management. One of the signaling pathways implicated in SLE disease activity is the type I interferon (IFN) signaling pathway. Up-regulation of genes associated with the activation of type I IFN signaling, referred to as a type I IFN signature, is seen in approximately 70% of patients with SLE (Bauer et al. 2006; Higgs et al. 2011). Not all autoimmune diseases are associated with a pronounced type I IFN signature; for example, internal data have suggested that only approximately 15% of the patients with rheumatoid arthritis (RA) in a Phase 2 baricitinib trial (I4V-MC-JADA [JADA]) had a similar type I IFN signature. However, in SLE, a high type I IFN signature was associated with increased disease severity as measured by SLEDAI score, increased anti double-stranded deoxyribonucleic acid (anti-dsDNA) levels, decreased complement levels, and increased risk of severe flares (Bauer et al. 2009; Statistics-Development/Discovery, Eli Lilly and Company, 2015). Multiple studies have demonstrated that patients with SLE have a pronounced IFN signature. This observation has been confirmed using microarray analyses from the tabalumab Phase 3 SLE studies in which approximately two-thirds of patients had an elevated IFN signature (Chaussabel et al. 2008; Berthier et al. 2012; Lauwerys et al. 2013). Additionally, monocytes from patients with SLE demonstrated an IFN-α2a imprint that included the upregulation of several signal transducer and activator of transcription (STAT) proteins (Smiljanovic et al. 2012). These studies and others have provided a scientific rationale for targeting the type I IFN signature as a therapeutic option for SLE (Mathian et al. 2015). Indeed, this signature is associated with a variety of chemokines that provide a basis for further lymphoid and myeloid cell infiltration into target organs (Gonzalez-Navajas et al. 2012). While approaches targeting specific type I IFNs, primarily alpha, have not been successful, these approaches fail to target all type I IFNs, including beta, and the involvement of other cytokines including IL-6, type II IFN, and others that signal through the Janus kinase/JAK/STAT pathways (Kirou and Gkrouzman 2013). Therefore, treatment of SLE with baricitinib or other JAK inhibitors is an area of intense interest.

Baricitinib (also previously known as LY3009104 and INCB028050) is a potent and selective small molecule inhibitor of JAK1 and JAK2 enzymes that is currently under development for the

treatment of inflammatory conditions such as RA, diabetic kidney disease, psoriasis, and atopic dermatitis.

Through 10 August 2015, approximately 4300 subjects have received baricitinib, including healthy subjects, and patients with RA, psoriasis, diabetic kidney disease, rare auto-inflammatory syndromes, with various degrees of renal impairment, and with hepatic dysfunction. Baricitinib has been administered as single doses ranging from 1- to 40-mg and as repeat oral doses ranging from 2- to 20-mg to healthy subjects. Baricitinib has also been administered to patients with RA at doses up to 15-mg daily for 4 weeks, 10-mg daily for 24 weeks, 8-mg daily for 76 weeks, and lower doses up to 4-mg daily for up to approximately 5 years.

2.2. Study Rationale

Baricitinib is an orally available, selective JAK inhibitor with excellent potency and selectivity for JAK1 and JAK2 and less potency for JAK3 or Tyrosine kinase 2 (TYK2; Fridman et al. 2010). This activity profile suggests that baricitinib may inhibit cytokines implicated in SLE such as type I IFN (JAK1/TYK2), type II IFN-γ, IL-6 (JAK1/JAK2/TYK2), and IL-23 (JAK2/TYK2) as well as other cytokines that may have a role in SLE, including granulocyte-macrophage colony stimulating factor (JAK2/JAK2) and IL-12 (JAK2/TYK2). The potential impact of baricitinib on the IFN pathway is highly relevant to SLE, as clinical and preclinical studies have established that this pathway is involved in the pathogenesis of SLE. Evidence that baricitinib will down-modulate this signature has been seen at the messenger ribonucleic acid (mRNA) level through analysis of samples from patients treated with baricitinib in the psoriasis and RA programs and at the protein level in the diabetic nephropathy (DN) program. Decreases in circulating levels of chemokines associated with this signature have been seen at the protein level in DN (Brosius et al. 2015; Tuttle et al. 2015) and in evaluating type I IFN transcripts in the small subset of RA patients that were characterized in a Phase 2 study as having an elevated type I IFN signature (Statistics-Development/Discovery, Eli Lilly and Company, 2015). Studies performed by the Goldbach-Mansky group at the National Institutes of Health (NIH) in patients with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures (CANDLE) have shown that treatment with baricitinib resulted in decreased IFN signature, and this reduction in IFN signature was consistent with an improvement in clinical symptoms (Montealegre et al. 2015). There are current investigations underway to decrease the IFN signature through the use of a monoclonal antibody (anifrolumab) that targets the type I IFN receptor. While targeting the IFN signature in this manner has shown to be effective in SLE (Furie et al. 2015), it may not be sufficient. Data from the tabalumab Phase 3 SLE studies demonstrated up-regulation of IL-6 related genes, IL-2 receptor, IL-12, and oncostatin M, all of which signal through the JAK/STAT pathways and would not be anticipated to be directly modulated by therapeutic strategies which only target the IFN pathway. Therefore, baricitinib may prove to be an effective treatment as it targets multiple cytokines that have been linked to SLE whose expression is dependent on JAK signaling.

Clinical studies have established that baricitinib is effective in treating autoimmune/ autoinflammatory diseases involving the joints, skin, and kidneys. Baricitinib was effective at reducing swollen and tender joints in patients with RA (JADA [Phase 2], and I4V-MC-JADW

and I4V-MC-JADX [JADW and JADX, Phase 3]), was effective at reducing disease severity in patients with moderate to severe plaque psoriasis (Menter et al. 2014), and was effective at reducing urinary albumin-to-creatinine ratio (UACR) in patients with diabetic kidney disease (Tuttle et al. 2015). The mechanism of action, combined with demonstration of clinical benefit in inflammatory diseases involving joints, skin, and kidneys, provides a compelling rationale for evaluating baricitinib in SLE.

2.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of baricitinib are to be found in the Investigator's Brochure (IB).

3. Objectives and Endpoints

Table JAHH.1 shows the objectives and endpoints of the study.

Table JAHH.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of baricitinib 4-mg daily (QD) or 2-mg QD compared to placebo on remission of SLE arthritis and/or rash in patients with SLE receiving concomitant standard therapy over 24 weeks.	Change in the proportion of patients who achieve remission of arthritis and/or rash as defined by the SLEDAI-2K at Week 24 compared to baseline.
Secondary	
To evaluate the effect of baricitinib 4-mg QD or 2-mg QD compared to placebo on overall SLE disease activity in patients with SLE receiving concomitant standard therapy over 24 weeks.	• Change in the proportion of patients achieving SLE Responder Index 4 (SRI-4) response at Week 24 compared to baseline. SRI-4 response is defined as: o Reduction of ≥4 points from baseline in SLEDAI-2K score; o No new British Isles Lupus Assessment Group (BILAG) A or no more than 1 new BILAG B disease activity scores; and o No worsening (defined as an increase of ≥0.3 points [10 mm] from baseline) in the Physician's Global Assessment of Disease Activity. • Change in the proportion of patients achieving a reduction of ≥4 points from baseline in SLEDAI-2K score at Week 24 compared to baseline. • Change in SLEDAI-2K total score at Week 24 compared to baseline.
To evaluate the effect of baricitinib 4-mg QD or 2-mg QD compared to placebo on the Patient's Global Assessment of Disease Activity in patients with SLE receiving concomitant standard therapy over 24 weeks.	• Change in the Patient's Global Assessment of Disease Activity at Week 24 compared to baseline.
To characterize the pharmacokinetics (PK) of baricitinib 4-mg QD or 2-mg QD in patients with SLE receiving concomitant standard therapy over 24 weeks.	• Plasma baricitinib concentrations will be analyzed using a population PK (popPK) approach.
Exploratory	
To evaluate the effect of baricitinib 4-mg QD or 2-mg QD compared to placebo on SLE arthritis and mucocutaneous disease activity in patients with SLE receiving concomitant standard therapy over 24 weeks.	• Continuous and categorical endpoints based on joint counts • Continuous and categorical endpoints based on the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI).
To evaluate the effect of baricitinib 4-mg QD or 2-mg QD compared to placebo on overall SLE disease activity in patients with SLE receiving concomitant standard therapy over 24 weeks.	• Time to and proportion of patients experiencing first flare (any severity), first mild/moderate flare, and first severe flare defined by the SLEDAI Flare Index (SFI). • Change in SLICC/ACR Damage index score at Week 24 compared to baseline.

Objectives	Endpoints
To evaluate the corticosteroid sparing effect of baricitinib 4-mg QD or 2-mg QD compared to placebo in patients with SLE receiving concomitant standard therapy over 24 weeks.	• Change in proportion of patients receiving ≥10 mg/day prednisone at baseline able to reduce prednisone (or equivalent) dose to ≤7.5-mg for 12 consecutive weeks between Week 12 and Week 24.
To evaluate the effect of baricitinib 4-mg QD or 2-mg QD compared to placebo on serologic markers of SLE in patients with SLE receiving concomitant standard therapy over 24 weeks.	• The difference in reduction of IFN signature between treatment groups at Week 12 and Week 24 compared to baseline. • In patients with elevated anti-dsDNA at baseline, change in anti-dsDNA level at Week 12 and Week 24 compared to baseline. • In patients with low C3 and C4 at baseline, change in C3 and C4 levels at Week 12 and Week 24 compared to baseline.
To evaluate the effect of baricitinib 4-mg QD or 2-mg QD compared to placebo on patient-reported outcomes (PROs) in patients with SLE receiving concomitant standard therapy over 24 weeks.	• Change in worst pain item from the Brief Pain Inventory (BPI) at Week 12 and 24 compared to baseline • Change in worst joint pain item from the BPI at Week 12 and 24 compared to baseline • Change in worst fatigue item from the Brief Fatigue Inventory (BFI) at Week 12 and 24 compared to baseline • Change in mental component score (MCS), physical component score (PCS), and domain scores in the Short-Form 36-item health survey version 2 (SF-36v2) acute at Week 12 and 24 compared to baseline.
To explore dose/exposure response relationships with key efficacy (such as SLEDAI-2K) and safety (such as hematologic parameters) endpoints of interest.	• The relationship between baricitinib PK and key efficacy and safety endpoints will be characterized using popPK/pharmacodynamics (popPK/PD) modeling.

4. Study Design

4.1. Overview of Study Design

Study I4V-MC-JAHH (JAHH) is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient, 24-week study evaluating the efficacy and safety of baricitinib 4-mg and 2-mg in patients with SLE receiving standard therapy.

Approximately 300 patients will be randomized 1:1:1 to receive baricitinib 4-mg daily, baricitinib 2-mg daily, or placebo (100 patients per treatment group). Patients will be stratified at randomization according to disease activity (SLEDAI-2K <10; SLEDAI-2K ≥10), anti-dsDNA status (positive; negative), and region (defined in the statistical analysis plan [SAP]).

The study consists of 3 periods:

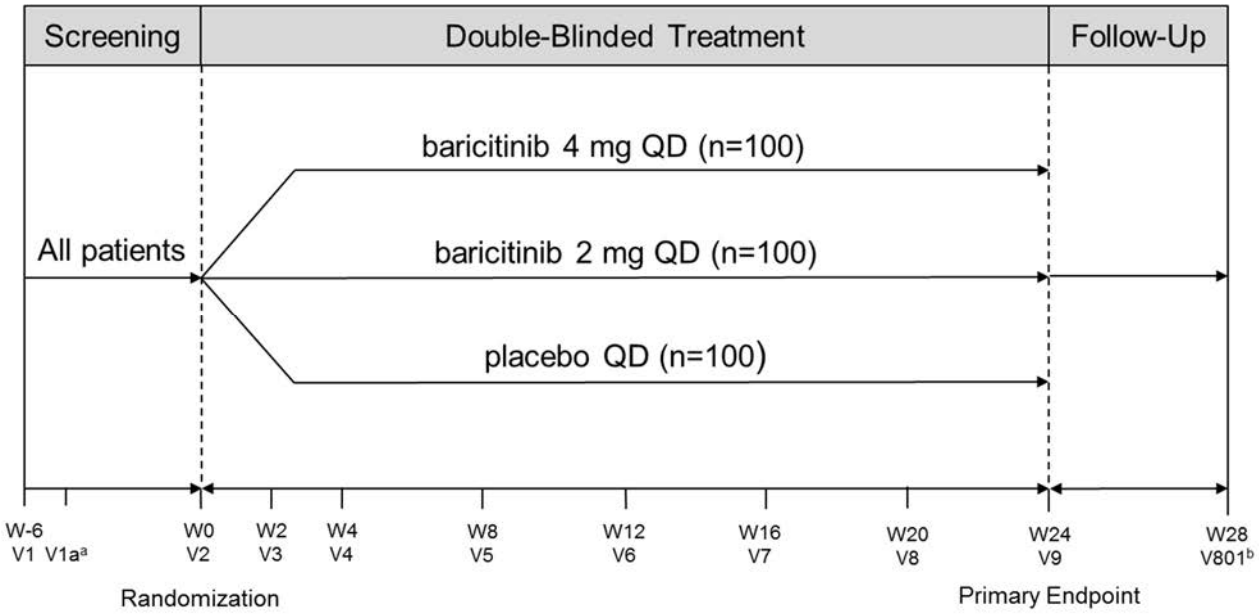
- **Screening Period:** Patients meeting entry criteria begin the 3- to 42-day screening period by signing the informed consent form (ICF). Patients will be screened for study enrollment eligibility at Visit 1, and eligible patients will be randomized at Visit 2 (Week 0).
- **Double-Blinded Treatment Period:** Randomized patients begin the 24-week double-blind, placebo-controlled treatment period at Visit 2 (Week 0) and administer investigational product daily through Visit 9 (Week 24).

  All patients will continue on stable background standard therapy consisting of corticosteroids, NSAIDs (for which the NSAID use is intended for treatment of signs and symptoms of SLE), a single antimalarial (such as hydroxychloroquine or chloroquine), and/or a single immunosuppressant (such as methotrexate [MTX], azathioprine, or mycophenolate). NSAID, antimalarial, and immunosuppressant doses should remain stable throughout the Double-Blinded Treatment Period. Decreases in corticosteroid dose, as well as subsequent increases to less than or equal to the baseline dose will be permitted between Week 0 and Week 16. No changes in corticosteroid dose (increases or decreases) will be permitted between Week 16 and Week 24. Further details regarding concomitant therapy are in Section 6.8.

  Initiation or increase in dose of NSAIDs (for which the NSAID use is intended for treatment of signs and symptoms of SLE), corticosteroids (above the baseline dose through Week 16, or any increase after Week 16), antimalarials, and/or immunosuppressants is not permitted after randomization. After randomization, patients requiring the abovementioned initiation or increase in dose of SLE SoC medications, as well as those meeting discontinuation criteria, will be discontinued from investigational product and complete the study procedures for an early termination visit (ETV).

- **Follow-Up Period:** Patients who complete the study through Visit 9 (Week 24), as well as those who discontinue study treatment early, will have a post-treatment follow-up visit (Visit 801) approximately 4 weeks after the last dose of investigational product.

Figure JAHH.1 illustrates the study design. The 3 dosing regimens are described in Section 6.1. As this is a double-blind study, the blinding procedure described in Section 6.3 will be followed.



Abbreviations: n = number of patient per treatment group; QD = daily; V = visit; W = week.

[a] For those patients with a purified protein derivative (PPD) placed at Visit 1, Visit 1a must occur 48 to 72 hours post-Visit 1 for PPD to be read.

[b] All patients should return for a post-treatment follow-up visit (V801) 4 weeks after the last dose of investigational product.

Figure JAHH.1. Illustration of study design for Clinical Protocol I4V-MC-JAHH.

4.2. End of Trial Definition

End of the trial is the date of the last visit, last scheduled procedure shown in the Schedule of Activities (Appendix 2), or date of discontinued participation for the last patient.

4.3. Scientific Rationale for Study Design

The scientific rationale for the primary endpoint of this study is based on analyses from 2 large tabalumab SLE Phase 3 trials with a similar patient population involving over 2200 patients (Isenberg et al. 2015; Merrill et al. 2015). The primary endpoint in these trials was SRI-5. The goal of these analyses was to characterize the clinical symptoms most responsible for achieving responder status with SRI-5, and then use this information to design a more efficient trial with clinically relevant endpoints.

To achieve SRI-5, one needs improvement in SLEDAI, with no worsening in BILAG or Physician's Global Assessment of Disease Activity. In the Phase 3 trials, BILAG and Physician's Global Assessment of Disease Activity contributed minimal information to SRI-5, as fewer than 1% of patients achieved a ≥5-point reduction in SLEDAI score, but failed the endpoint due to worsening of BILAG or Physician's Global Assessment of Disease Activity. These data provided the rationale to focus on SLEDAI as the primary driver of clinical response.

The SLEDAI is a weighted disease activity index that measures presence or absence of disease in 9 organ systems. Disease activity in the mucocutaneous, musculoskeletal, or immunologic organ systems was present in over 70% of patients at baseline, with over 98% of patients having mucocutaneous and/or musculoskeletal disease at baseline. In contrast, in the other 6 organ systems these diseases were present in ≤15% of patients. These data provided the rationale to focus on mucocutaneous and musculoskeletal disease as the primary driver of clinical response.

The 9 SLEDAI organ systems are composed of specific disease symptoms. The musculoskeletal organ system consists of arthritis and myositis. Arthritis was the most prevalent symptom at baseline (>80% of patients) while myositis was rare (~1% of patients). The mucocutaneous organ system includes rash, alopecia, and mucosal ulcer. Rash was the most common symptom in this organ system (~70% of patients), followed by alopecia (~55%) and mucosal ulcer (~30%). These data, in consultation with SLE experts, provided the rationale to focus on remission of arthritis and rash as the primary endpoint in the clinical trial.

This study is designed to allow for an efficient evaluation of efficacy using clinically relevant endpoints, while still allowing examination of the full range of SLE disease signs and symptoms. SLEDAI, BILAG, and CLASI assessments will be completed at most visits, enabling the evaluation of the entire spectrum of SLE disease activity in this trial, although the primary endpoint is focused on arthritis and rash.

The observation that baricitinib was effective at reducing albuminuria in patients with diabetic kidney disease is also relevant to the design of the trial (Tuttle et al. 2015). As in most SLE trials, patients with severe, active glomerulonephritis are excluded. However, there is interest in collecting preliminary data on a subset of patients to determine if baricitinib has a positive impact on the symptoms of lupus nephritis. Thus, patients with a history of nephritis and current stable renal disease are encouraged to enroll.

This study will be double-blinded and placebo-controlled to minimize bias. The selection of placebo as a comparator for this study is warranted as there are few approved therapies for SLE and all patients in the study are allowed to receive concomitant SoC, including corticosteroids, NSAIDs, antimalarials, and/or immunosuppressants.

In order to minimize the confounding effects of concomitant medications, no increases above baseline are allowed for corticosteroids, immunosuppressants, NSAIDs, or antimalarials during the trial. This strict control over corticosteroids and immunosuppressants is supported by data from the Phase 3 SLE trials discussed above, where less than 20% of patients in any group required an increase in prednisone over the first 24 weeks, and fewer than 10% required an increase in prednisone in the first 8 weeks.

Patients with intolerable or exacerbating disease requiring initiation or increase in doses of corticosteroids, NSAIDs, antimalarials, or immunosuppressants will be discontinued from study treatment and will be treated as nonresponders for the efficacy analyses.

4.4. Justification for Dose

The baricitinib doses of 4-mg and 2-mg administered orally once daily were selected for SLE based on RA studies (JADA [Phase 2] and JADW and JADX [Phase 3]) and a psoriasis study (I4V-MC-JADP, Phase 2) described in the IB.

In these studies, doses of 4-mg and 2-mg daily were generally well tolerated based on the AE profile and infrequent discontinuations of baricitinib dosing. The anticipated on-target, dose-limiting toxicity is a small decline in hemoglobin and hematocrit values resulting from the finding that erythropoietin signals via the JAK2/STAT5 signal transduction pathway (Klingmüller et al. 1997; Vera et al. 2008). This decline in hemoglobin and hematocrit has been seen to occur in higher-dose groups (≥8-mg daily) upon initiation of treatment and then stabilize.

Baricitinib 4-mg and 2-mg daily doses have shown efficacy in RA with an acceptable safety profile. There was no additional efficacy associated with an 8-mg dose in the Phase 2 RA study; thus, only 4-mg and 2-mg have been studied in the RA Phase 3 program. The 4-mg daily dose has demonstrated an earlier onset and a more consistent efficacy than 2-mg daily in RA studies.

In psoriasis, baricitinib doses between 4-mg and 10-mg were associated with statistically significant reductions in measures of disease activity, with greater efficacy at the higher doses. However, the 8-mg and 10-mg doses were associated with a higher rate of AEs related to laboratory abnormalities (decreases in hemoglobin, neutrophils, and lymphocytes), while the 2-mg and 4-mg dose groups had a pattern of AEs similar to placebo. The 2-mg dose did show numeric improvements in efficacy compared with placebo.

The only patient factor thus far that has been identified to have a clinically relevant effect on the PK of baricitinib in completed RA, psoriasis, and DN studies is overall renal function. Although it is currently not clear whether different disease conditions (such SLE versus RA) might result in different PK, aside from varying renal function associated with the disease states, the difference, if any, is not expected to be substantial. It is therefore assumed that exposure at 2-mg and 4-mg in patients with SLE will be similar to that in RA, psoriasis, and DN patients studied, after accounting for renal function. Thus, the highest baricitinib dose to be tested in SLE will be 4-mg, which would be anticipated to show efficacy together with an acceptable safety profile, and also provide the opportunity to cross-reference to the large safety database from the RA Phase 3 program. The lower dose of 2-mg also has the opportunity to show efficacy in SLE.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

Patients are entered into the study once they have signed the ICF. Patients may be assessed for study entry on the basis of readily available information (that is, information that does not require informed consent from the patient).

5.1. Inclusion Criteria

5.1.1. Entry Criteria

Patients are eligible for entry into the study (eligible to sign the ICF) only if they are anticipated to meet all of the following entry criteria at screening (Visit 1):

Type of Patient and Disease Characteristics

[1] Are at least 18 years of age.

[2] Have received a clinical diagnosis of SLE at least 24 weeks prior to screening, meeting at least 4 of the 11 Revised Criteria for Classification of Systemic Lupus Erythematosus according to the 1997 Update of the 1982 ACR (Tan et al. 1982; Hochberg et al. 1997) OR meeting at least 4 of the 2012 SLICC classification criteria (Petri et al. 2012), including at least 1 clinical criterion and 1 immunologic criterion.

[3] Have history of a positive antinuclear antibody (ANA) or a positive anti-dsDNA (if available).

[4] Have active arthritis and/or rash due to SLE.

Informed Consent

[5] Are able to read, understand, and give written informed consent.

5.1.2. Enrollment Criteria

Entered patients are eligible for enrollment into the study (eligible for randomization) only if they continue to meet all of the entry criteria above, and meet all of the following enrollment criteria at the time of randomization (Visit 2):

Type of Patient and Disease Characteristics

[6] Have a positive ANA (HEp-2 ANA titer ≥1:80) and/or a positive anti-dsDNA (≥30 IU) as assessed by a central laboratory at screening.

Note: The ANA and/or anti-dsDNA measurement may be repeated once within approximately 2 weeks of the initial value, and the value resulting from repeat testing may be accepted for enrollment eligibility if it meets the eligibility criterion.

[7] Have a SLEDAI-2K score ≥4 based on clinical symptoms (not including lab values) at randomization.

[8] Have active arthritis and/or active rash as defined by the SLEDAI-2K at randomization.

5.2. Exclusion Criteria

5.2.1. Entry Criteria

Patients are ineligible for entry into the study (ineligible to sign the ICF) if they are anticipated to meet any of the following entry exclusion criteria at screening (Visit 1):

Medical Conditions

[9] Have active severe lupus nephritis as defined in exclusion criterion [50].

[10] Have active severe central nervous system (CNS) lupus as defined in exclusion criterion [51].

[11] Have experienced a clinically significant thrombotic event within 24 weeks of screening or are on anticoagulants and in the opinion of the investigator are not well controlled.

[12] Have active fibromyalgia that, in the investigator's opinion, would make it difficult to appropriately assess SLE activity for the purposes of this study.

[13] Have been treated for or had an active occurrence of a systemic inflammatory condition other than SLE such as, but not limited to, RA, juvenile chronic arthritis, spondyloarthropathy, Crohn's disease, ulcerative colitis, or psoriatic arthritis in the 12 weeks prior to screening.

a. Patients with secondary Sjogren's syndrome are not excluded.

[14] Have had any major surgery within 8 weeks prior to screening or will require major surgery during the study that, in the opinion of the investigator in consultation with Lilly or its designee, would pose an unacceptable risk to the patient.

[15] Have experienced any of the following within 12 weeks of screening: myocardial infarction (MI), unstable ischemic heart disease, stroke, or New York Heart Association Stage IV heart failure.

[16] Have a history or presence of cardiovascular, respiratory, hepatic, gastrointestinal, endocrine, hematological, neurological, or neuropsychiatric disorders or any other serious and/or unstable illness that, in the opinion of the investigator, could constitute an unacceptable risk when taking investigational product or interfere with the interpretation of data.

[17] Are largely or wholly incapacitated permitting little or no self-care, such as being bedridden or confined to wheelchair.

[18] Have an estimated glomerular filtration rate (eGFR) based on the most recent available serum creatinine of <50 mL/min/1.73 m^2 (if available).

[19] Have a history of chronic liver disease with the most recent available aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 times the upper limit of normal (>2 x ULN) or the most recent available total bilirubin ≥1.5 x ULN (if available).

[20] Have a history of lymphoproliferative disease; or have signs or symptoms suggestive of possible lymphoproliferative disease, including lymphadenopathy or splenomegaly (other than primarily due to SLE); or have active primary or recurrent malignant disease; or have been in remission from clinically significant malignancy for <5 years.

a. Patients with cervical carcinoma in situ that has been resected with no evidence of recurrence or metastatic disease for at least 3 years may participate in the study.

b. Patients with basal cell or squamous epithelial skin cancers that have been completely resected with no evidence of recurrence for at least 3 years may participate in the study.

[21] Have a current or recent (<4 weeks prior to screening) clinically serious viral, bacterial, fungal, or parasitic infection.

Note: For example, a recent viral upper respiratory tract infection or uncomplicated urinary tract infection should not be considered clinically serious.

[22] Have had symptomatic herpes zoster infection within 12 weeks prior to screening.

[23] Have a history of disseminated/complicated herpes zoster (for example, multidermatomal involvement, ophthalmic zoster, CNS involvement, or post-herpetic neuralgia).

[24] In the opinion of the investigator, are at an unacceptable risk for participating in the study.

[25] Have active or chronic viral infection from hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).

[26] Have had household contact with a person with active tuberculosis (TB) and did not receive appropriate and documented prophylaxis for TB.

[27] Have evidence of active TB or have previously had evidence of active TB and did not receive appropriate and documented treatment.

Prior/Concomitant Therapy

[28] Are currently receiving oral corticosteroids at doses >20-mg per day of prednisone (or equivalent) or have adjusted the dose of corticosteroids within 2 weeks of planned randomization.

[29] Have received topical corticosteroids, other than stable doses of class 6 (mild, such as desonide) or class 7 (least potent, such as hydrocortisone), within 2 weeks of screening or within 4 weeks of planned randomization.

[30] Have received oral or parenteral [intravenous (IV) or intramuscular (IM)] corticosteroids at doses >40-mg per day of prednisone (or equivalent) within 6 weeks of screening or within 8 weeks of planned randomization, or are anticipated to require parenteral injection of corticosteroids during the study.

[31] Have had a joint injected with intra-articular corticosteroids or hyaluronic acid within 2 weeks of screening or within 4 weeks of planned randomization.

[32] Have started treatment with or adjusted the dose of NSAIDs (for which the NSAID use is intended for treatment of signs and symptoms of SLE) within 2 weeks of screening or within 4 weeks of planned randomization.

[33] Have started treatment with or adjusted the dose of an antimalarial (such as hydroxychloroquine, chloroquine, quinacrine) within 10 weeks of screening or within 12 weeks of planned randomization.

[34] Have started treatment with or adjusted the dose of an immunosuppressant (such as MTX, azathioprine, mycophenolate) within 10 weeks of screening or within 12 weeks of planned randomization.

[35] Have received cyclophosphamide (or any other cytotoxic agent) within 12 weeks prior to screening.

[36] Have received etanercept, infliximab, certolizumab, adalimumab, golimumab, or anakinra within 12 weeks of screening; tocilizumab, abatacept, ustekinumab, rituximab, belimumab, or any other B cell targeted therapies (approved or investigational) within 24 weeks of screening; or any other biologic therapy within 4 weeks or 5 half-lives of screening, whichever is longer.

[37] Have received intravenous immunoglobulin (IVIg) within 24 weeks of screening.

[38] Have received plasmapheresis within 12 weeks of screening.

[39] Have been exposed to a live vaccine within 12 weeks prior to planned randomization or are expected to need/receive a live vaccine during the course of the study (with the exception of herpes zoster vaccination).

a. All patients who have not received the herpes zoster vaccine at screening will be encouraged (per local guidelines) to do so prior to randomization; vaccination must occur >4 weeks prior to randomization and start of investigational product. Patients will be excluded if they were exposed to herpes zoster vaccination within 4 weeks of planned randomization.

b. Investigators should review the vaccination status of their patients and follow the local guidelines for vaccination of those ≥18 years of age with nonlive vaccines intended to prevent infectious disease prior to entering patients into the study.

Other Exclusions

[40] Are pregnant or nursing at the time of screening.

[41] Are females of childbearing potential who do not agree to use 2 forms of highly effective birth control when engaging in sexual intercourse with a male partner while enrolled in the study and for at least 4 weeks following the last dose of investigational product.

a. Females of nonchildbearing potential are defined as women ≥60 years of age, women ≥40 and <60 years of age who have had a cessation of menses for at least 12 months, or women who are congenitally or surgically sterile (that is, have had a hysterectomy or bilateral oophorectomy or tubal ligation).

b. The following birth control methods are considered highly effective (the patient should choose 2 to be used with their male partner):

- oral, injectable, or implanted hormonal contraceptives
- condom with a spermicidal foam, gel, film, cream, or suppository
- occlusive cap (diaphragm or cervical/vault caps) with a spermicidal foam, gel, film, cream, or suppository
- intrauterine device
- intrauterine system (for example, progestin-releasing coil)
- vasectomized male (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)

Note: When local guidelines concerning highly effective methods of birth control differ from the above, the local guidelines must be followed.

[42] Are males who do not agree to use 2 forms of highly effective birth control (see above) while engaging in sexual intercourse with female partners of childbearing potential while enrolled in the study and for at least 4 weeks following the last dose of investigational product.

[43] Have donated more than a single unit of blood within 4 weeks prior to screening or intend to donate blood during the course of the study.

[44] Have a history of chronic alcohol abuse, IV drug abuse, or other illicit drug abuse within the 2 years prior to screening.

[45] Have previously been randomized in this study or any other study investigating baricitinib.

[46] Are unable or unwilling to make themselves available for the duration of the study and/or are unwilling to follow study restrictions/procedures.

[47] Are currently enrolled in, or discontinued within 4 weeks prior to screening from any other clinical trial involving an investigational product or nonapproved use of a drug or device or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[48] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[49] Are Lilly or Incyte employees or either's designee.

5.2.2. Enrollment Criteria

Entered patients are ineligible for enrollment into the study (ineligible for randomization) and should be discontinued from the study if they meet any of the entry exclusion criteria above, or meet any of the following enrollment exclusion criteria at the time of randomization (Visit 2):

Medical Conditions

[50] Have severe active lupus nephritis, including urine protein/creatinine ratio >300 mg/mmol (as an estimate of approximate proteinuria >3g/day) or active urinary sediment with red blood cell cast(s), or histological evidence (if available) of diffuse proliferative glomerulonephritis within the 12 weeks prior to screening.

Note: The lab measurements related to lupus nephritis may be repeated once within approximately 2 weeks of the initial values, and the values resulting from repeat testing may be accepted for enrollment eligibility if they meet the eligibility criterion.

[51] Have active severe CNS lupus including aseptic meningitis, cerebral vasculitis, demyelinating syndrome, myelopathy, acute confusional state, psychosis, acute inflammatory demyelinating polyradiculoneuropathy, mononeuropathy (single/multiplex), cranial neuropathy, plexopathy, status epilepticus, or cerebellar ataxia.

[52] Have symptomatic herpes simplex at the time of randomization.

[53] Have screening electrocardiogram (ECG) abnormalities that, in the opinion of the investigator or the sponsor, are clinically significant and indicate an unacceptable risk for the patient's participation in the study.

[54] Have evidence of active TB as documented by a positive purified protein derivative (PPD) test (≥5-mm induration between approximately 2 and 3 days after application, regardless of vaccination history), medical history, clinical symptoms, and abnormal chest x-ray at screening.

- The QuantiFERON®-TB Gold test or T-SPOT®.TB test (as available and if compliant with local TB guidelines) may be used instead of the PPD test. Patients are excluded from the study if the test is not negative and there is clinical evidence of active TB.

[55] Have evidence of latent TB (as documented by a positive PPD test, no clinical symptoms consistent with active TB, and a normal chest x-ray at screening, or as outlined below) unless patient completes at least 4 weeks of appropriate treatment prior to randomization and agrees to complete the remainder of treatment while in the trial.

- If the PPD test is positive and the patient has no medical history or chest x-ray findings consistent with active TB, the patient may have a QuantiFERON®-TB Gold test or T-SPOT®.TB test (as available and if compliant with local TB guidelines). If the test results are not negative, the patient will be considered to have latent TB (for purposes of this study) and will be excluded.
- The QuantiFERON®-TB Gold test or T- SPOT®.TB test (as available and if compliant with local TB guidelines) may be used instead of the PPD test. If the test results are positive, the patient will be considered to have latent TB and will be excluded. If the test is not negative, the test may be repeated once within 2 weeks of the initial value. If the repeat test results are again not negative, the patient will be considered to have latent TB (for purposes of this study) and will be excluded.
- Exceptions include patients with a history of active or latent TB who have documented evidence of appropriate treatment and with no history of re-exposure since their treatment was completed. (Such patients would not be required to undergo the protocol specific TB testing for PPD, QuantiFERON®-TB Gold test or T-SPOT®.TB test, but would still require a baseline chest x-ray.)

[56] Have a positive test for HBV defined as:

a. positive for hepatitis B surface antigen (HBsAg), or

b. positive for anti-hepatitis B core antibody (HBcAb) but negative for hepatitis B surface antibody (HBsAb), or

c. positive for HBcAb and positive for hepatitis B virus deoxyribonucleic acid (HBV DNA)

d. Patients in Japan (or elsewhere if required), are excluded if they are positive for HBsAg; or, are positive for HBcAb and/or HBsAb and positive for HBV DNA.

If any of the HB tests have an indeterminate result, confirmatory testing will be performed by an alternate method.

[57] Have HCV (positive for anti-hepatitis C antibody with confirmed presence of HCV).

[58] Have evidence of HIV infection and/or positive HIV antibodies.

Diagnostics Assessments

[59] Have screening laboratory test values, including thyroid-stimulating hormone (TSH), outside the reference range for the population or investigative site that, in the opinion of the investigator, pose an unacceptable risk for the patient's participation in the study.

- Patients who are receiving thyroxine as replacement therapy may participate in the study, provided stable therapy has been administered for ≥12 weeks and TSH is within the laboratory's reference range. Patients who are receiving stable thyroxine replacement therapy who have TSH marginally outside the laboratory's normal reference range may participate if the treating physician has documented that the thyroxine replacement therapy is adequate for the patient.

Laboratory tests may be repeated once within approximately 2 weeks of the initial value, and the value resulting from repeat testing may be accepted for enrollment eligibility if it meets the eligibility criterion.

[60] Have any of the following specific abnormalities on screening laboratory tests:

a. ALT or AST >2 x ULN

b. total bilirubin ≥1.5 x ULN

c. hemoglobin <9 g/dL (90.0 g/L)

d. total white blood cell (WBC) count <2500 cells/μL (<2.50x10^3/μL or <2.50 GI/L)

e. neutropenia (absolute neutrophil count [ANC] <1200 cells/μL) (<1.20x10^3/μL or <1.20 GI/L)

f. lymphopenia (lymphocyte count <750 cells/μL) (<0.75x10^3/μL or <0.75 GI/L)

Note: Patients may be enrolled with a lymphocyte count <750 cells/μL but ≥500 cells/μL (<0.50x10^3/μL or <0.50 GI/L) if the low lymphocyte count is considered by the investigator to be a result of the underlying SLE disease or concomitant medications.

g. thrombocytopenia (platelets <50,000 cells/μL) (<50x10^3/μL or <50 GI/L)

h. eGFR (Modification of Diet in Renal Disease [MDRD]) <50 mL/min/1.73 m^2.

In the case of any of the aforementioned laboratory abnormalities, the tests may be repeated once within approximately 2 weeks of the initial values, and values resulting from repeat testing may be accepted for enrollment eligibility if they meet the eligibility criterion.

Other Exclusions

[61] Are women ≥40 and <60 years of age who have had a cessation of menses for at least 1 year, have a follicle-stimulating hormone (FSH) value <40 mIU/mL, and do not agree to use 2 forms of highly effective methods of birth control when engaging in sexual intercourse with a male partner while enrolled in the study and for at least 4 weeks following the last dose of investigational product, unless they are congenitally or surgically sterile (that is, have had a hysterectomy, bilateral oophorectomy, or tubal ligation).

5.3. Screen Failures

Patients who are entered into the study but do not meet the enrollment criteria for participation in this study (screen failure) may be re-screened once. The interval between screen failure and re-screenings should be at least 4 weeks. At the time of re-screening, the individual must sign a new ICF, repeat all necessary screening procedures, and will be assigned a new identification number.

5.4. Lifestyle and/or Dietary Requirements

Study participants should be instructed not to donate blood or blood products during the study or for 30 days following the last dose of investigational product.

6. Treatment

6.1. Treatments Administered

This study involves a comparison of baricitinib 4-mg and baricitinib 2-mg administered orally once daily with placebo. Table JAHH.2 shows the treatment regimens.

Table JAHH.2. Treatment Regimens

Regimen	Dose Week 0 through Week 24
Baricitinib 4-mg QD	1 baricitinib 4-mg tablet and 1 placebo tablet matching baricitinib 2-mg
Baricitinib 2-mg QD	1 baricitinib 2-mg tablet and 1 placebo tablet matching baricitinib 4-mg
Placebo	2 placebo tablets: 1 matching baricitinib 4-mg and 1 matching baricitinib 2-mg

Abbreviations: QD = daily.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational product to the patient or legal representative
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- at the end of the study, returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

6.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized in a 1:1:1 ratio (baricitinib 4-mg; baricitinib 2-mg; placebo) to double-blind treatment at Visit 2 (Week 0). Randomization will be stratified by disease activity (SLEDAI-2K <10; SLEDAI-2K ≥10), anti-dsDNA status (positive; negative), and region (defined in the SAP). Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign 2 bottles (Bottle A and Bottle B), each containing 36 double-blind investigational product tablets to each patient, starting at Visit 2 (Week 0), and at each visit through Visit 8 (Week 20). Site personnel will confirm that they have located the correct bottles by entering a confirmation number found on the bottles into the IWRS. Patients will be instructed to take 1 tablet from Bottle A and 1 tablet from Bottle B each day.

6.2.1. Selection and Timing of Doses

The investigational product (1 tablet from Bottle A and 1 tablet from Bottle B) should be taken without regard to food and, if possible, at approximately the same time every day to aid patient compliance. Refer to Section 8.5, Pharmacokinetics, for specific instructions on dose timing at certain visits where a PK sample is drawn.

6.3. Blinding

This is a double-blind study. All study assessments will be done by study personnel who are blinded to the patient's treatment group. Except in clinical circumstances where unblinding is required, the patients, investigators, Lilly study team, and any personnel interacting directly with patients or investigative sites will remain blinded to baricitinib and placebo assignment until after completion of the Double-Blinded Treatment Period. It is expected that the need for unblinding a patient's treatment prior to completion of the Double-Blinded Treatment Period will be extremely rare. Every effort should be made to preserve the blind unless there is a compelling reason that knowledge of the specific treatment would alter the medical care of the patient.

Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the patient's acute well-being requires knowledge of the patient's treatment assignment. All unblinding events are recorded and reported by the IWRS.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly clinical research physician (CRP) or designee prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

If an investigator, site personnel performing assessments, or patient is unblinded, patient discontinuation should be considered after discussion with the sponsor. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from the Lilly CRP for the patient to continue in the study.

6.4. Packaging and Labeling

The sponsor (or its designee) will provide the following investigational products:

- tablets containing 4-mg of baricitinib (Bottle A)
- tablets containing 2-mg of baricitinib (Bottle B)
- placebo tablets to match baricitinib 4-mg tablets (Bottle A)
- placebo tablets to match baricitinib 2-mg tablets (Bottle B).

Baricitinib 4-mg and 2-mg tablets and packaging will be identical in appearance to the respective placebo tablets in order to maintain the blind.

Investigational product tablets will be provided in bottles containing 36 tablets.

Clinical trial materials will be labeled according to the country's regulatory requirements.

6.5. Preparation/Handling/Storage

All investigational product (used and partially used) will be returned to the sponsor or destroyed at site level with the sponsor's written approval. In some cases, sites may destroy the material if,

during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical trial materials.

Follow storage and handling instructions on the investigational product packaging.

6.6. Dose Modification

Not applicable.

6.7. Treatment Compliance

Patient compliance with investigational product will be assessed at each visit during the treatment period (Visit 3 through Visit 9) by counting returned tablets. Deviations from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

A patient will be considered significantly noncompliant if he or she misses more than 20% of the prescribed doses of investigational product (full doses) during the study, unless the patient's investigational product is withheld by the investigator for safety reasons. Similarly, a patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken 20% more than the prescribed amount of medication.

Patients will be counseled by study staff on the importance of taking the investigational product as prescribed, as appropriate.

Patients' compliance will be further defined in the SAP.

6.8. Concomitant Therapy

Patients will maintain their usual medication regimen for SLE and for any other concomitant diseases throughout the study unless specifically excluded in the protocol (see Section 5.2, Exclusion Criteria). Patients taking these medications should be on chronic stable doses at the time of randomization, as specified by the Entry Criteria (Section 5.2.1).

Concomitant SoC for SLE in this study can include corticosteroids, NSAIDs, a single antimalarial (such as chloroquine or hydroxychloroquine), and/or a single immunosuppressant (such as azathioprine, MTX, or mycophenolate).

Corticosteroid dose must be ≤20-mg per day of prednisone (or equivalent) and stable for 2 weeks prior to randomization. Increases in corticosteroid dose are not permitted after randomization. Decreases in corticosteroid dose will be permitted between Week 0 and Week 16. If corticosteroid dose is decreased during this time period, subsequent increases, only to less than or equal to the baseline dose, will be permitted until Week 16. No changes in corticosteroids (increases or decreases) will be permitted between Week 16 and Week 24. Patients who require initiation or increase in dose of corticosteroids after randomization should be discontinued from investigational product, have an ETV, and proceed to the Follow-Up Period of the study.

Doses of NSAIDs (for which the NSAID use is intended for treatment of signs and symptoms of SLE), antimalarials, and immunosuppressants should not be adjusted during the Double-Blinded Treatment Period. Patients who require initiation or increase in dose of NSAIDs (for which the

NSAID use is intended for treatment of signs and symptoms of SLE), antimalarials, or immunosuppressants after randomization should be discontinued from investigational product, have an ETV, and proceed to the Follow-Up Period of the study.

Any changes to the patient's medication must be discussed with the investigator. Patients should be instructed to consult the investigator or other appropriate study personnel at the site before taking any new medications or supplements.

Additional medications are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. If the need for concomitant medication arises, inclusion or continuation of the patient may be at the discretion of the investigator after consultation with Lilly or its designee. Any additional medication, whether prescription or over-the-counter, used at baseline and/or during the course of the study must be documented in the eCRF with start and stop dates.

6.9. Treatment after Study Completion

6.9.1. Continued Access

Baricitinib will not be made available after conclusion of the study. Patients will be referred to their local treatment centers for continued therapy as clinically indicated.

7. Discontinuation Criteria

7.1. Discontinuation from Study Treatment

7.1.1. Interruption of Investigational Product

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of AEs or abnormal laboratory values that may have an unclear relationship to investigational product. Except in cases of emergency, it is recommended that the investigator consult with Lilly (or its designee) before temporarily interrupting therapy for reasons other than those defined in Table JAHH.3 below. Retest timing and frequency is at the investigator's discretion.

The investigator must obtain approval from Lilly (or its designee) before restarting investigational product that was temporarily discontinued because of an AE or abnormal laboratory value. Investigational product must be held in the following situations and may be resumed as noted in Table JAHH.3.

Table JAHH.3. Criteria for Temporary Interruption of Investigational Product

Hold investigational product if the following laboratory test results occur:	Investigational product may be resumed after approval from Lilly (or its designee) when:
WBC count <2000 cells/µL (<2.00x10^3/µL or <2.00 GI/L)	WBC count ≥2500 cells/µL (≥2.50x10^3/µL or ≥2.50 GI/L)
ANC <1000 cells/µL (<1.00x10^3/µL or <1.00 GI/L)	ANC ≥1200 cells/µL (≥1.20x10^3/µL or ≥1.20 GI/L)
Lymphocyte count <500 cells/µL (<0.50x10^3/µL or <0.50 GI/L) Note: IP can be continued with a lymphocyte count <500 cells/µL but ≥300 cells/µL (<0.30x103/µL or <0.30 GI/L) if the low lymphocyte count is considered by the investigator to be a result of the underlying SLE disease or concomitant medications. IP must be held for lymphocyte count <300 cells/µL, regardless of cause.	Lymphocyte count ≥750 cells/µL (≥0.75x10^3/µL or ≥0.75 GI/L) Note: If IP is held for lymphocyte count <300 cells/µL, it may be resumed after approval from Lilly (or its designee) when the lymphocyte count is ≥500 cells/µL if the low lymphocyte count is considered by the investigator to be a result of the underlying SLE disease or concomitant medications.
Platelet count <25,000/µL (<25x10^3/µL or <25 GI/L)	Platelet count ≥50,000/µL (≥50x10^3/µL or ≥50 GI/L)
eGFR <40 mL/min/1.73 m^2 (from serum creatinine)	eGFR ≥50 mL/min/1.73 m^2
ALT or AST >5 x ULN	ALT and AST return to <2 x ULN, and IP is not considered to be the cause of enzyme elevation
Hemoglobin <8 g/dL (<80.0 g/L)	Hemoglobin ≥9 g/dL (≥90.0 g/L)
Symptomatic herpes zoster	All skin lesions have crusted and are resolving
Severe infection that, in the opinion of the investigator, merits the IP being discontinued	Resolution of infection

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; IP = investigational product; ULN = upper limit of normal; WBC = white blood cell.

7.1.2. Permanent Discontinuation of Investigation Product

Any patient who is permanently discontinued from investigational product for an AE or abnormal laboratory result should have the reason for investigational product discontinuation reported as the AE or abnormal laboratory value.

Discontinuation of the investigational product for abnormal liver tests **should be considered** by the investigator when a patient meets one of the following conditions after consultation with the Lilly designated medical monitor:

- ALT or AST >8 x ULN
- ALT or AST >5 x ULN for more than 2 weeks after temporary interruption of investigational product
- ALT or AST >3 x ULN and either total bilirubin level (TBL) >2 x ULN or INR >1.5 x ULN
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3 x ULN
- ALP >2.5 x ULN and TBL >2 x ULN
- ALP >2.5 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Patients should be discontinued from the investigational product in the following circumstances:

- WBC count <1000 cells/μL ($1.00x10^3$/μL or 1.00 GI/L)
- ANC <500 cells/μL ($0.50x10^3$/μL or 0.50 GI/L)
- Lymphocyte count <200 cells/μL ($0.20x10^3$/μL or 0.20 GI/L)
- Hemoglobin <6.5 g/dL (<65.0 g/L).

For lab values that meet permanent discontinuation thresholds, investigational product should be discontinued unless, in the opinion of the investigator, the lab abnormality is due to intercurrent illness or another identified factor. After consultation with the Lilly-designated medical monitor, the patient may be able to continue receiving investigational product. Lab tests may be repeated within 1 week to confirm whether discontinuation criteria have been met. Furthermore, if investigational product is not discontinued due to intercurrent illness, the investigator must confirm the lab value no longer meets discontinuation thresholds following the resolution of the intercurrent illness or other identified factor.

In addition, patients will be discontinued from investigational product in the following circumstances:

- Pregnancy

- Malignancy (except for successfully treated basal cell or squamous epithelial skin cancers)
- HBV DNA above the lower limit of quantification (LLOQ)

  Note: If the HBV DNA result is "target detected" (above the LLOQ), then the patient should be referred to a hepatology specialist immediately. In selected cases, investigators may temporarily continue investigational product in accordance with current immunomodulator management in the setting of HBV DNA positivity. This option may be considered in consultation with Lilly (or its designee) and evaluation of individual patient risks and benefits. Refer to Section 8.4.4 for additional instruction on HBV DNA monitoring.

Some possible reasons that may lead to permanent discontinuation include:

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator Decision
  - the investigator decides that the patient should be discontinued from the study
  - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication (including initiation or increase in dose of NSAIDs [for which the NSAID use is intended for treatment of signs and symptoms of SLE], corticosteroids [above the baseline dose], antimalarials, and/or immunosuppressants) discontinuation from the investigational product occurs prior to introduction of the new agent
- Patient Decision
  - the patient requests to be withdrawn from the study.

Patients who discontinue the investigational product early will have ETV procedures performed as shown in the Schedule of Activities (Appendix 2) and proceed to the Follow-Up Period of the study.

7.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor CRP and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product.

7.1.4. Patients Lost to Follow-Up

Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site. A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

8. Study Assessments and Procedures

Appendix 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

Appendix 3 lists the laboratory tests that will be performed for this study.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessment Scale

8.1.1.1. SLEDAI-2K

The SLEDAI-2K is a validated global disease activity instrument that focuses on high-impact disease manifestations across 9 organ systems. It includes 24 clinical and laboratory variables with manifestations graded by the affected organ system. CNS: Seizure, Psychosis, Organic Brain Syndrome, Visual Disturbance, Cranial Nerve Disorder, Lupus Headache, CVA; Vascular: Vasculitis; Musculoskeletal: Arthritis, Myositis; Renal: Urinary Casts, Hematuria, Proteinuria, Pyuria; Mucocutaneous: Rash, Alopecia, Mucosal Ulcers; Cardiovascular and Respiratory: Pleurisy, Pericarditis; Immunologic: Low complement, Increased DNA Binding; Constitutional: Fever; Hematologic: Thrombocytopenia, Leukopenia. The primary endpoint in this study will assess remission of arthritis and/or rash as defined by the SLEDAI-2K.

8.1.2. Secondary Efficacy and Exploratory Assessments

8.1.2.1. SLE Responder Index-4 (SRI-4)

The SRI-4 is a composite index used to assess disease activity in SLE. The SLEDAI-2K component is used to capture clinically meaningful improvement in disease activity, while the BILAG and Physician's Global Assessment of Disease Activity components ensure that the improvement in overall disease is not accompanied by disease worsening in other organ systems. SRI-4 response is defined as:

- Reduction of ≥4 points from baseline in SLEDAI-2K score;
- No new BILAG A or no more than 1 new BILAG B disease activity scores; and
- No worsening (defined as an increase of ≥0.3 points [10 mm] from baseline) in Physician's Global Assessment of Disease Activity.

8.1.2.2. Physician's Global Assessment of Disease Activity

The Physician's Global Assessment of Disease Activity is the physician's assessment of the patient's overall disease activity due to SLE, as compared with all possible patients with SLE. The Physician's Global Assessment of Disease Activity is scored using a 100 mm visual analog scale (VAS), where 0 mm (measured from the left starting point of the line) indicates no disease

activity and 100 mm (measured from the left starting point of the line) indicates the most severe disease activity possible for all patients with SLE (or death). The Physician's Global Assessment of Disease Activity score is indicated by making a vertical tick mark on the line between 0 and 100 mm. There are benchmarks of 0 (0 mm), 1 (33 mm), 2 (67 mm), and 3 (100 mm) on the line corresponding to no, mild, moderate, and severe SLE disease activity, respectively.

8.1.2.3. BILAG2004

The BILAG2004 index is a validated global disease activity index designed on the basis of the physician's intention to treat (ITT), focusing on changes in disease manifestations (not present, improving, same, worse, or new) occurring in the last 4 weeks compared with the previous 4 weeks. The instrument assesses 97 clinical signs, symptoms, and laboratory parameters across 9 organ system domains: constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal, and hematology. A BILAG A disease activity score is severe disease activity requiring high-dose oral or IV corticosteroids, immunomodulators, or high-dose anticoagulation along with high-dose corticosteroids or immunomodulators. A BILAG B disease activity score is moderate disease activity requiring low-dose oral corticosteroids, intramuscular or intra-articular corticosteroid injections, topical corticosteroids or immunomodulators, antimalarials, or symptomatic therapy. BILAG C corresponds to stable mild disease, BILAG D is inactive disease that was active previously, and BILAG E indicates the system was never involved.

8.1.2.4. 28 Tender Joint Count & 28 Swollen Joint Count

The 28 joints to be examined and assessed as tender or not tender for tender joint count and as swollen or not swollen for swollen joint count include 14 joints on each side of the patient's body: the 2 shoulders, the 2 elbows, the 2 wrists, the 10 metacarpophalangeal joints, the 2 interphalangeal joints of the thumb, the 8 proximal interphalangeal joints, and the 2 knees.

8.1.2.5. Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)

The CLASI is a validated scale used to assess cutaneous manifestations of SLE consisting of 2 scores. The first summarizes the activity of the disease while the second is a measure of the damage done by the disease. Activity is scored on the basis of erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss, and nonscarring alopecia. Damage is scored in terms of dyspigmentation and scarring, including scarring alopecia.

8.1.2.6. SLEDAI Flare Index (SFI)

The SFI uses the SLEDAI-2K score, disease activity scenarios, treatment changes, and Physician's Global Assessment of Disease Activity to define mild/moderate and severe flares. The index takes into account the absolute change in total scores, new or worsening symptoms, and increases in medication use or hospitalization due to the disease activity.

8.1.2.7. SLICC/ACR Damage Index

The SLICC/ACR damage index is scored on 41 items representing damage to 12 organ systems. The index records damage occurring in patients with SLE regardless of its cause and includes specific comorbidities associated with SLE that may be due to treatment-related toxicity.

8.1.3. Appropriateness of Assessments

All assessments made in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant.

8.2. Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each patient's preexisting conditions, except SLE, as it is the disease under treatment in the study. In addition, site personnel will record via eCRF any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, studied disease state, and/or investigational product via eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

8.2.1. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment

Although all AEs after signing the ICF are recorded in the eCRF, SAE reporting begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient summary eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

8.2.2. Adverse Events and Laboratory Tests of Special Interest (AESIs)

Adverse events of special interest (AESIs) or laboratory results of special interest will include severe or opportunistic infections; myelosuppressive events of anemia, leukopenia, neutropenia, lymphopenia, and thrombocytopenia; thrombocytosis; and elevations in ALT or AST (>3 x ULN) and total bilirubin (>2 x ULN).

8.2.2.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording

and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

8.2.2.2. Reasonably Anticipated Serious Adverse Events

In the SLE population, the occurrence of renal failure/nephropathy, major cerebrocardiovascular events (including cardiovascular—death, MI, hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock due to MI, coronary revascularization procedure; neurologic—stroke; and peripheral vascular events), skeletal-related events (including osteoporosis), SLE flares, and serious infections are reasonably anticipated due to the disease state, comorbid conditions, and use of concomitant medications. The serious instances of these reasonably anticipated AEs will be reviewed in aggregate on a regular periodic basis to evaluate any numerical imbalances between treatment groups in SAEs for reporting to the Food and Drug Administration in the US.

8.2.3. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

8.3. Treatment of Overdose

Refer to the IB.

8.4. Safety Assessments

8.4.1. Electrocardiograms

For each patient, 12-lead standard ECGs should be collected locally according to the Schedule of Activities (Appendix 2). Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational treatment should be reported to Lilly or its designee as an AE via eCRF.

8.4.2. Vital Signs

For each patient, vital signs measurements should be conducted according to the Schedule of Activities (Appendix 2).

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the patient receives the first dose of investigation product should be reported to Lilly or its designee as an AE via eCRF.

8.4.3. Laboratory Tests

For each patient, laboratory tests detailed in (Appendix 3) should be conducted according to the Schedule of Activities (Appendix 2).

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE via eCRF.

8.4.4. Hepatitis B Virus (HBV) DNA Monitoring

HBV DNA testing will be performed in enrolled patients who tested positive for HBcAb at screening. Patients who are HBcAb positive and HBV DNA negative (undetectable) at Visit 1 will require HBV DNA monitoring every 3 months and at the patient's last visit, regardless of their HBsAb status.

If the HBV DNA result is above the LLOQ, then the patient should be referred to a hepatology specialist immediately. In selected cases, investigators may temporarily continue investigation product in accordance with current immunomodulator management in the setting of HBV DNA positivity. This option may be considered in consultation with the sponsor (or its designee) and evaluation of individual patient risks and benefits.

If a single result of "target detected" is obtained (a result above the LLOQ), the test should be repeated within approximately 2 weeks. If the repeat test result is "target not detected," monitoring may resume according to the Schedule of Activities.

For study sites in Japan (or elsewhere if required), if a patient is HBcAb positive and/or HBsAb positive and negative for HBV DNA at Visit 1, HBV DNA needs to be checked at least monthly and at the patient's last visit.

8.4.5. Chest X-ray and Tuberculosis Testing

A posterior-anterior view chest x-ray will be obtained locally, unless results from a chest x-ray obtained within 6 months prior to the study are available. The chest x-ray will be reviewed by the investigator or his/her designee to exclude patients with active TB infection. In addition, patients will be tested at screening and entry for evidence of active or latent TB as described in the Exclusion Criteria (Section 5.2).

8.4.6. Quick Inventory of Depressive Symptomatology Self-Rated–16 (QIDS-SR$_{16}$)

The QIDS-SR$_{16}$ is a 16-item, self-report instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (APA 1994). Patients are asked to consider each statement as it relates to the way they have felt for the past 7 days. There is a 4-point scale for each item ranging from 0 to 3. The 16 items corresponding to 9 depression domains are summed to give a single score ranging from 0 to 27, with higher scores denoting greater symptom severity. The domains assessed by the instrument include: sad mood, concentration,

self-criticism, suicidal ideation, interest, energy/fatigue, sleep disturbance (initial, middle, and late insomnia or hypersomnia), decrease/increase in appetite/weight, and psychomotor agitation/retardation. Additional information and the QIDS-SR_{16} questions may be found on the University of Pittsburgh Epidemiology Data Center web site (Inventory of Depressive Symptomatology/Quick Inventory of Depressive Symptomatology [WWW]) (Rush et al. 2003; Trivedi et al. 2004).

8.4.7. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

The Lilly CRP will monitor safety data throughout the course of the study. Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP will, as is appropriate, consult with the functionally independent Global Patient Safety (GPS) therapeutic area physician or clinical scientist and periodically review trends in safety data and laboratory analytes. Any concerning trends in frequency or severity noted by an investigator and/or Lilly or its designee may require further evaluation.

All deaths and SAE reports will be reviewed in a blinded manner by Lilly during the clinical trial. These reports will be reviewed to ensure completeness and accuracy but will not be unblinded to Lilly during the clinical trial. If a death or clinical AE is deemed serious, unexpected, and possibly related to investigational product, only Lilly GPS will be unblinded for regulatory reporting and safety monitoring purposes. These measures will preserve the integrity of the data collected during this trial and minimize any potential for bias while providing for appropriate safety monitoring.

If a study patient experiences elevated ALT ≥3 x ULN, ALP ≥2 x ULN, or elevated TBL ≥2 x ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests (see Appendix 4).

8.5. Pharmacokinetics

Blood samples for PK analyses will be collected from all randomized patients in accordance with the Schedule of Activities (Appendix 2). Plasma samples will be assayed for baricitinib using a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method at a laboratory approved by Lilly or its designee.

On the day of Visit 2, after completion of baseline assessments (including baseline laboratory tests as outlined in the Schedule of Activities) and administration of investigational product, a single PK sample will be collected 15 to 30 minutes postdose. It is important that apart from this single PK sample, all other baseline laboratory samples are taken PREdose.

On the day of Visit 4 and Visit 7, a single predose PK sample will be collected for each visit. Patients will be advised not to take their investigational product prior to visiting the clinic. To reduce the number of blood draws, the predose PK sample may be drawn at the same time as other routine labs required at that visit. Patients can subsequently take their investigational product at any time during their visit to the clinic. The patient should be instructed to take a dose of investigational product from the new packages assigned at that visit. If a patient arrives at the clinic on the day of Visit 4 or Visit 7 after having taken the dose, the PK sample should be drawn with other routine labs randomly at any time postdose; the inability to collect predose samples will not be considered a protocol violation.

On the day of Visit 5, one PK sample will be taken between 1 and 3 hours postdose. The visit should be scheduled to accommodate this sampling. Patients will be advised to record the exact time when the dose was taken at home and report it to the site personnel. Alternatively, patients may take their investigational product upon arrival to the clinic for their visit. To reduce the number of blood draws, the postdose PK sample may be drawn at the same time as other routine labs required at that visit. The inability to collect postdose samples at the specified time will not be considered a protocol violation.

A single PK sample also is to be collected, if possible, from patients who discontinue the study early. In the event of an SAE, up to 2 additional blood samples may be taken at the investigator's discretion. If collected, the PK samples should be collected after the reported event, approximately 6 hours apart and within 24 hours of the patient's last dose.

For any PK samples taken, the actual date and time of PK sample collection and the date and time of last 2 doses prior to the PK sample should be recorded. PK samples will be kept in storage at a laboratory facility designated by Lilly or its designee. Only samples from active doses will be assayed (PK samples from patients on placebo will not be assayed). PK samples may also be assayed for additional exploratory analyses. Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following the last patient visit for the study.

8.6. Pharmacodynamics

Plasma, serum, and urine samples will be collected for evaluation of pharmacodynamic (PD) markers, including, but not limited to anti-dsDNA, complement, anti-Sm, anti-RNP, anti-SSA/Ro, and anti-SSB/La.

The markers will not include any markers of the patient's genetic makeup. Samples will be collected at the times noted in the Schedule of Activities.

Bioanalytical samples collected to measure PD markers will be identified by the patient number (coded) and retained for a maximum of 1 year following last patient visit for the study at a facility selected by Lilly or its designee.

8.7. Genetics

8.7.1. Whole Blood Sample for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Appendix 2) where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to baricitinib and to investigate genetic variants thought to play a role in SLE. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs)/investigational review boards (IRBs) impose shorter time limits, at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of baricitinib or after baricitinib become(s) commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, and candidate gene studies. Regardless of technology utilized genotyping data generated will be used only for the specific research scope described in this section.

8.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

Serum, plasma, urine, and whole blood RNA samples for non-pharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Appendix 2) where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to baricitinib, pathways associated with SLE, IFN signature, mechanism of action of baricitinib, and/or research method or in validating diagnostic tools or assay(s) related to SLE.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained for a maximum 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits, at a facility selected by

Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of baricitinib or after baricitinib becomes commercially available.

8.9. Health Outcomes

The self-reported questionnaires will be administered prior to any clinical assessments according to the Schedule of Activities (Appendix 2) in countries where the questionnaires have been translated into the native language of the region and linguistically validated. These instruments will be captured at the site via an electronic patient-reported outcomes (ePRO) device.

8.9.1. Patient's Global Assessment of Disease Activity

The Patient's Global Assessment of Disease Activity is a single-item, patient reported scale developed for the assessment of the patient's overall rating of their disease activity due to SLE. The scale measures disease activity through a 5 point Likert scale ranging from 0 ("No disease activity") to 4 ("Severe disease activity") at its worst over the past 7 days (Felson et al. 1993; van Tuyl and Boers 2012).

8.9.2. Brief Pain Inventory (BPI)–Worst Pain Numeric Rating Scale (NRS)

The BPI-sf modified is a 5-item, self-administered questionnaire developed for the rapid assessment of pain, and provides information on the intensity of pain (the sensory dimension) as well as the degree to which pain interferes with function (the reactive dimension). The BPI-sf modified also asks questions about pain relief, pain quality, and the patient's perception of the cause of pain. The worst pain item of the BPI-sf modified is a 1-item, self-administered question developed for the rapid assessment of pain intensity. The worst pain item uses an 11-point scale from 0 ("No pain") to 10 ("Pain as bad as you can imagine") NRS. Since pain can be quite variable over a day, the worst pain item asks patients to rate their pain at its worst over the past 7 days (Cleeland 1991; Cleeland and Ryan 1994).

8.9.3. Brief Pain Inventory (BPI)–Worst Joint Pain NRS

The worst joint pain item is adapted from the worst pain item of the BPI-sf modified. It is a single-item, self-administered question developed for the rapid assessment of pain intensity of the joints. The worst joint pain item uses an 11-point scale from 0 ("No joint pain") to 10 ("Joint pain as bad as you can imagine") NRS. Since pain can be quite variable over a day, the worst joint pain item asks patients to rate their joint pain at its worst over the past 7 days (Cleeland1991; Cleeland and Ryan 1994).

8.9.4. Brief Fatigue Inventory (BFI)–Worst Fatigue NRS

The BFI is a brief patient-reported questionnaire for the rapid assessment of fatigue severity and the impact of fatigue on daily functioning. The BFI contains 10 items; however, the first item is not included in the overall scoring of the scale as it asks about usual fatigue over the past week with the respondent answering "yes" or "no." The remaining 9 items assess fatigue severity

(3 items) and impact of fatigue on daily functioning (6 items). The worst fatigue item of the BFI is a brief patient-reported question for the rapid assessment of worst fatigue severity. The item features an 11-point numeric scale (0 ["No fatigue"] to 10 ["Fatigue as bad as you can imagine"]) and asks patients to rate their fatigue at its worst over the past 7 days. The BFI is implemented without a user manual. The instructions for the completion are embedded within the questionnaire, and patients will read the instructions before responding to the corresponding item (Mendoza et al. 1999; Wolfe 2004).

8.9.5. Short-Form 36-item Health Survey v2 (SF-36)

The SF-36v2 Acute measure is a subjective, generic, health-related quality of life instrument that is patient-reported and consists of 36 questions covering 8 health domains: physical functioning, bodily pain, role limitations due to physical problems, role limitations due to emotional problems, general health perceptions, mental health, social function, and vitality. Each domain is scored by summing the individual items and transforming the scores into a 0 to 100 scale with higher scores indicating better health related quality of life. In addition, 2 summary scores, the PCS and the MCS, will be evaluated based on the 8 SF-36v2 Acute domains. The acute version of this instrument has a 1 week recall period (Brazier et al. 1992; Ware and Sherbourne 1992).

9. Statistical Considerations and Data Analysis

9.1. Determination of Sample Size

Approximately 300 patients will be randomized in a 1:1:1 ratio to the baricitinib 4-mg, 2-mg, and placebo treatment groups. With 100 patients per treatment group, this study will have approximately 81% power to detect a difference between baricitinib 4-mg or 2-mg and placebo of ≥20% in remission rates of rash and/or arthritis at Week 24. The sample size was determined based on the chi-square test with 2-sided type I error of 5% and 40% remission rate of rash and/or arthritis in placebo treatment group. The sample size calculation was performed using nQuery® Advisor 7.0 software.

9.2. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company.

Efficacy analyses will be conducted on the modified intent-to-treat (mITT) population. This set includes all data from all randomized patients receiving at least 1 dose of the investigational product according to the treatment the patients were assigned.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated.

Any change to the planned data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

The SAP will provide analysis details.

9.2.1. General Considerations for Analyses

In general, continuous data will be summarized in terms of the mean, standard deviation, minimum, maximum, median, and number of observations. Categorical data will be summarized as frequency counts and percentages.

Comparisons between the baricitinib 4-mg or baricitinib 2-mg and placebo groups will be performed for all analyses for the Double-Blinded Treatment Period. No adjustment for multiplicity will be done for these comparisons.

Treatment comparisons of categorical efficacy variables will be made using a logistic regression analysis with treatment, baseline disease activity (SLEDAI-2K <10 versus SLEDAI-2K ≥10), baseline anti-dsDNA status (positive; negative), and region in the model. The proportions and 95% confidence interval (CI) will be reported. Missing data will be imputed using the NRI method.

Treatment comparisons of continuous efficacy and health outcome variables will be made using mixed-effects models for repeated measures (MMRM) model with treatment, baseline score,

baseline disease activity (SLEDAI-2K <10 versus SLEDAI-2K ≥10), baseline anti-dsDNA status (positive; negative), region, visit, and the interaction of treatment-by-visit as fixed factors. An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. Type III sums of squares for the least squares (LS) means will be used for the statistical comparison; the 95% CI will also be reported. Treatment group comparisons with placebo at Week 24 and other visits will be tested.

Fisher exact test will be used for all AE, baseline, discontinuation, and other categorical safety data. Continuous vital signs and laboratory values will be analyzed by an analysis of covariance (ANCOVA) with treatment and baseline values in the model. Other continuous safety variables will be analyzed based on t-tests, or as otherwise stated.

9.2.2. Analysis Populations

Unless otherwise specified, the efficacy, health outcomes, and safety analyses will be conducted on the mITT population, defined as all randomized patients who received at least one dose of investigational product, even if the patient does not receive the correct treatment, or otherwise does not follow the protocol. Patients will be analyzed according to the treatment to which they were assigned. Significant protocol violations will be described in the SAP.

Safety analyses for the post-treatment Follow-up Period will be conducted on the follow-up population, defined as all randomized patients who received at least 1 dose of investigational product and have entered the post-treatment Follow-Up Period. Patients will be analyzed according to the dosing regimen to which they were assigned in the Treatment Period.

9.2.3. Baseline Definition

Baseline will be defined as the last available value before the first dose of investigational product for both efficacy and safety analyses. In most cases, this will be the measure recorded at Week 0 (Visit 2). Change from baseline will be calculated as the visit value of interest minus the baseline value. For the post-treatment Follow-up Period, the baseline is defined as the last nonmissing assessment on or prior to entering the post-treatment Follow-up Period, that is, on or prior to the Week 24 visit (Visit 9), or the end of treatment visit (including ETV).

9.2.4. Missing Data Imputation

The patients will be considered nonresponders for the NRI analysis if they do not meet the clinical response criteria (for example, remission of rash/arthritis, SRI-4) at Week 24. All nonresponders at Week 24 as well as all patients who discontinue study treatment at any time prior to Week 24, for any reason, will be defined as nonresponders for the NRI analysis for all categorical analyses at Week 24. Patients who require initiation or increase in dose of NSAIDs, corticosteroids, antimalarials, or immunosuppressants after randomization (as outlined in Section 6.8, Concomitant Therapy) will be analyzed as nonresponders from the day of initiation or increase in medication. Randomized patients without at least 1 postbaseline observation will also be defined as nonresponders for the NRI analysis. MMRM is the primary analysis method for analyzing the continuous efficacy endpoints. In this method no imputation is needed. However, a sensitivity analysis, the placebo multiple imputation (pMI) method will be used for

the selected analyses of the continuous endpoints at Visit 9 (Week 24). The pMI assumes that the statistical behavior of drug- and placebo-treated patients after discontinuing investigational product becomes that of placebo-treated patients.

9.2.5. Adjustment for Multiple Comparisons

No adjustment for multiple comparisons will be done.

9.2.6. Adverse Events/Laboratory Results of Special Interest

Adverse events or laboratory results of special interest include severe or opportunistic infections, myelosuppressive events of anemia, leukopenia, neutropenia, lymphopenia, thrombocytopenia, thrombocytosis; and elevations in ALT/AST (≥3 x ULN) and total bilirubin (≥2 x ULN). The number of AESIs as well as the percentage of patients who experienced at least 1 AESI will be summarized by treatment group.

9.3. Treatment Group Comparability

9.3.1. Patient Disposition

A detailed description of patient disposition by treatment will be summarized with reasons for discontinuation.

9.3.2. Patient Characteristics

Summary tables by treatment group will be generated for demographics and patient characteristics at baseline (Visit 2), for historic diagnoses, and for preexisting conditions.

9.3.3. Concomitant Therapy

Concomitant therapy will be summarized and reported for the Double-Blinded Treatment Period. A listing of patients using excluded medications during the period will be provided.

9.3.4. Treatment Compliance

Compliance to therapy will be reported for the Double-Blinded Treatment Period as described in Section 6.7.

9.4. Primary and Secondary Analyses

9.4.1. Primary Analyses

The primary endpoint is the proportion of patients who achieve remission of arthritis and/or rash as defined by the SLEDAI-2K at Week 24. Either arthritis or rash (as defined by the SLEDAI-2K) are required to be present at baseline. If only arthritis is present at baseline, then arthritis has to be absent at Week 24 to meet the primary endpoint. If only rash is present at baseline, then rash has to be absent at Week 24 to meet the primary endpoint. If both arthritis and rash are present at baseline, then the primary endpoint is met if either arthritis, or rash, or both arthritis and rash are absent at Week 24.

Treatment comparison between baricitinib dose regimens (4-mg or 2-mg) and placebo in the proportion of patients achieving remission of arthritis and/or rash at Week 24 (Visit 9) will be analyzed using the logistic regression analysis with treatment and baseline disease activity (SLEDAI-2K <10 versus SLEDAI-2K ≥10), baseline anti-dsDNA status (positive; negative), and region in the model. The proportions and 95% CI will be reported. Missing data will be imputed using the NRI method.

9.4.2. Secondary Analyses

Treatment comparison between baricitinib dose regimens (4-mg or 2-mg) and placebo for the change from baseline in SLEDAI-2K score at Week 24, and the change from baseline in patient's global assessment of disease activity at Week 24 will be analyzed using MMRM method with treatment, baseline disease activity (SLEDAI-2K <10 versus SLEDAI-2K ≥10), baseline anti-dsDNA status (positive; negative), region, visit, and the interaction of treatment-by-visit as fixed factors. An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. Type III sums of squares for the LS means will be used for the statistical comparison; the 95% CI will also be reported. Treatment group comparisons with placebo at Week 24 and other visits will be tested.

Treatment comparison between baricitinib dose regimens (4-mg or 2-mg) and placebo for the proportion of patients achieving a SRI-4 response and for the proportion of patients achieving a reduction of ≥4 points in SLEDAI-2K score at Week 24 will be analyzed using the logistic regression model with treatment, baseline disease activity (SLEDAI-2K <10 versus SLEDAI-2K ≥10), baseline anti-dsDNA status (positive; negative), and region in the model. The proportions and 95% CI will be reported. Missing data will be imputed using the NRI method.

9.4.3. Exploratory Analyses

Study JAHH exploratory analyses are summarized in Table JAHH.4. Details of the exploratory analyses will be outlined in the SAP.

Table JAHH.4. Study JAHH Exploratory Analyses

Efficacy/Safety Measures	Variable	Analysis
SLEDAI-2K	Change in proportion of patients who achieve remission of arthritis and/or rash at Week 12	Logistic Regression
28 Tender/Swollen Joint Count	Change in number of joints affected by SLE arthritis at Week 12 and Week 24 compared to baseline	MMRM
	Change in proportion of patients with ≥50% reduction in number of joints affected by SLE arthritis at Week 12 and Week 24 compared to baseline	Logistic Regression
CLASI Activity Score	Change at Week 12 and Week 24 compared to baseline	MMRM
	Change in proportion of patients with ≥50% reduction at Week 12 and Week 24 compared to baseline	Logistic Regression
Physician Global Assessment of Disease Activity	Change at Week 12 and Week 24 compared to baseline	MMRM
SLEDAI Flare Index (SFI)	Proportion of patients experiencing severe, mild/moderate, or any severity flare	Logistic Regression
	Time to first severe, mild/moderate, or any severity flare	Kaplan-Meier Product Limit
SLICC/ACR Damage Index Score	Change at Week 24 compared to baseline	MMRM
Corticosteroid Sparing	Change in proportion of patients receiving ≥10mg/day prednisone at baseline able to reduce prednisone (or equivalent) dose ≤7.5 mg/day for 12 consecutive weeks between Week 12 and Week 24	Logistic Regression
Serologic Markers	The difference in reduction of IFN signature between treatment groups at Week 12 and Week 24 compared to baseline	MMRM
	Change in anti-dsDNA level at Week 12 and Week 24 compared to baseline in patients with elevated anti-dsDNA at baseline	MMRM
	Change in C3 and C4 levels at Week 12 and Week 24 compared to baseline in patients with low C3 and C4 at baseline	MMRM

Abbreviations: ACR = American College of Rheumatology; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; dsDNA = double-stranded deoxyribonucleic acid; IFN = interferon; MMRM = mixed-effects models for repeated measures; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC = Systemic Lupus Erythematosus International Collaborating Clinics.

Note: Additional methods may be used for analysis as deemed appropriate.

9.5. Safety Analyses

All safety data will be descriptively summarized by treatment groups and analyzed based on the mITT population. The safety analyses include AEs, laboratory analytes, QIDS-SR_{16}, and vital signs. The duration of dosing exposure will also be summarized. For the Double-Blinded Treatment period, the safety data will be summarized and analyzed with pairwise comparisons between each baricitinib dose and placebo. For the post-treatment Follow-Up Period, safety data will be summarized according to the dosing regimen to which they were assigned during the

treatment period. The categorical safety measures will be summarized with incidence rates and analyzed by Fisher exact test. The mean change in the continuous safety measures of the vital signs, QIDS-SR_{16}, physical characteristics, and laboratory values will be summarized by visits and analyzed by ANCOVA with treatment and baseline values in the model. Other continuous safety variables will be analyzed by t-tests, unless otherwise stated. Missing values will be imputed by modified last observation carried forward (mLOCF) for continuous vital signs and QIDS-SR_{16} safety variables.

9.5.1. Adverse Events

Adverse events are classified based upon the Medical Dictionary for Regulatory Activities (MedDRA). An overall summary of AEs will be provided for the Double-Blinded Treatment Dosing Period. Fisher exact test will be used to perform treatment comparisons between each baricitinib group and placebo.

Treatment-emergent adverse events (TEAEs) are defined as AEs that first occurred or worsened in severity on or after the date of the first dose of investigational product. The number of TEAEs as well as the number and percentage of patients who experienced at least 1 TEAE will be summarized using MedDRA for each system organ class (or a body system) and each preferred term by treatment group. For events that are gender-specific, the denominator and computation of the percentage will only include patients from the given gender. TEAEs will also be summarized by relationship to investigational product and by severity within each treatment group. Fisher exact test will be used to perform treatment comparisons between each baricitinib group and placebo.

SAEs including deaths, treatment-emergent AESIs, and AEs that lead to investigational product discontinuation will also be summarized using MedDRA for each system organ class and each preferred term by treatment group. Fisher exact test will be used to perform treatment comparisons between each baricitinib group and placebo.

A follow-up emergent adverse event (FEAE) is defined as an event that first occurred or worsened in severity after the date of the Week 24 visit (Visit 9) or the ETV. Follow-up emergent AEs (all, by maximum severity, and FEAEs possibly related to investigational product by the investigator) will be summarized by MedDRA system organ class and preferred term.

9.5.2. Clinical Laboratory Tests

All clinical laboratory results will be descriptively summarized by treatment group. Individual results that are outside the normal reference ranges will be flagged in data listings. Quantitative clinical hematology, chemistry, and urinalysis variables obtained at the baseline to postbaseline visits will be summarized as changes from baseline by treatment group and analyzed using ANCOVA with treatment and baseline value in the model. Categorical variables, including the incidence of abnormal values and incidence of AESIs, will be summarized by frequency and percentage of patients in corresponding categories. Shift tables will be presented for selected measures.

9.5.3. Vital Signs, Physical Findings, and Other Safety Evaluation

Observed values and changes from baseline (predose or screening if missing) for vital signs, QIDS-SR_{16}, and physical characteristics will be descriptively summarized by treatment group and visit.

Change from baseline to postbaseline in vital signs, QIDS-SR_{16}, and physical characteristics will be analyzed using ANCOVA with treatment and baseline value in the model.

9.6. Pharmacokinetic/Pharmacodynamic Analyses

Sparse blood samples will be collected at selected visits for population PK analyses. PD endpoints will include both efficacy and safety measures including, but not limited to, for example, SLEDAI-2K, hemoglobin, and neutrophil count. Samples for inflammatory and exploratory biomarkers will also be collected.

PK data for baricitinib will be analyzed using a population approach via nonlinear mixed effects modeling (NONMEM) with the NONMEM software. PopPK parameters will be examined for relationships with dose, renal function, and patient factors including but not limited to age, weight, and sex. Empirical Bayesian estimates of clearance will be used to calculate individual estimates of area under the plasma concentration-time curve (AUC).

Time-course models of the relationship between exposure and efficacy (SLEDAI-2K) as well as safety laboratory measures (such as hemoglobin and neutrophil counts) will be explored. Evaluations of covariate effects (such as age, sex, renal function, baseline values, and so on) on PK/PD relationships may also be evaluated. Other exploratory analyses, such as the relationship between baricitinib exposure and biomarkers of pharmacologic activity, may be undertaken as deemed appropriate.

The relationship between dose/predicted concentrations and efficacy (such as SLEDAI-2K) and key safety markers (such as hematological endpoints) will be explored.

9.7. Other Analyses

9.7.1. Health Outcomes

The analyses of health outcome measures include the Patient's Global Assessment of Disease Activity, worst pain, worst joint pain, worst fatigue, and SF-36. The categorical and continuous health outcome variables will be analyzed using logistic and MMRM methods, respectively. The analyses will be based on the mITT population, unless otherwise specified.

More detailed analytical methods will be described in the SAP.

9.7.2. Subgroup Analyses.

Subgroup analysis may be conducted on the primary endpoint and selected secondary endpoints. Subgroups to be evaluated may include gender, age, race, disease severity, region, exploratory biomarkers, and background SoC therapy. The definitions for the levels of the subgroup

variables and the analysis methodology will be provided in the SAP. Additional subgroup analyses may be performed as deemed appropriate.

9.8. Interim Analyses

No interim analyses (IA) are planned for this study. If an unplanned IA is deemed necessary, the appropriate Lilly medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol. Adjustments to type I error will be made in case an unplanned IA for efficacy is performed.

10. Study Governance Considerations

10.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

10.1.1. Informed Consent

The investigator is responsible for ensuring:

- that the patient understands the potential risks and benefits of participating in the study
- that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

10.1.2. Ethical Review

The investigator must give assurance that the ERB was properly constituted and convened as required by International Conference on Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERB(s) should be provided with the following:

- the current IB and updates during the course of the study
- ICF
- relevant curricula vitae.

10.1.3. Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third-party.

10.1.4. Investigator Information

Physicians with a specialty in rheumatology will participate as investigators in this clinical trial. Physicians with other specialties and experience in treatment of patients with SLE may also participate as investigators.

10.1.5. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

10.1.6. Final Report Signature

Lilly will select a qualified investigator(s) from among investigators participating in the design, conduct, and/or analysis of the study to serve as the CSR coordinating investigator. If this investigator(s) is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The CSR coordinating investigator(s) will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

10.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its

representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

10.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Electronic patient-reported outcome (ePRO) measures are entered into an ePRO instrument at the time that the information is obtained. In these instances where there is no prior written or electronic source data at the site, the ePRO instrument record will serve as the source.

If ePRO records are stored at a third party site, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the ePRO instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

10.3. Study and Site Closure

10.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.3.2. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

11. References

Bauer JW, Baechler EC, Petri M, Batliwalla FM, Crawford D, Ortmann WA, Espe KJ, Li W, Patel DD, Gregersen PK, Behrens TW. Elevated serum levels of interferon-regulated chemokines are biomarkers for active human systemic lupus erythematosus. *PLoS Med.* 2006;3(12),e491:2274-2284.

Bauer JW, Petri M, Batliwalla FM, Koeuth T, Wilson J, Slattery C, Panoskaltsis-Mortari A, Gregersen PK, Behrens TW, Baechler EC. Interferon-regulated chemokines as biomarkers ofsystemic lupus erythematosus disease activity: a validation study. *Arthritis Rheum.* 2009;60(10):3098–3107.

Berthier CC, Bethunaickan R, Gonzalez-Rivera T, Nair V, Ramanujam M, Zhang W, Bottinger EP, Segerer S, Lindenmeyer M, Cohen CD, Davidson A, Kretzler M. Cross-species transcriptional network analysis defines shared inflammatory responses in murine and human lupus nephritis. *J Immunol.* 2012;189(2):988-1001.

Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, Westlake L. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ.* 1992;305(6846):160-164.

Brosius FC, Tuttle KR, Adler SG, Kretzler M, Mehta RL, Tumlin JA, Duffin KL, Haas JV, Liu J, Silk ME, Macias WL, Janes JM. Baricitinib in diabetic kidney disease: biomarker analysis from a Phase 2, randomized, double-blind, placebo-controlled study [abstract]. In: American Society of Nephrology Kidney Week; 2015 Nov 3-8; San Diego, CA. *J Am Soc Nephrol.* 2015;26(Suppl). Abstract TH-OR034.

Bruce IN, O'Keeffe AG, Farewell V, Hanly JG, Manzi S, Su L, et al. Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort. *Ann Rheum Dis.* 2015;74(9):1706-1713.

Chaussabel D, Quinn C, Shen J, Pinakeen P, Glaser C, Baldwin N, et al. A modular analysis framework for blood genomics studies: application to systemic lupus erythematosus. *Immunity.* 2008;29:150-164.

Cleeland C. Pain assessment in cancer. In: Osoba D, ed. *Effect of Cancer on Quality of Life*. Boca Raton: CRC Press, Inc.; 1991:293-305.

Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore.* 1994;23(2):129-138.

Cooper GS, Treadwell EL, St.Clair EW, Gilkeson GS, Dooley MA. Sociodemographic associations with early disease damage in patients with systemic lupus erythematosus. *Arthritis Rheum*. 2007;57(6):993-999.

Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, Furst D, Goldsmith C, Kieszak S, Lightfoot R, Paulus H, Tugwell P, Weinblatt M, Widmark R, Williams HJ, Wolfe F. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *Arthritis Rheum*. 1993;36(6):729-740.

Fridman JS, Scherle PA, Collins R, Burn TC, Li Y, Li J, et al. Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050. *J Immunol.* 2010;184(9):5298-5307.

Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18(6):499-502.

Furie R, Merrill JT, Werth VP, Khamashta M, Kalunian K, Brohawn P, Illei G, Drappa J, Wang L, Yoo S. Anifrolumab, an anti-interferon alpha receptor monoclonal antibody, in moderate to severe systemic lupus erythematosus (SLE) [abstract]. In: 2015 ACR/ARHP Annual Meeting; 2015 Nov 7-11; San Francisco, CA. *Arthritis Rheum.* 2015;67(S10):S3865-3866. Abstract number 3223.

Gonzalez-Navajas JM, Lee J, David M, Raz E. Immunomodulatory functions of type I interferons. *Nat Rev Immunol*. 2012;12(2):125-135.

Higgs BW, Liu Z, White B, Zhu W, White WI, Morehouse C, Brohawn P, Kiener PA, Richman L, Forentino D, Greenberg SA, Jallal B, Yao Y. Patients with systemic lupus erythematosus, myositis, rheumatoid arthritis and scleroderma share activation of a common type I interferon pathway. *Ann Rheum Dis*. 2011;70:2029-2036.

Hochberg MC, for the Diagnostic and Therapeutic Criteria Committee of the American College of Rheumatology. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. *Arthritis Rheum*. 1997;40:1725.

Isenberg DA, Petri M, Kalunian K, Tanaka Y, Urowitz MB, Hoffman RW, Morgan-Cox M, Iikuni N, Silk M, Wallace DJ. Efficacy and safety of subcutaneous tabalumab in patients with systemic lupus erythematosus: results from ILLUMINATE-1, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. *Ann Rheum Dis.* 2015 Sep 3. pii: annrheumdis-2015-207653. doi: 10.1136/annrheumdis-2015-207653.

Kirou KA, Gkrouzman E. Anti-interferon alpha treatment in SLE. *Clin Immun.* 2013;148(3):303–312.

Klingmüller U, Wu H, Hsiao JG, Toker A, Duckworth BC, Cantley LC, Lodish HF. Identification of a novel pathway important for proliferation and differentiation of primary erythroid progenitors. *Proc Natl Acad Sci USA*. 1997;94(7):3016-3021.

Lauwerys BR, Hachulla E, Spertini F, Lazaro E, Jorgensen C, Mariette X, Haelterman E, Grouard-Vogel G, Fanget B, Dhellin O, Vandepapeliere P, Houssiau FA. Down-regulation of interferon signature in systemic lupus erythematosus patients by active immunization with interferon α-kinoid. *Arthritis Rheum.* 2013;65(2):447-456.

Lim SS, Bayakly AR, Helmick CG, Gordon C, Easley KA, Drenkard C. The incidence and prevalence of systemic lupus erythematosus, 2002-2004: The Georgia Lupus Registry. *Arthritis Rheum*. 2014;66(2):357-368.

Mathian A, Hie M, Cohen-Aubart F, Amoura Z. Targeting interferons in systemic lupus: current and future prospects. *Drugs.* 2015;75:835-846.

Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, Huber SL. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer*. 1999;85(5):1186-1196.

Menter A, Disch D, Clemens J, Janes J, Papp K, Macias W. A Phase 2b trial of baricitinib, an oral JAK inhibitor, in patients with moderate-to-severe psoriasis [abstract]. In: American Academy of Dermatology 72nd Annual Meeting; March 21-25, 2014; Denver (CO). *J Am Acad Dermatol*. 2014;70(5(1)).Abstract AB162.

Merrill JT, van Vollenhoven RF, Buyon JP, Furie RA, Stohl W, Morgan-Cox M, Dickson C, Anderson PW, Lee C, Berclaz PY, Dörner T. Efficacy and safety of subcutaneous tabalumab, a monoclonal antibody to B-cell activating factor, in patients with systemic lupus erythematosus: results from ILLUMINATE-2, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. *Ann Rheum Dis.* 2015 Aug 20. pii: annrheumdis-2015-207654. doi: 10.1136/annrheumdis-2015-207654.

Montealegre G, Reinhardt A, Brogan P, Berkun Y, Zlotogorski A, Brown D, et al. Preliminary response to Janus kinase inhibition with baricitinib in chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures (CANDLE). *Pediatr Rheumatol Online J.* 2015;13(Suppl 1):O31.

Petri M, Orbai A-M, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics Classificiation Criteria for Systemic Lupus Erythematosus. *Arthritis Rheum.* 2012;64(8):2677-2686.

Pons-Estel BA, Catoggio LJ, Cardiel MH, Soriano ER, Gentiletti S, Villa AR, Abadi I, Caeiro F, Alvarellos A, Alarcon-Segovia D. The GLADEL multinational Latin American Prospective Inception Cohort of 1,214 patients with systemic lupus erythematosus ethnic and disease heterogeneity among ‘‘Hispanics.’’ *Medicine.* 2004;83(1):1-17.

Rush AJ, Trivedia MH, Ibrahima HM, Carmody TJ, Arnowc B, Kleind DN, Markowitze JC, Ninanf PT, Kornsteing S, Manberc R, Thaseh ME, Kocsise JH, Kelleri MB. The 16-Item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573-583.

Smiljanovic B, Grun JR, Biesen R, Schulte-Wrede U, Baumgrass R, Stuhlmuller B, Maslinski W, Hiepe F, Burmester G-R, Radbruch A, Haupl T, Grutzkau A. The multifaceted balance of TNF-α and type I/II interferon responses in SLE and RA: how monocytes manage the impact of cytokines. *J Mol Med.* 2012; 90:1295-1309.

Somers EC, Marder W, Cagnoli P, Lewis EE, DeGuire P, Gordon C, Helmick CG, Wang L, Wing JJ, Dhar P, Leisen J, Shaltis D, McCune WJ. Population-based incidence and prevalence of systemic lupus erythematosus. *Arthritis Rheum*. 2014;66(2):369-378.

Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1982;25(11):1271–1277.

Trivedi MH, Rush AJ, Ibrahim HM, Carmody TJ, Biggs MM, Suppes T, Crismon ML, Shores-Wilson K, Toprac MG, Dennehy EB, Witte B, Kashner TM. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick

Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. *Psychol Med*. 2004;34(1):73-82.

Tuttle KR, Brosius FC III, Adler SG, Kretzler M, Mehta RL, Tumlin JA, Liu J, Silk ME, Cardillo TE, Duffin KL, Haas JV, Macias WL, Janes JM. Baricitinib in diabetic kidney disease: results from a phase 2, multicenter, randomized, double-blind, placebo-controlled study [abstract]. In: American Diabetes Association 75th Scientific Sessions; 2015 June 5-9; Boston (MA). *Diabetes.* 2015;64(Suppl 1A). Abstract 114-LB.

University of Pittsburgh Epidemiology Data Center. Inventory of Depressive Symptomatology (IDS)/Quick Inventory of Depressive Symptomatology (QIDS). Available at: http://www.ids-qids.org/. Accessed October 19, 2015.

van Tuyl LHD, Boers M. Patient's Global Assessment of Disease Activity: What are we measuring? *Arthritis Rheum*. 2012;64(9):2811-2813.

Vera J, Millat T, Kolch W, Wolkenhauer O. Dynamics of receptor and protein transducer homodimerisation. *BMC Syst Biol.* 2008;2:92.

Ware JE, Jr, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36): I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-483.

Wolfe F. Fatigue assessments in rheumatoid arthritis: comparative performance of visual analog scales and longer fatigue questionnaires in 7760 patients. *J Rheumatol*. 2004;31(10):1896-1902.

Yurkovich M, Vostretsova K, Chen W, Avina-Zubieta JA. Overall and cause-specific mortality in patients with systemic lupus erythematosus: a meta-analysis of observational studies. *Arthritis Care Res*. 2014;66(4):608-616.

Appendix 1. Abbreviations and Definitions

Term	Definition
ACR	American College of Rheumatology
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BFI	Brief Fatigue Inventory
BPI	Brief Pain Inventory
BILAG	British Isles Lupus Assessment Group
blinding/masking	A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BPI	Brief Pain Inventory
CI	confidence interval
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
CNS	central nervous system
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.

CSR	clinical study report
dsDNA	double-stranded deoxyribonucleic acid
DN	diabetic nephropathy
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ePRO	electronic patient-reported outcome
ERB	ethical review board
ETV	early termination visit
FEAE	follow-up emergent adverse event
FSH	follicle-stimulating hormone
GCP	good clinical practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IA	interim analyses
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IFN	interferon

IM	intramuscular
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRBs	investigational review boards
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous
IVIg	intravenous immunoglobulin
IWRS	interactive web-response system
JAK	Janus kinase
LLN	lower limit of normal
LLOQ	lower limit of quantification
LS means	least squares means
MCS	mental component score
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mITT	modified intent-to-treat
MMRM	mixed-effects models for repeated measures
mRNA	messenger ribonucleic acid
MTX	methotrexate
NONMEM	nonlinear mixed effects modeling
NRI	nonresponder imputation
NRS	numeric rating scale
NSAIDs	nonsteroidal anti-inflammatory drugs

PCS	physical component score
PD	pharmacodynamics(s)
PK	pharmacokinetic(s)
pMI	placebo multiple imputation
popPK/PD	population pharmacokinetics/pharmacodynamics
PPD	purified protein derivative
QD	daily
QIDS-SR$_{16}$	Quick Inventory of Depressive Symptomatology Self-Rated–16
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SF-36	Short-Form 36-item health survey version 2
SFI	SLEDAI Flare Index
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC	Systemic Lupus Erythematosus International Collaborating Clinics
SoC	standard of care
SRI	SLE Responder Index
STAT	signal transducer and activator of transcription
SUSARs	suspected unexpected serious adverse reactions
TB	tuberculosis
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
TSH	thyroid-stimulating hormone

TYK	Tyrosine kinase
UACR	urinary albumin-to-creatinine ratio
ULN	upper limit of normal
WBC	white blood cells

Appendix 2. Schedule of Activities

Schedule of Activities, Protocol I4V-MC-JAHH

	Screening		Double-Blinded Treatment									Follow-Up
Visit Number	**V1**	**V1a[a]**	**V2[b]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ET[c,d]**	**V801[d,e]**
Study Week	**-6**		**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**any**	**28 or last dose + 4 weeks**
Study Day	**-42 to -3**		**1**	**15 ± 3**	**29 ± 4**	**57 ± 4**	**85 ± 4**	**113 ± 4**	**141 ± 4**	**169 ± 4**	**any**	**197 ± 5 or last dose + 28 ± 5 days**
Procedure												
Informed consent	X											
Medical history	X											
Physical examination	X											
Symptom-directed physical examination			X	X	X	X	X	X	X	X	X	X
Previous SLE therapy	X		X									
Patient demographics	X											
Height			X									
Weight	X		X	X	X	X	X	X	X	X	X	X
Waist circumference			X				X			X	X	
Vital signs (BP, pulse, temperature)	X		X	X	X	X	X	X	X	X	X	X
Habits[f]	X											
ECG[g]	X											
Inclusion/exclusion criteria review for entry	X											
Inclusion/exclusion criteria review for enrollment			X									
Administer TB test[h]	X											
Read PPD test if used for TB testing		X										
Chest x-ray[i]	X											
Preexisting conditions	X		X									
Adverse events			X	X	X	X	X	X	X	X	X	X

	Screening		Double-Blinded Treatment									Follow-Up
Visit Number	**V1**	**V1a[a]**	**V2[b]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ET[c,d]**	**V801[d,e]**
Study Week	**-6**		**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**any**	**28 or last dose + 4 weeks**
Study Day	**-42 to -3**		**1**	**15 ± 3**	**29 ± 4**	**57 ± 4**	**85 ± 4**	**113 ± 4**	**141 ± 4**	**169 ± 4**	**any**	**197 ± 5 or last dose + 28 ± 5 days**
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X
Randomization			X									
Log in IWRS	X		X	X	X	X	X	X	X	X	X	X
Investigational product dispensed			X	X	X	X	X	X	X			
Investigational product returned and compliance assessed				X	X	X	X	X	X	X	X	
Clinical Efficacy												
SLEDAI-2K	X		X	X	X	X	X	X	X	X	X	X
BILAG2004			X	X	X	X	X	X	X	X	X	X
SLEDAI Flare Index (SFI)			X	X	X	X	X	X	X	X	X	X
SLICC			X							X	X	
CLASI			X	X	X	X	X	X	X	X	X	X
28-Tender and Swollen Joint counts			X	X	X	X	X	X	X	X	X	X
Physician's Global Assessment of Disease Activity (VAS)			X	X	X	X	X	X	X	X	X	X
Patient's Global Assessment of Disease Activity[j]	X		X	X	X	X	X	X	X	X	X	X
BPI (Worst Pain)[j]	X		X	X	X	X	X	X	X	X	X	X
BPI (Worst Joint Pain)[j]	X		X	X	X	X	X	X	X	X	X	X
BFI (Worst Fatigue)[j]	X		X	X	X	X	X	X	X	X	X	X
SF-36[j]			X				X			X	X	X
QIDS-SR_{16}[j]	X		X	X	X	X	X	X	X	X	X	X
Laboratory Tests												
TSH	X											

	Screening		Double-Blinded Treatment									Follow-Up
Visit Number	**V1**	**V1a[a]**	**V2[b]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ET[c,d]**	**V801[d,e]**
Study Week	**-6**		**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**any**	**28 or last dose + 4 weeks**
Study Day	**-42 to -3**		**1**	**15 ± 3**	**29 ± 4**	**57 ± 4**	**85 ± 4**	**113 ± 4**	**141 ± 4**	**169 ± 4**	**any**	**197 ± 5 or last dose + 28 ± 5 days**
HIV	X											
Hepatitis C antibody testing	X											
Hepatitis B testing (HBsAg, HBcAb, HBsAb)	X											
HBV DNA[k]	X						X			X	X	X
Serum pregnancy test[l]	X		X									
Urine pregnancy test[l]			X	X	X	X	X	X	X	X	X	X
FSH[m]	X											
Clinical chemistry[n]	X		X	X	X	X	X	X	X	X	X	X
Fasting lipid panel[o]			X				X			X		
Hematology	X		X	X	X	X	X	X	X	X	X	X
Iron studies (iron, TIBC, and ferritin)	X						X			X		
hsCRP			X				X			X		
Urinalysis	X		X	X	X	X	X	X	X	X	X	X
ANA	X						X			X		
anti-dsDNA	X		X	X	X	X	X	X	X	X	X	X
Autoantibodies (anti-Sm, anti-RNP, anti-SSA/Ro, anti-SSB/La)			X				X			X		
Antiphospholipid antibodies			X				X			X		
Complement (C3 and C4)	X		X	X	X	X	X	X	X	X	X	X
Immunoglobulins (IgG, IgA, IgM)			X		X		X			X	X	X
Lymphocyte subsets (T, B, NK, and T-cell subsets)			X		X		X			X	X	X

	Screening		Double-Blinded Treatment									Follow-Up
Visit Number	**V1**	**V1a[a]**	**V2[b]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**ET[c,d]**	**V801[d,e]**
Study Week	**-6**		**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**any**	**28 or last dose + 4 weeks**
Study Day	**-42 to -3**		**1**	**15 ± 3**	**29 ± 4**	**57 ± 4**	**85 ± 4**	**113 ± 4**	**141 ± 4**	**169 ± 4**	**any**	**197 ± 5 or last dose + 28 ± 5 days**
Exploratory storage samples (serum and plasma)			X		X		X			X		
Exploratory storage samples (urine)			X		X		X			X		
Exploratory storage samples (RNA)			X	X	X		X			X		
Baricitinib plasma concentrations (PK sample)			X[p]		X[q]	X[r]		X[q]			X[s]	
Pharmacogenetic (DNA) collection			X									

Abbreviations: ANA = antinuclear antibody; BFI = Brief Fatigue Inventory; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; BPI = Brief Pain Inventory; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; dsDNA = double-stranded deoxyribonucleic acid; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HBV DNA = hepatitis B virus deoxyribonucleic acid; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; IWRS = interactive web-response system; PK = pharmacokinetics; PPD = purified protein derivative; QIDS-SR_{16} = Quick Inventory of Depressive Symptomatology Self-Rated-16; RNA = ribonucleic acid; SF-36 = Short-Form 36-item Health Survey; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC = Systemic Lupus Erythematosus International Collaborating Clinics; TB = tuberculosis; TIBC = total iron binding capacity; TSH = thyroid-stimulating hormone; V = visit; VAS = visual analog scale.

[a] For those patients with a PPD placed at Visit 1, Visit 1a must occur 48 to 72 hours post-Visit 1 for PPD to be read. PPD does not need to be read at the site, but must be read by a trained medical professional and results must be presented to the site at Visit 2.

[b] All baseline assessments at Visit 2 must be performed and baseline laboratory samples must be drawn PRIOR to administration of the first dose of investigational product.

[c] Those patients who discontinue from investigational product early should complete the ET visit and proceed to post-treatment follow-up.

[d] The ET visit can serve as Visit 801 if it occurs at least 28 days following the last dose of investigational product.

[e] All patients should return for a post-treatment follow-up visit 28 days after the last dose of investigational product.

[f] Includes recording of habits such as caffeine, alcohol, and tobacco consumption.

[g] ECGs will be performed locally and will be locally (machine) read.

[h] If the PPD test results are positive and the patient has no medical history or chest x-ray findings consistent with active TB, the patient may have a QuantiFERON-TB Gold or T-SPOT.TB test (if available). If the QuantiFERON-TB Gold or T-SPOT.TB test results are not negative, the patient will be

considered to have latent TB. If the QuantiFERON-TB Gold or T-SPOT.TB test is available and, in the judgment of the investigator, is preferred as an alternative to the PPD skin test for the evaluation of TB infection, it may be used instead of the PPD TB test. If the QuantiFERON-TB Gold or TSPOT.TB test is positive, the patient will be considered to have latent TB. If the test is not negative, the test may be repeated once within 2 weeks of the initial value. If the repeat test results are again not negative, the patient will be considered to have latent TB.

[i] A chest x-ray will be taken at screening unless one has been obtained within 6 months prior to the study (provided the x-ray and/or report are available for review).

[j] Patient-reported questionnaires will be administered via an electronic patient-reported outcomes (ePRO) device and should be administered prior to any clinical assessments.

[k] HBV DNA testing will be performed in patients who tested positive for HBcAb at screening. Patients who are HBcAb positive and HBV DNA negative at Visit 1 will require HBV DNA monitoring every 3 months, at an ET visit, and at Visit 801, regardless of their HBsAb status. If the HBV DNA result is above the lower limit of quantification (LLOQ), refer to Section 7.1.2 and Section 8.4.4. For study sites in Japan (or elsewhere if required), if a patient is HBcAb positive and/or HBsAb positive and negative for HBV DNA at Visit 1, HBV DNA needs to be checked at least monthly and at the patient's last visit.

[l] For all women of childbearing potential, a serum pregnancy test (central laboratory) will be performed at Visits 1 and 2. Urine pregnancy tests (local laboratory) will also be performed at Visit 2 and at all subsequent study visits.

[m] To confirm postmenopausal status for women ≥40 and <60 years of age who have had a cessation of menses, an FSH test will be performed. Nonchildbearing potential is defined as an FSH ≥40 mIU/mL and a cessation of menses for at least 12 months.

[n] Clinical chemistry will include the following values calculated from serum creatinine: estimated glomerular filtration rate (eGFR; calculated using the Modification of Diet in Renal Disease [MDRD] isotope dilution mass spectrometry traceable method).

[o] Fasting lipid profile. Patients should not eat or drink anything except water for 12 hours prior to sample collection. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation.

[p] At Visit 2, one PK sample will be collected 15 to 30 minutes POSTdose, as described in Section 8.5. Apart from this single PK sample, all other baseline laboratory samples are taken PREdose.

[q] A single PK sample will be collected at Visit 4 and Visit 7 at any time predose, as described in Section 8.5. To reduce the number of blood draws, the predose PK sample may be drawn at the same time as other labs required at the visit. If a patient arrives at the clinic on Visit 4 or Visit 7 after having taken the dose, the PK sample should be drawn with other routine labs randomly at any time postdose.

[r] A single PK sample will be collected at Visit 5 between 1 and 3 hours postdose, as described in Section 8.5. To reduce the number of blood draws, the postdose PK sample may be drawn at the same time as other routine labs required at the visit.

[s] A single PK sample is to be collected, if possible, from patients who discontinue the study early. In the event of a serious adverse event (SAE), up to 2 additional blood samples may be taken at the investigator's discretion. If collected, the PK samples should be collected after the reported event, approximately 6 hours apart and within 24 hours of the patient's last dose.

Appendix 3. Clinical Laboratory Tests

Clinical Laboratory Tests[a]

Hematology[b]	**Clinical Chemistry**[b]
Hemoglobin	Serum Concentrations of:
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Absolute reticulocyte count	Total bilirubin
Mean cell volume (MCV)	Direct bilirubin
Mean cell hemoglobin (MCH)	Alkaline phosphatase (ALP)
Mean cell hemoglobin concentration (MCHC)	Alanine aminotransaminase (ALT)/serum glutamic pyruvic transaminase
Leukocytes (WBC)	
Absolute count of	Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase
Neutrophils, segmented	
Neutrophils, juvenile (bands)	Blood urea nitrogen (BUN)
Lymphocytes	Creatinine
Monocytes	Estimated glomerular filtration rate (eGFR)[c]
Eosinophils	Uric acid
Basophils	Calcium
Platelets	Glucose[d]
Cell morphology	Albumin
Differential and blood smear[e]	Creatine phosphokinase (CPK)
	Total protein
Iron studies (iron, TIBC, and ferritin)	
Lymphocyte subsets (T, B, NK, and T-cell subsets)	**Lipid Profile**[d,f]
	Total cholesterol
Urinalysis[b]	High-density lipoprotein cholesterol (HDL-C)
Color	Low-density lipoprotein cholesterol (LDL-C)
Specific gravity	Triglycerides
pH	
Protein	**Other Tests**
Glucose	Serum pregnancy test (females only)[g]
Ketones	Urine pregnancy test (females only)[g]
Blood	Follicle-stimulating hormone (FSH) (females only)[h]
Bilirubin	Hepatitis B surface antigen (HBsAg)
Urobilinogen	Hepatitis B surface antibody (HBsAb)
Leukocyte esterase	Hepatitis B core antibody (HBcAb)
Nitrite	Hepatitis C antibody[i]
Urine creatinine	HBV DNA[k]
Microscopic examination of sediment[j]	Human immunodeficiency virus (HIV) serology
	PPD or QuantiFERON®-TB Gold, or T-SPOT®.TB[l]
Anti-nuclear antibody (ANA)	Thyroid-stimulating hormone (TSH)
Anti-double-stranded DNA (anti-dsDNA) antibody	High-sensitivity C-reactive protein (hsCRP)
Autoantibodies (anti-RNP, anti-Sm, anti-SSA/Ro, anti-SSB/La)	Stored serum, plasma, urine, mRNA[m], and DNA samples for exploratory biomarker analyses
Antiphospholipid antibodies	Serum immunoglobulins (IgG, IgA, IgM)
Complement C3 and C4	Baricitinib plasma concentration (PK sample)

Abbreviations: HBV DNA = hepatitis B virus deoxyribonucleic acid; mRNA = messenger ribonucleic acid; PK = pharmacokinetics; PPD = purified protein derivative; RBC = red blood cells; TIBC = total iron binding capacity; WBC = white blood cells.

[a] All labs will be assayed/calculated by a Lilly-designated laboratory unless otherwise noted.

[b] Unscheduled blood chemistry (including CPK), hematology, and urinalysis panels may be performed at the discretion of the investigator. If tests are done to evaluate laboratory results to resume investigational product, samples must be assayed centrally.

[c] eGFR for serum creatinine will be calculated by the central laboratory using the Modification of Diet in Renal Disease (MDRD) isotope dilution mass spectrometry traceable method.

[d] Fasting laboratory values for glucose and lipids will be required at baseline, Week 12, and Week 24. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation. These tests may be performed nonfasting at all other visits.

[e] Differential and blood smear may be performed if necessary.

[f] Lipid panel consists of direct HDL-C, triglycerides, cholesterol, and LDL-C (calculation from Friedewald et al. 1972).

[g] For all women of childbearing potential, a serum pregnancy test (central laboratory) will be performed at Visit 1, and both urine (local laboratory) and serum pregnancy (central laboratory) tests will be performed at Visit 2 to determine study eligibility. Urine pregnancy tests (local laboratory) will also be performed at each subsequent study visit per the Schedule of Activities.

[h] To confirm postmenopausal status for women ≥40 and <60 years of age, an FSH test will be performed. Nonchildbearing potential is defined as an FSH ≥40 mIU/mL and a cessation of menses for at least 12 months.

[i] A positive hepatitis C antibody result will be confirmed with a positive hepatitis C virus result.

[j] Microscopic examination of sediment will be performed if abnormalities are noted on the routine urinalysis.

[k] HBV DNA testing will be performed in patients who tested positive for HBcAb at screening. Patients who are HBcAb positive and HBV DNA negative at Visit 1 will require HBV DNA monitoring every 3 months, at an early termination (ET) visit, and at Visit 801, regardless of their HBsAb status. If the HBV DNA result is above the lower limit of quantification (LLOQ), refer to Section 7.1.2 and Section 8.4.4. For study sites in Japan (or elsewhere if required), if a patient is HBcAb positive and/or HBsAb positive and negative for HBV DNA at Visit 1, HBV DNA needs to be checked at least monthly and at the patient's last visit.

[l] PPD, QuantiFERON®-TB Gold, and T-SPOT®.TB tests may be performed locally. Test will be required at Visit 1 only to determine eligibility of patient for the study. In countries where the QuantiFERON-TB Gold or T-SPOT.TB test is available and, in the judgment of the investigator, medically preferred as an alternative to the PPD test for the evaluation of mycobacterium tuberculosis (MTB) infection, either may be used instead of the PPD test (positive tests excluded).

[m] Interferon (IFN) signature will be assayed from stored mRNA sample.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, CRP.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin**[a]
Hemoglobin	
Hematocrit	**Hepatic Coagulation**[a]
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies**[a,b]
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
ALP	
ALT	**Anti-Nuclear Antibody (ANA)**[a]
AST	
GGT	**Alkaline Phosphatase Isoenzymes**[a]
CPK	
	Anti-Smooth Muscle Antibody (or anti-actin antibody)[a]

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by Lilly-designated or local laboratory.

b Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Leo Document ID = 4a1b1699-ff86-4f60-85c4-c62821a732f9

Approver: PPD
Approval Date & Time: 11-Dec-2015 20:06:16 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 11-Dec-2015 20:41:38 GMT
Signature meaning: Approved