Protocol I4V-MC-JAIM(a)

# A Phase 3, Double-Blind, Multicenter Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Patients with Systemic Lupus Erythematosus (SLE)

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## Confidential Information



Baricitinib (LY3009104)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

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# 1. Synopsis

**Title of Study:**
A Phase 3, Double-Blind, Multicenter Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Patients with Systemic Lupus Erythematosus (SLE).

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

Baricitinib is an oral, reversible, selective inhibitor of Janus kinase (JAK)1 and JAK2 (Fridman et al. 2010). This activity profile suggests that baricitinib may inhibit cytokines implicated in SLE, most notably type I interferon (IFN; JAK1/tyrosine kinase [TYK]2), interleukin ([IL]-6; JAK1/JAK2/TYK2), and type II IFNγ, as well as other cytokines that may have a role in SLE, including IL-23 (JAK2/TYK2), granulocyte-macrophage colony stimulating factor (JAK2/JAK2) and IL-12 (JAK2/TYK2). In a recently completed Phase 2 study (I4V-MC-JAHH [JAHH]), baricitinib demonstrated clinical efficacy in patients with SLE. Baricitinib plus standard of care was superior to placebo plus standard of care in the proportion of patients achieving remission of rash and/or arthritis as defined by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), as well as the proportion of patients achieving a Systemic Lupus Erythematosus Responder Index-4 (SRI-4) response at Week 24.

Given the efficacy of baricitinib demonstrated in clinical trials for treating autoimmune/autoinflammatory diseases involving joints, skin, and kidney (including SLE), the acceptable safety profile of baricitinib observed through the current stage of development, and a continuing unmet medical need in patients with SLE, there is a compelling rationale for the initiation of a Phase 3 program to evaluate baricitinib in the treatment of SLE.

## Objective(s)/Endpoints:

| Objectives | Endpoints |
|---|---|
| **Primary**<br>To evaluate the long-term safety and tolerability of baricitinib in patients with SLE. | Safety and tolerability assessments will include:<br>• Proportion of patients with treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs).<br>• Proportion of patients with temporary investigational product interruptions and permanent discontinuations. |
| **Secondary**<br>• To evaluate the long-term effect of baricitinib 4-mg or 2-mg QD and background standard-of-care therapy on SLE disease activity. | • Proportion of patients achieving SRI-4 response through Week 156, defined as:<br>o Reduction of ≥4 points from baseline in SLEDAI-2K score; and<br>o No new British Isles Lupus Assessment Group (BILAG) A or no more than 1 new BILAG B disease activity score; and<br>o No worsening (defined as an increase of ≥0.3 points [10 mm] from baseline) in the Physician's Global Assessment of Disease Activity.<br>• Proportion of patients achieving an SRI-5, -6, -7, or -8 response through Week 156.<br>• Proportion of patients achieving an LLDAS response through Week 156.<br>• Change from baseline in mean total SLEDAI-2K scores through Week 156.<br>• Change from baseline in Physician's Global Disease Activity score through Week 156. |
| • To evaluate the long-term corticosteroid sparing effect of baricitinib 4-mg or 2-mg QD.<br>• To evaluate the long-term effect of baricitinib 4-mg or 2-mg QD on SLE flares. | • Change from baseline in prednisone dose through Week 156.<br>• Annualized mild/moderate flare rate.<br>• Annualized severe flare rate.<br>• Annualized flare rate (any severity). |
| • To evaluate the long-term effect of baricitinib 4-mg or 2-mg QD on mucocutaneous manifestations of SLE. | • Proportion of patients with CLASI total activity score ≥10 at baseline with ≥50% reduction in CLASI total activity score through Week 156. |

**Objective(s)/Endpoints:**

| Objectives | Endpoints |
|---|---|
| • To evaluate the long-term effect of baricitinib 4-mg or 2-mg QD on musculoskeletal manifestations of SLE. | • Change from baseline in tender joint count through Week 156.<br>• Change from baseline in swollen joint count through Week 156. |
| • To evaluate the long-term effect of baricitinib 4-mg or 2-mg QD on individual organ system disease activity. | • Proportion of patients with improvement in each SLEDAI-2K organ system versus baseline through Week 156.<br>• Proportion of patients with worsening in each SLEDAI-2K organ system versus baseline through Week 156. |
| • To evaluate the long-term effect of baricitinib 4-mg or 2-mg QD on damage. | • Change from baseline in SLICC/ACR damage index total score through Week 156. |
| • To evaluate the long-term effect of baricitinib 4-mg or 2-mg QD on patient-reported outcomes (PROs). | • Change from baseline in Worst Pain NRS through Week 156.<br>• Change from baseline in Worst Joint Pain NRS through Week 156.<br>• Change from baseline in Worst Fatigue NRS through Week 156.<br>• Change from baseline in Patient Global Impression of Severity through Week 156.<br>• Change from baseline 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 through Week 156.<br>• Change from baseline in FACIT-F total score through Week 156.<br>• Change from baseline in the EQ-5D-5L through Week 156.<br>• Change from baseline in the WPAI-Lupus through Week 156. |

Abbreviations: CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; EQ-5D-5L = 5-level EuroQol-5 Dimensions; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; LLDAS = Lupus Low Disease Activity State; NRS = Numeric Rating Scale; QD = once daily; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC/ACR = Systemic Lupus Erythematosus International Collaborating Clinics/American College of Rheumatology; SRI-4 = Systemic Lupus Erythematosus Responder Index-4; WPAI = Work Productivity and Activity Impairment.

**Summary of Study Design:**

Study I4V-MC-JAIM [JAIM] is a Phase 3, multicenter, randomized, outpatient, long term extension trial to evaluate the long-term safety and efficacy of baricitinib in eligible patients with SLE who have completed the treatment period in an originating study (such as, Study I4V-MC-JAHZ [JAHZ] or Study I4V-MC-JAIA [JAIA]).

**Treatment Arms and Duration:**

Patients randomized to active treatment, baricitinib 4-mg daily or baricitinib 2-mg daily, during Study JAHZ or Study JAIA will continue on the same, blinded, dose of baricitinib in Study JAIM. Patients randomized to placebo during Study JAHZ or Study JAIA will be randomized 1:1 to receive baricitinib 4-mg or baricitinib 2-mg daily during Study JAIM. The treatment period will last up to 156 weeks (3 years) from enrollment into Study JAIM.

**Number of Patients:**

The study will enroll approximately 1100 patients.

**Statistical Analysis:**

Unless otherwise specified, the efficacy and health outcome analyses will be conducted on the modified intent-to-treat population, which includes patients who received at least 1 dose of investigational product in Study JAIM. Safety analyses for JAIM will be conducted on those patients who receive at least 1 dose of investigational product in JAIM who do not discontinue at the first post-baseline visit of JAIM for the reason "Lost to Follow-up".

Efficacy and health outcomes analyses will generally be summarized using descriptive statistics. The number and percentage of patients maintaining or achieving a categorical efficacy or health outcomes response will be summarized. The mean changes of the continuous measures will be summarized using mixed model repeated measures. The model will include treatment, region, visit, treatment-by-visit interaction as fixed categorical effects, and baseline value and baseline value-by-visit interaction as fixed continuous effects to estimate change from baseline across postbaseline visits. Missing data will be imputed at specified time points utilizing methodologies, including last observation carried forward and nonresponder imputation.

All safety data will be descriptively summarized by treatment group and analyzed using the safety population. Safety assessments will include adverse events, laboratory analytes, vital signs, and questionnaires to assess the existence and severity of depression. Some of the safety endpoints may be better assessed in the context of combining the safety data from the originating studies. These details will be included in the statistical analysis plan (SAP) for this study or the integrated SAP (which will detail how all Phase 2 and 3 studies will be combined).

The categorical safety measures will be summarized with percentages and incidence rates, where appropriate. The mean changes of the continuous safety measures will be summarized using descriptive statistics.

# 2. Schedule of Activities

**Table JAIM.1. Schedule of Activities**

| | Baseline | Treatment Phase: Study Drug Administration | | | | | | | | | | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9** | **V10** | **V11** | **ET[a]** | **V801[b]** |
| **Study Week** | **W0** | **W4** | **W12** | **W24** | **W36** | **W48** | **W60** | **W84** | **W108** | **W132** | **W156** | **Any** | **W160 or last dose + 4 weeks** |
| **Study Day** | **1** | **29 ± 4** | **85 ± 7** | **169 ± 10** | **253 ± 10** | **337 ± 10** | **421 ± 10** | **589 ± 14** | **757 ± 14** | **925 ± 14** | **1093 ± 14** | **Any** | **Last dose + 28 ± 5 days** |
| **Procedure** | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | |
| Abbreviated patient demographics | X | | | | | | | | | | | | |
| Symptom-directed physical examination | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| Weight | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| Waist circumference | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital signs (BP[d], pulse, temperature) | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| Review JAIM inclusion/exclusion criteria | X | | | | | | | | | | | | |
| Adverse events | X[e] | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications | X[f] | X | X | X | X | X | X | X | X | X | X | X | X |
| C-SSRS[g] & Self-Harm Supplement Form | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| Self-Harm Follow-up Form[h] | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| QIDS-SR16 [i] | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| Log in IWRS | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Randomization[j] | X | | | | | | | | | | | | |

| | Baseline | Treatment Phase: Study Drug Administration | | | | | | | | | | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9** | **V10** | **V11** | **ET[a]** | **V801[b]** |
| **Study Week** | **W0** | **W4** | **W12** | **W24** | **W36** | **W48** | **W60** | **W84** | **W108** | **W132** | **W156** | **Any** | **W160 or last dose + 4 weeks** |
| **Study Day** | **1** | **29 ± 4** | **85 ± 7** | **169 ± 10** | **253 ± 10** | **337 ± 10** | **421 ± 10** | **589 ± 14** | **757 ± 14** | **925 ± 14** | **1093 ± 14** | **Any** | **Last dose + 28 ± 5 days** |
| Investigational product dispensed | X | | X | X | X | X | X | X | X | X | | | |
| Investigational product returned and compliance assessed | | X[k] | X | X | X | X | X | X | X | X | X | X | |
| **Physician-Completed Scales[l]** | | | | | | | | | | | | | |
| SLEDAI-2K | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| BILAG2004 | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| Physician's Global Assessment of Disease Activity | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| SLEDAI Flare Index | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| SLICC/ACR Damage Index | X[c] | | | | | X | | | | | X | X | |
| CLASI | X[c] | X | X | X | X | X | | | | | X | X | X |
| 28-Tender and Swollen Joint Counts | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| **Patient-Reported Questionnaires** | | | | | | | | | | | | | |
| Worst Pain NRS[i] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Worst Joint Pain NRS[i] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Worst Fatigue NRS[i] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Patient's Global Impression of Severity (PGI-S)[i] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| SF-36v2[i] | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| FACIT-Fatigue[i] | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |

| | Baseline | Treatment Phase: Study Drug Administration | | | | | | | | | | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9** | **V10** | **V11** | **ET[a]** | **V801[b]** |
| **Study Week** | **W0** | **W4** | **W12** | **W24** | **W36** | **W48** | **W60** | **W84** | **W108** | **W132** | **W156** | **Any** | **W160 or last dose + 4 weeks** |
| **Study Day** | **1** | **29 ± 4** | **85 ± 7** | **169 ± 10** | **253 ± 10** | **337 ± 10** | **421 ± 10** | **589 ± 14** | **757 ± 14** | **925 ± 14** | **1093 ± 14** | **Any** | **Last dose + 28 ± 5 days** |
| WPAI-Lupus[i] | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| EQ-5D-5L[i] | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| **Laboratory Tests** | | | | | | | | | | | | | |
| HBV DNA[m] | X[c] | | X | X | X | X | X | X | X | X | X | X | X |
| Urine pregnancy test[n] | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| Clinical chemistry[o] | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| Fasting lipid panel[p] | X[c] | | X | X | | X | | | X | | X | | |
| Hematology | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| Urinalysis | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| Urine Creatinine and Protein, Ratio | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| ANA | X[c] | | | | | X | | | | | X | | |
| Anti-dsDNA | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| Autoantibodies (anti-Smith, anti-RNP, anti-SSA/Ro, anti-SSB/La) | X[c] | | | | | X | | | | | X | | |
| Anti-cardiolipin antibodies IgG, IgA, IgM) | X[c] | | | | | X | | | | | X | X | X |
| Anti-beta2 glycoprotein-I (IgG, IgM) | X[c] | | | | | X | | | | | X | X | X |
| Lupus anticoagulant (dRVVT) | X[c] | | | | | X | | | | | X | X | X |

| | Baseline | Treatment Phase: Study Drug Administration | | | | | | | | | | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9** | **V10** | **V11** | **ET[a]** | **V801[b]** |
| **Study Week** | **W0** | **W4** | **W12** | **W24** | **W36** | **W48** | **W60** | **W84** | **W108** | **W132** | **W156** | **Any** | **W160 or last dose + 4 weeks** |
| **Study Day** | **1** | **29 ± 4** | **85 ± 7** | **169 ± 10** | **253 ± 10** | **337 ± 10** | **421 ± 10** | **589 ± 14** | **757 ± 14** | **925 ± 14** | **1093 ± 14** | **Any** | **Last dose + 28 ± 5 days** |
| Complement (C3 and C4) | X[c] | X | X | X | X | X | X | X | X | X | X | X | X |
| Immunoglobulins (IgG, IgA, IgM) | X[c] | | | | | X | | | | | X | X | X |
| Exploratory storage samples (serum and plasma) | X[c] | | | | | X | | | | | X | | |
| Exploratory storage samples (urine) | X[c] | | | | | X | | | | | X | | |

Abbreviations: ANA = antinuclear antibody; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; C-SSRS = Columbia-Suicide Severity Rating Scale; dRVVT = Dilute Russell's Viper Venom Time; dsDNA = double-stranded deoxyribonucleic acid; EQ-5D-5L = 5-level EuroQol-5 Dimensions; ET = early termination; FACIT = Functional Assessment of Chronic Illness Therapy; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBV DNA = hepatitis B virus deoxyribonucleic acid; Ig = immunoglobulin; IWRS = interactive web-response system; NRS = numerical rating scale; PGI-S = Patient's Global Impression of Severity; RNP = ribonucleoprotein; QIDS-SR16 =16-Item Quick Inventory of Depressive Symptomatology-Self Report; SF-36v2 = Short-Form 36-item Health Survey version 2; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC/ACR = Systemic Lupus Erythematosus International Collaborating Clinics/American College of Rheumatology; SSA/Ro = Sjögren's-Syndrome-related antigen A; SSB/La = Sjögren syndrome type B antigen/Lupus La protein; V = visit; W = week; WPAI = Work Productivity and Activity Impairment.

[a] Patients who discontinue from investigational product (IP) early should complete the ET visit and proceed to post-treatment follow-up.

[b] All patients should return for Visit 801, a post-treatment follow-up visit, 28±5 days after the last dose of IP. Patients who discontinue IP but remain in the study for at least 28±5 days without IP, can combine their Visit 11/ET with their Visit 801 (post-treatment follow-up visit).

[c] Visit 1 of Study JAIM should occur on the same day as the final visit of the originating study. Assessments/procedures required for both Visit 1 of Study JAIM and the final visit of the origination study should only be performed once.

[d] At each time point, 3 replicate readings should be made at approximately 30- to 60-second intervals. Blood pressure is recorded as the average of these 3 readings. A single pulse measurement should be made simultaneously with at least 1 of the readings at each time point (Section 9.4.1. for details on vital signs).

[e] Adverse events that are ongoing at the completion of the originating trial should be reported as pre-existing conditions at Visit 1 for Study JAIM.

[f] Concomitant medications ongoing at the completion of the originating trial should be reported as concomitant medications at Visit 1 for Study JAIM.

[g] Suicidal ideation and behavior subscales excerpt; adapted for the assessment of 11 preferred ideation and behavior categories. C-SSRS and Self-Harm Supplemental Form should be completed after collection of unsolicited adverse events.

[h] The Self-Harm Follow-up Form is only required if triggered by the Self-Harm Supplement Form.

[i] Patient-reported questionnaires will be administered via an on-site electronic clinical outcome assessment (eCOA) device and should be administered prior to any clinical assessments.

[j] At Visit 1, patients randomized to active treatment during the originating study will be assigned to the same, blinded dose of baricitinib in Study JAIM. Patients randomized to placebo during the originating study will be randomized 1:1 to blinded baricitinib 2-mg or baricitinib 4-mg. Dose adjustment for patients newly randomized to baricitinib, if necessary, will be based on the last available estimated glomerular filtration rate (eGFR) from the originating study.

[k] New bottles of study drug tablets will NOT be dispensed at Week 4 (Visit 2) unless the patient requires additional tablets for the next visit window. Patients will continue to take tablets from the bottles dispensed at Week 0 (Visit 1). Compliance will be checked, and the bottles with remaining tablets will be returned to the patient for dosing the following visit window. If new bottles are required, the patient will not have their previous bottles returned.

[l] SLE assessments must be completed by a physician and will be documented on an eCOA (electronic clinical outcome assessment) device.

[m] Patients who were enrolled in the originating study with positive HBcAb and negative HBV DNA, regardless of HBsAb status or level, must undergo HBV DNA testing per the schedule of events (see Section 9.4.6 for details of HBV DNA monitoring).

[n] For all women of childbearing potential, urine pregnancy tests (local laboratory) will be performed at all study visits. If required per local regulations and/or institutional guidelines, pregnancy testing can occur more frequently during the study treatment period. Unscheduled urine pregnancy tests may also be performed if a regular monthly menstruation is absent in a woman of childbearing potential.

[o] Clinical chemistry will include the following value calculated from serum creatinine: eGFR (calculated using the Modification of Diet in Renal Disease [MDRD] isotope dilution mass spectrometry traceable method).

[p] 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, the sample should still be collected. This will not be considered a protocol violation.

# 3. Introduction

## 3.1. Study Rationale

Baricitinib is an oral, reversible, selective inhibitor of Janus kinase (JAK)1 and JAK2 (Fridman et al. 2010). This activity profile suggests that baricitinib may inhibit cytokines implicated in systemic lupus erythematosus (SLE), most notably type I interferon (IFN; JAK1/tyrosine kinase [TYK]2), interleukin (IL)-6 (JAK1/JAK2/TYK2), and type II IFN-γ, as well as other cytokines that may have a role in SLE, including IL-23 (JAK2/TYK2), granulocyte-macrophage colony stimulating factor (JAK2/JAK2) and IL-12 (JAK2/TYK2). The potential impact of baricitinib on the IFN pathway is relevant to SLE, as clinical and preclinical studies have established that this pathway is involved in the pathogenesis of SLE (Hoffman et al. 2017). Suppressing the IFN signature through the use of a monoclonal antibody that targets the type I IFN receptor, has been shown to be effective in SLE (Furie et al. 2017). Baseline gene expression in SLE, examined as part of the ILLUMINATE Phase 3 trials, demonstrated upregulation of IL-6-related genes, IL-2 receptor, IL-12, and oncostatin M in patients with SLE compared to control subjects, all of which signal through the JAK/signal transducers and activators of transcription (STAT) pathways, and would not be anticipated to be directly modulated by therapeutic strategies which only target the IFN pathway (Hoffman et al. 2017). Thus, baricitinib is anticipated to be effective as it modulates not only IFN but also other potential SLE-relevant pathways, providing a biologic rationale for its evaluation in this disease.

Baricitinib has demonstrated clinical efficacy and safety in patients with autoimmune (SLE, rheumatoid arthritis [RA]) (Genovese et al. 2016; Dougados et al. 2017; Fleischmann et al. 2017; Taylor et al. 2017) and autoinflammatory diseases (Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature [CANDLE], Stimulator of Interferon Genes [STING]-Associated Vasculopathy With Onset During Infancy [SAVI], Juvenile Dermatomyositis [JDM], and Aicardi-Goutières Syndrome [AGS]) (Sanchez et al. 2018). A Phase 2 study of baricitinib in patients with SLE demonstrated that baricitinib 4-mg plus standard of care (SoC) was superior to placebo plus SoC in the proportion of patients achieving remission of rash and/or arthritis as defined by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) at Week 24 (67.3% baricitinib 4-mg, 58.1% baricitinib 2-mg, 53.3% placebo, $p<0.05$ for baricitinib 4-mg versus placebo). Patients treated with baricitinib 4-mg also had a higher Systemic Lupus Erythematosus Responder Index-4 (SRI-4) response rate at Week 24 compared to patients treated with placebo (64.4% baricitinib 4-mg, 51.4% baricitinib 2-mg, 47.6% placebo, $p<0.05$ for baricitinib 4-mg versus placebo) (Wallace et al. 2018). Additionally, completed Phase 2 studies of baricitinib also demonstrated efficacy in patients with moderate-to-severe plaque psoriasis (Papp et al. 2016), diabetic kidney disease (Tuttle et al. 2015), and atopic dermatitis (Guttman-Yassky et al. 2018).

Given the efficacy of baricitinib demonstrated in clinical trials for treating autoimmune/autoinflammatory diseases, involving joints, skin, and kidney (including SLE), the acceptable safety profile of baricitinib observed through the current stage of development, and a continuing unmet medical need in patients with SLE, there is a compelling rationale for initiation of a Phase 3 program to evaluate baricitinib in the treatment of SLE.

## 3.2. Background

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

Systemic lupus erythematosus is predominately a disease affecting women (approximately 9:1 female to male ratio), which can begin at any age but most commonly begins in adolescence or early adulthood (Yu et al. 2017). It affects 20 to 150 people per 1,000,000 people in the US (UpToDate® 2018 [WWW]) and is more common in African-Americans (Lim et al. 2014; Somers et al. 2014), with as many as 1 in 537 African-American women afflicted with SLE (Somers et al. 2014). Additionally, SLE appears to be more severe in African-Americans, Asian-Americans, and Latinos compared to Caucasians (Kaslow 1982; Alarcón et al. 2001).

Clinically, SLE presents with varying signs and symptoms, including fever, arthralgia/arthritis, skin rash, alopecia, pleuritis, pericarditis, nephritis, vasculitis, stroke, seizure, leukopenia, thrombocytopenia, anemia, photosensitivity, and the presence of autoantibodies reactive with nuclear antigens. Fatigue is the most prevalent symptom reported among patients with SLE (Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria for Fatigue 2007). Pain that interferes with daily living activities is also commonly reported (Özel and Argon 2015). Skin and joint disease are also among the most prevalent features of the illness. Age, African-American race/ethnicity, 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 the risk of death in patients with SLE compared with the general population (Yurkovich et al. 2014). Morbidity remains substantial as measured by various tools for features, such as health-related quality of life, loss of work productivity, pain, and fatigue (Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria for Fatigue 2007; Özel and Argon 2015). Thus, there remains substantial unmet medical need for individuals who have SLE.

Standard of care for SLE includes antimalarial agents, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), immunosuppressive agents, and cytotoxic agents; however, there are relatively few drugs approved for the treatment of SLE. For example, in the US,

approved therapies for SLE include aspirin, antimalarials, corticosteroids, and belimumab. In general, treatment regimens are broadly similar around the world and are tailored to the severity of disease and the specific organs involved. 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 so called "corticosteroid-sparing agents" to reduce chronic exposure to corticosteroids.

The current SoC therapies have broad effects on immune and inflammatory pathways, including host defense, and have been associated with short- and long-term morbidity. For example, long-term use of corticosteroids is associated with cataracts, osteoporosis, avascular necrosis, increased infection, cardiovascular events, 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 overall morbidity and mortality, many patients still have incompletely controlled disease, which progresses 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 and 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 IFN signaling pathway. Upregulation of genes associated with the activation of type I IFN signaling, referred to as a type I IFN signature, is observed in approximately 75% of patients with SLE (Hoffman et al. 2017). 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), decreased complement, and increased risk of severe flares (Hoffman et al. 2017). Another cytokine implicated in the pathogenesis of SLE is IL-6. Increased expression of IL-6 has been found in murine models of SLE and in patients with SLE, and inhibition of IL-6 signaling was associated with a decrease in disease activity (Linker-Israeli et al. 1999, Illei et al. 2010). Both type I IFNs and IL-6 signal through the JAK/STAT pathway; therefore, treatment of SLE with baricitinib or other JAK inhibitors is an area of intense interest.

## 3.3. Benefit/Risk Assessment

**Phase 2 SLE Data**

In the baricitinib Phase 2 SLE clinical Study I4V-MC-JAHH (JAHH), significant benefit for baricitinib 4-mg once daily (QD) treatment over placebo was demonstrated for the primary efficacy endpoint of resolution of arthritis and/or rash, the major secondary efficacy endpoint of SRI-4 response, and important supporting measures, such as flare and lupus low disease activity score (LLDAS) after 24 weeks of treatment. Baricitinib 2-mg QD was numerically better than placebo across these measures, although the results were not statistically significant.

The percentage of patients with at least 1 treatment-emergent adverse event (TEAE) during the 24-week treatment period was 64.8% for placebo, 71.4% for baricitinib 2-mg QD, and 73.1% for baricitinib 4-mg QD. The most common TEAEs (occurring in ≥5% of patients in either baricitinib dose group over 24 weeks) were viral upper respiratory tract infection, urinary tract infection, upper respiratory tract infection, pharyngitis, and headache. The proportions of patients who reported viral upper respiratory tract infections were higher for baricitinib-treated patients compared to placebo, but the proportions were similar for the baricitinib 2-mg and 4-mg dose groups. It is important to consider that in SLE, patients are at an increased risk for infections due to predisposing conditions related to impaired cellular and humoral immune functions (Danza and Ruiz-Irastorza 2013), as well as concomitant use of immunosuppressive agents, such as corticosteroids. In the Phase 2 study of baricitinib, there were more serious infections reported in the baricitinib 4-mg group versus the baricitinib 2-mg group or placebo. There were no cases of serious herpes zoster or opportunistic infection, and no reports of tuberculosis (TB). There were no malignancies or major adverse cardiovascular events (MACE) reported. One serious adverse event (SAE) of deep vein thrombosis (DVT) was reported in the baricitinib 4-mg group in a patient with pre-existing antiphospholipid antibodies and pain in the affected limb (right calf) prior to study entry, who was taking a concomitant oral corticosteroid and celecoxib during the study.

**Risks Identified in the Baricitinib Program**

Serious infections, venous thromboembolism, hepatotoxicity, and fetal malformations were identified as important potential risks with baricitinib. Inclusion/Exclusion criteria in the protocol limit enrolment of SLE patients who are at risk for these important potential risks. Although infections were seen in about half of the SLE study population, the incidence rate of serious infection in patients exposed to baricitinib in the RA program was 3.0 per 100 patient-years. During the controlled period (through 16 weeks), rates were similar in both baricitinib- and placebo-treated patients. The nonserious infections (upper respiratory tract infections, herpes zoster, and herpes simplex) associated with baricitinib in the RA program are readily diagnosed, manageable, and typically resolve without long-term sequelae. It is recommended that where indicated, herpes zoster vaccination be offered to patients prior to receiving baricitinib.

Increases in levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin have been seen in patients with RA. Most of these increases improved with continued use or temporary discontinuation of baricitinib with no long-term effects. No cases of severe drug-induced liver injury were observed with baricitinib treatment.

Fetal malformations were reported in toxicology studies at higher doses than what is used in human patients. Only a small number of patients have become pregnant in baricitinib clinical trials, and there have been no reports of fetal malformations in these pregnancies.

Venous thromboembolic events (VTEs) have been determined to be an important potential risk for baricitinib. There was a numerical imbalance in reports of VTEs in the 24-week placebo-controlled period of the Phase 3 trials of patients with RA. Available evidence does not

establish a causal association. With long-term exposures, the exposure-adjusted incidence rate of VTE for baricitinib-treated patients with RA was similar to the background rates published in the literature for the target population. There was no pattern of increased or decreased risk with continuing, long-term exposures, and cases observed with baricitinib were confounded by one or more recognized risk factors for VTE. Venous thromboembolic event risk can be managed through risk mitigation strategies. Exclusion and discontinuation criteria have been included in this protocol and the originating study protocols to limit participation of patients who are at an increased risk of VTE.

In the context of the cumulative knowledge, the benefit/risk balance for baricitinib in the treatment of adult patients with SLE is assessed to be favorable.

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

## 3.4. Scientific Rationale for Study Design

Study JAIM is a long-term extension study for patients who complete the treatment period of an originating study, such as Study JAHZ or JAIA. The primary intent of Study JAIM is to evaluate safety associated with long-term exposure to baricitinib. The absence of a placebo arm in Study JAIM is consistent with other studies evaluating the long-term safety of investigational drugs in patients with SLE.

Background concomitant SoC therapy, including corticosteroids, antimalarials, and immunosuppressants are permitted during the study.

Safety assessments will be based on the total duration of baricitinib exposure, including exposure during the originating study. Efficacy assessments will also use disease severity measures obtained at the time of initial randomization in the originating study as baseline values.

# 4. Objectives and Endpoints

Table JAIM.2 shows the objectives and endpoints of the study.

**Table JAIM.2. Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary**<br>To evaluate the long-term safety and tolerability of baricitinib in patients with SLE. | Safety and tolerability assessments will include:<br>• Proportion of patients with treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs).<br>• Proportion of patients with temporary investigational product interruptions and permanent discontinuations. |
| **Secondary**<br>• To evaluate the long-term effect of baricitinib 4-mg or 2-mg QD and background standard-of-care therapy on SLE disease activity. | • Proportion of patients achieving SRI-4 response through Week 156, defined as:<br>o Reduction of ≥4 points from baseline in SLEDAI-2K score; and<br>o No new British Isles Lupus Assessment Group (BILAG) A or no more than 1 new BILAG B disease activity score; and<br>o No worsening (defined as an increase of ≥0.3 points [10 mm] from baseline) in the Physician's Global Assessment of Disease Activity.<br>• Proportion of patients achieving an SRI-5, -6, -7, or -8 response through Week 156.<br>• Proportion of patients achieving an LLDAS response through Week 156.<br>• Change from baseline in mean total SLEDAI-2K scores through Week 156.<br>• Change from baseline in Physician's Global Disease Activity score through Week 156. |
| • To evaluate the long-term corticosteroid sparing effect of baricitinib 4-mg or 2-mg QD.<br>• To evaluate the long-term effect of baricitinib 4-mg or 2-mg QD on SLE flares. | • Change from baseline in prednisone dose through Week 156.<br>• Annualized mild/moderate flare rate<br>• Annualized severe flare rate<br>• Annualized flare rate (any severity). |

**Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| • To evaluate the long-term effect of baricitinib 4-mg or 2-mg QD on mucocutaneous manifestations of SLE. | • Proportion of patients with CLASI total activity score ≥ 10 at baseline with ≥50% reduction in CLASI total activity score through Week 156. |
| • To evaluate the long-term effect of baricitinib 4-mg or 2-mg QD on musculoskeletal manifestations of SLE. | • Change from baseline in tender joint count through Week 156.<br>• Change from baseline in swollen joint count through Week 156. |
| • To evaluate the long-term effect of baricitinib 4-mg or 2-mg QD on individual organ system disease activity. | • Proportion of patients with improvement in each SLEDAI-2K organ system versus baseline through Week 156.<br>• Proportion of patients with worsening in each SLEDAI-2K organ system versus baseline through Week 156. |
| • To evaluate the long-term effect of baricitinib 4-mg or 2-mg QD on damage. | • Change from baseline in SLICC/ACR damage index total score through Week 156. |
| • To evaluate the long-term effect of baricitinib 4-mg or 2-mg QD on patient-reported outcomes (PROs). | • Change from baseline in Worst Pain NRS through Week 156.<br>• Change from baseline in Worst Joint Pain NRS through Week 156.<br>• Change from baseline in Worst Fatigue NRS through Week 156.<br>• Change from baseline in Patient Global Impression of Severity through Week 156.<br>• Change from baseline 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 through Week 156.<br>• Change from baseline in FACIT-F total score through Week 156.<br>• Change from baseline in the EQ-5D-5L through Week 156.<br>• Change from baseline in the WPAI-Lupus through Week 156. |

Abbreviations: CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; EQ-5D-5L = 5-level EuroQol-5 Dimensions; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; LLDAS = Lupus Low Disease Activity State; NRS = Numeric Rating Scale; QD = once daily; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC/ACR = Systemic Lupus Erythematosus International Collaborating Clinics/American College of Rheumatology; SRI-4 = Systemic Lupus Erythematosus Responder Index-4; WPAI = Work Productivity and Activity Impairment.

# 5. Study Design

## 5.1. Overall Design

Study I4V-MC-JAIM [JAIM] is a Phase 3, multicenter, randomized, outpatient, long term extension trial to evaluate the long-term safety and efficacy of baricitinib in eligible patients with SLE who have completed the treatment period in an originating study (such as, Study I4V-MC-JAHZ [JAHZ] or Study I4V-MC-JAIA [JAIA]).

Figure JAIM.1 illustrates the study design.

The study consists of 3 periods:

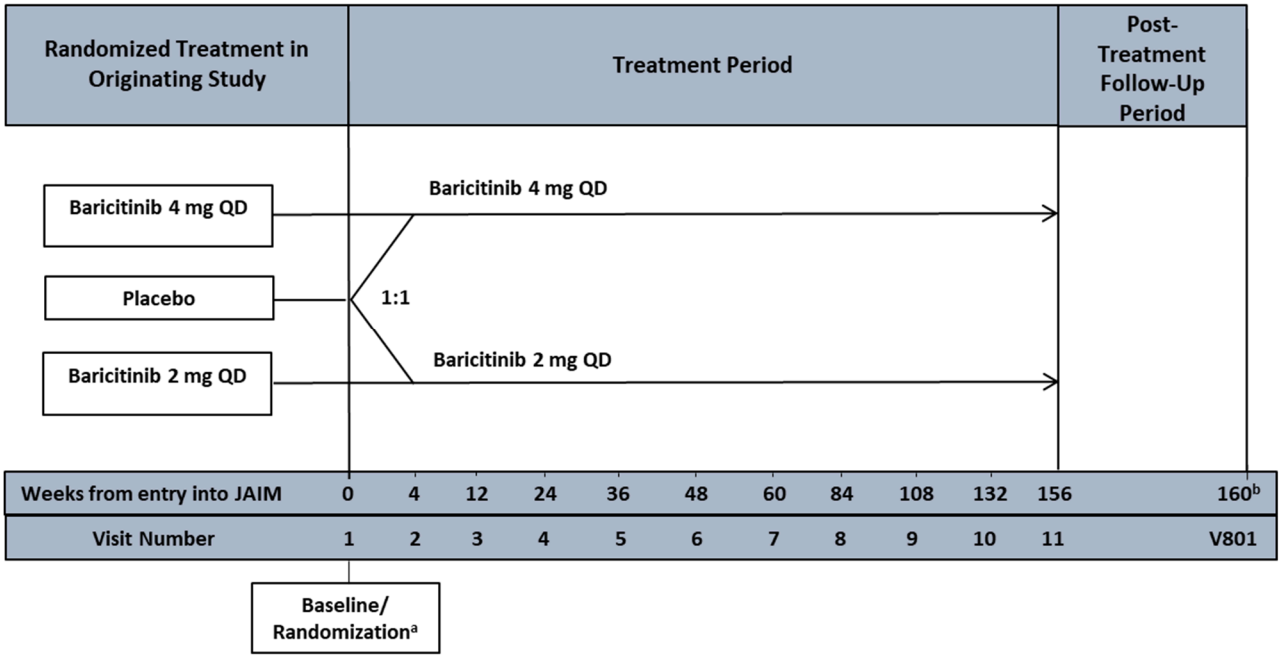
**Screening Period**: Screening for JAIM (Week 0, Visit 1) should occur during the last visit of the originating study. However, in particular circumstances, this duration may be extended after consultation with the sponsor.

**Treatment Period**: Patients randomized to active treatment, baricitinib 4-mg daily or baricitinib 2-mg daily, during the originating studies will continue on the same, blinded dose of baricitinib in Study JAIM. Patients randomized to placebo during the originating studies will be randomized 1:1 to receive blinded baricitinib 2-mg or 4-mg daily during Study JAIM. Randomization will be stratified by corticosteroid dose on the day of randomization (<10 mg/day; ≥10 mg/day of prednisone or equivalent), and region (defined in the statistical analysis plan [SAP]). Patients originally randomized to active treatment in originating study with renal impairment at baseline of the originating study will not receive doses higher than 2-mg baricitinib QD. Patients randomized to placebo in the originating study with renal impairment (defined as estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 $m^2$) at the time of randomization to JAIM (assessed by the most recent eGFR from the originating study) will receive 2-mg baricitinib QD. The treatment period will last up to 156 weeks from enrollment into Study JAIM.

Patients may continue to receive the background standard therapies for SLE, including a corticosteroid, a single antimalarial, and/or a single immunosuppressant, that they were receiving at completion of the originating study.

Throughout the trial, investigators should continue to assess individual benefit-risk for patients to remain in the trial and should consider discontinuing patients if sufficient clinical benefit is not observed with protocol-permitted treatments.

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




Abbreviations: QD = once daily; V visit

a. Visit 1 of Study JAIM should be completed on the same calendar day as the Week-52 visit of the originating study.
b. The follow-up visit should occur 4 weeks (±5 days) after the last dose of study drug.

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

## 5.2. Number of Participants

Approximately 1100 participants will be enrolled.

## 5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.

## 5.4. Justification for Dose

The 4-mg and 2-mg QD doses of baricitinib selected for this study are based on the Phase 2 SLE study, Study JAHH, and are additionally supported by pharmacokinetic (PK), safety, and efficacy data for baricitinib in Phase 2 and Phase 3 RA studies and the Phase 2 psoriasis study. If, after final analysis of the SLE Phase 3 originating studies, it is determined that either dose of baricitinib does not have a positive benefit/risk profile, then that dose arm may be discontinued and all patients transferred to the remaining dose arm.

In the Phase 2 SLE study, baricitinib 4-mg QD demonstrated statistically significant efficacy compared to placebo across several relevant measures, including remission of arthritis and/or rash (SLEDAI-2K), SRI-4, flare, and LLDAS. Baricitinib 2-mg QD was numerically better than placebo across these measures, although the results were not statistically significant. Dose response patterns favoring baricitinib 4-mg were evident across measures, and improvement was observed for both doses in patient-reported outcomes, including worst pain and worst joint pain. Pharmacokinetic/pharmacodynamic (PK/PD) modeling suggests the maximum response after dosing with 2-mg was not attained by 24 weeks. Therefore, there is potential that baricitinib 2-mg will also demonstrate efficacy at Week 52. No notable safety findings emerged compared to the results from baricitinib studies for other indications.

In Phases 2 and 3 RA studies, baricitinib 4-mg QD has demonstrated consistent efficacy; baricitinib 2-mg QD was also effective, but was less consistent than 4-mg QD across measures of efficacy and patient populations. Both doses were acceptably safe and well tolerated in the context of the efficacy observed and the benefit/risk profiles of other disease-modifying antirheumatic drugs. There was no substantial increase in efficacy noted with doses higher than 4-mg, where studied.

In the Phase 2 psoriasis study, 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. The 2-mg dose did show numeric improvements in efficacy compared with placebo. The 8-mg and 10-mg doses were associated with a higher frequency 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.

***Dose Adjustment for Renal Impairment***

As detailed in the IB, baricitinib exposure increases with decreased renal function (Study I4V-MC-JADL). Based on PK simulations, dose adjustment is not required for patients with eGFR ≥60 mL/min/1.73 $m^2$. Patients with eGFR <60 mL/min/1.73 $m^2$ at screening, who are randomized to the 4-mg dose will receive a dose of 2-mg QD, which will ensure that exposures do not exceed those of the 4-mg QD dose in patients with eGFR ≥60 mL/min/1.73 $m^2$. For patients randomized to the 2-mg dose, there will be no dose reduction based on renal function.

See Section 7.2.2 for method of treatment assignment in patients with renal impairment.

# 6. Study Population

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

The study population will be comprised of patients diagnosed with SLE who have completed the treatment period of an originating study such as Study JAHZ or Study JAIA. Study investigators will review patient records to determine if the patient meets all inclusion and none of the exclusion criteria to qualify for participation in the study.

## 6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at screening:

**Type of Patient and Disease Characteristics**

[1] Have completed the final treatment study visit of an originating study, such as Study JAHZ or Study JAIA.

**Patient Characteristics**

[2] Male or nonpregnant, nonbreastfeeding female patient

a. Patients of child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with the opposite sex.

b. Total abstinence is defined as refraining from intercourse during the entirety of the study and for at least 1 week following the last dose of investigational product. Periodic abstinence, such as calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal, are not acceptable methods of contraception.

c. Otherwise, patients of childbearing potential together with their partners must agree to use 2 effective methods of contraception, where at least 1 form is highly effective, for the entirety of the study and for at least 1 week following the last dose of investigational product.

d. The following contraception methods are considered acceptable (the patient should choose 2, and 1 must be highly effective [defined as less than 1% failure rate per year when used consistently and correctly]):

- Highly effective birth control methods:
  - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal

- Progestogen-only containing hormonal contraception associated with inhibition of ovulation: oral, injectable, or implantable
- Intrauterine device (IUD)/intrauterine hormone-releasing system (IUS)
- Vasectomized male (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

- Effective birth control methods:
  - Male or female condom with spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.
  - Diaphragm with spermicide
  - Cervical sponge
  - Cervical cap with spermicide

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

Patients of non–child-bearing potential are not required to use birth control and they are defined as:

- Women who are infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation)
- Post-menopausal – defined either as
  - A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either
    - Cessation of menses for at least 1 year
    - At least 6 months of spontaneous amenorrhea with follicle-stimulating hormone >40 mIU/mL
  - Women aged 55 years or older who are not on hormone therapy, and who have had at least 6 months of spontaneous amenorrhea
  - Women aged 55 years or older who have a diagnosis of menopause

**Informed Consent**

[3] Must read and understand the informed consent approved by Eli Lilly and Company (Lilly), or its designee, and the institutional review board (IRB)/ethics review board (ERB) governing the site, and provide written informed consent.

## 6.2. Exclusion Criteria

**Medical Conditions**

[4] Have significant uncontrolled cerebro-cardiovascular (for example, myocardial infarction, unstable angina, unstable arterial hypertension, severe heart failure, or cerebrovascular accident), respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neuropsychiatric disorders, or abnormal laboratory values that, in the opinion of the investigator, pose an unacceptable risk to the patient if investigational product continues to be administered.

[5] Have a known hypersensitivity to baricitinib or any component of this investigational product.

[6] Had investigational product permanently discontinued at any time during a previous baricitinib study.

[7] Had temporary investigational product interruption at the final study visit of a previous baricitinib study **and**, in the opinion of the investigator, this poses an unacceptable risk for the patient's participation in the study.

[8] Have any other condition that, in the opinion of the investigator, renders the patient unable to understand the nature, scope, and possible consequences of the study or precludes the patient from following and completing the protocol.

[9] Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research, judged not to be scientifically or medically compatible with this study.

## 6.3. Lifestyle Restrictions

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.

## 6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

# 7. Treatments

## 7.1. Treatments Administered

This study involves baricitinib tablets 4-mg or 2-mg administered orally QD with placebo tablets administered orally QD to maintain the blind. Table JAIM.3 shows the treatment regimens.

**Table JAIM.3. Treatment Regimens**

| Treatment Group | Treatments Administered Day 1 through Day 1092 |
|---|---|
| Baricitinib 4-mg QD[a] | 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 |

Abbreviations: eGFR = estimated glomerular filtration rate; QD=once daily.

[a] Patients randomized to placebo during the originating study with eGFR <60 mL/min/1.73 $m^2$ (based on the last eGFR assessment prior to entry into Study JAIM) who are randomized to the 4-mg dose will receive a dose of 2-mg QD. Patients randomized to active treatment during the originator study who were receiving an adjusted dose due to renal impairment will continue on the same adjusted dose in Study JAIM.

Note: Patients randomized to placebo during the originating study will be randomized 1:1 to blinded baricitinib 2-mg or baricitinib 4-mg. Dose adjustment for patients newly randomized to baricitinib, if necessary, will be based on the last available estimated glomerular filtration rate (eGFR) from the originating study.

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

- Explaining the correct use of the investigational agent(s) to the patient
- 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 that all unused medication is to be destroyed by the site, as allowed by local law.

### *7.1.1. Packaging and Labelling*

Lilly (or designee) will provide the following primary study materials:

- Tablets containing 4-mg of baricitinib
- Tablets containing 2-mg of baricitinib
- Tablets containing placebo to match 4-mg baricitinib
- Tablets containing placebo to match 2-mg baricitinib

Investigational product will be dispensed to the patient at the principal investigator's study site. Investigational product packaging will contain enough tablets for the longest possible interval between visits.

Investigational product will be labeled according to the country's regulatory requirements.

**Patients will be instructed to take 2 tablets, 1 tablet from 2 different bottles, each day**.

All investigational products will be stored, inventoried, reconciled, and destroyed according to applicable regulations. Investigational products will be supplied by Lilly or its representative in accordance with current Good Manufacturing Practices and will be supplied with lot numbers, expiry dates, and certificates of analysis (as applicable).

## 7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be assigned to baricitinib treatment (2-mg QD or 4-mg QD) according to the treatment they were receiving in the originating study. Patients randomized to active treatment during the originating study will be assigned to the same, blinded dose of baricitinib in Study JAIM. Patients randomized to placebo during the originating study will be randomized 1:1 to blinded baricitinib treatment (2-mg QD or 4-mg QD). Randomization will be stratified by corticosteroid dose on the day of randomization (<10 mg/day; ≥10 mg/day prednisone or equivalent), and region (defined in the SAP). Patients with renal impairment (as defined in Section 7.2.2) who are randomized to baricitinib 4-mg QD will receive baricitinib 2-mg QD.

Assignment to treatment groups will be determined using an interactive web-response system (IWRS). The IWRS will be used to assign packages containing blinded investigational product to each patient. Site personnel will confirm that they have located the correct packages by entering a confirmation number found on the packages into the IWRS before dispensing to the patient.

### *7.2.1. Selection and Timing of Doses*

Investigational product will be provided to patients at Visit 1.

Two tablets should be taken orally each day, without regard to food and, if possible, at approximately the same time every day.

### *7.2.2. Dose Adjustment for Renal Impairment*

The dose adjustment for renal impairment will be managed by IWRS to ensure maintenance of the treatment blind. For patients randomized to active treatment during the originating studies, the eGFR value from the originating screening visit will be used by IWRS to assign the treatment doses accordingly. For patients randomized to placebo in the originating studies, the last available eGFR value from the originating study will used by IWRS to assign the treatment doses accordingly.

- Patients with documented renal impairment (defined as eGFR ≥40 to <60 mL/min/1.73 $m^2$), who are assigned to active treatment (either to the baricitinib 4-mg arm or the baricitinib 2-mg arm) will receive a baricitinib 2-mg QD dose by the IWRS.
- No dose adjustment will be made for patients with eGFR ≥60 mL/min/1.73 $m^2$.

The rationale of dose adjustment for patients with documented renal impairment is detailed in Section 5.4.

Interruption criteria due to eGFR during the treatment period is discussed in Section 8.1.1.

## 7.3. Blinding

This is a double-blind study. After database lock of trials JAHZ and JAIA, site personnel and patients will remain blinded to treatment assignment.

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 sponsor-designated medical monitor 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.

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

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Lilly-designated medical monitor for the patient to continue in the study.

## 7.4. Dosage Modification

During this study, treatment assignment and dose adjustment of investigational product will be followed strictly as indicated in Section 7.2.1 and Section 7.2.2.

If, after final analysis of the SLE Phase 3 originating studies, it is determined that either dose of baricitinib does not have a positive benefit/risk profile, then that dose arm may be discontinued and all patients transferred to the remaining dose arm. This modification would be made via an amendment to this protocol.

See Section 7.7 for permitted concomitant therapy.

## 7.5. Preparation/Handling/Storage/Accountability

All investigational product (used and partially used) will be returned to the sponsor or destroyed at the site 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.

Storage and handling instructions are provided on the investigational product packaging and should be followed.

## 7.6. Treatment Compliance

Patient compliance with investigational product will be assessed at each visit and at Early Termination during the treatment period 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 >20% of the prescribed doses during the treatment period, unless the patient's investigational product was 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 more than the prescribed amount of investigational product. Patients found to be noncompliant with the investigational product should be assessed to determine the reason for noncompliance and educated and/or managed as deemed appropriate by the investigator to improve compliance.

## 7.7. Concomitant Therapy

Patients may continue to receive the background standard therapies for SLE they were receiving at completion of the originating study. Changes in dose of background standard therapies for SLE, such as an increase in dose of antimalarials or immunosuppressants, are permitted during the study. Initiation of new antimalarials or immunosuppressants are prohibited during the study.

In addition, changes in concomitant medication, such as an increase in corticosteroids to manage any increase in disease activity or corticosteroid tapering, are permitted during the study in accordance with long term management of disease activity and at the investigator's discretion. Any required corticosteroid bursts should be aligned with clinical practice.

Prohibited concomitant treatments include those outlined in the exclusion criteria of the originating trials.

- Scheduled parenteral corticosteroids, biologic treatments for immunologic disease, cyclophosphamide, belimumab, anifrolumab (or any other anti-IFN therapy), rituximab, any other B cell depleting therapies, intravenous immunoglobulin or any other JAK inhibitors.

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.

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.

## 7.8. Treatment after the End of the Study

### *7.8.1. Treatment after Study Completion*

Baricitinib will be made available to patients until the conclusion of the study. Patients will be referred to their local treatment centers for continued therapy as clinically indicated.

# 8. Discontinuation Criteria

## 8.1. Discontinuation from Study Treatment

### *8.1.1. Temporary 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. It is recommended that the investigator consult with Lilly (or its designee) before temporarily interrupting therapy for reasons other than those defined in Table JAIM.4. Retest timing and frequency is at the investigator's discretion.

Investigational product that was temporarily interrupted because of an AE or abnormal laboratory value, not specifically covered in Table JAIM.4, may be restarted at the discretion of the investigator. Investigational product must be held in the following situations and may only be resumed as noted in the table.

**Table JAIM.4. Criteria for Temporary Interruption of Investigational Product**

| Hold Investigational Product if the Following Abnormalities Occur: | Investigational Product May be Resumed When: |
|---|---|
| WBC count <2000 cells/µL (<2.00 x $10^3$/µL or <2.00 GI/L) | WBC count ≥2500 cells/µL (≥2.50 x $10^3$/µL or ≥2.50 GI/L) |
| ANC <1000 cells/µL (<1.00 x $10^3$/µL or <1.00 GI/L) | ANC ≥1200 cells/µL (≥1.2 x $10^3$/µL or ≥1.2 GI/L) |
| Lymphocyte count <300 cells/µL (<0.30 x $10^3$/µL or <0.30 GI/L) | Lymphocyte count ≥500 cells/µL (≥0.50 x $10^3$/µL or ≥0.50 GI/L) |
| Platelet count <25,000/µL (<25 x $10^3$/µL or <25 GI/L) | Platelet count ≥50,000/µL (≥50 x $10^3$/µL or ≥50 GI/L) |
| eGFR <40 mL/min/1.73 $m^2$ for patients with eGFR ≥60 mL/min/1.73 $m^2$ | eGFR ≥50 mL/min/1.73 $m^2$ |
| ALT or AST >5 x ULN | ALT and AST return to <2 x ULN and possible DILI has been ruled out, 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 |
| Infection that, in the opinion of the investigator, merits the IP being withheld[a] | Resolution of infection that, in the opinion of the investigator, merits the IP being restarted |

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.

[a] Permanent discontinuation of IP should be considered for patients who develop a serious infection that, in the opinion of the investigator, would pose an unacceptable risk if IP were resumed.

### 8.1.2. Permanent Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of investigational product:

- **Subject Decision**
  - The patient requests to discontinue investigational product.
- **Investigator Decision**
  - The investigator decides that the patient should be discontinued from investigational product.
- **Discontinuation due to a hepatic event or liver test abnormality.** Patients who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via eCRF.

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 upper limit of normal (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 international normalized ratio >1.5
  - 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 quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- **Discontinuation due to Other Laboratory Abnormalities:**
  - White blood cell count <1000 cells/µL (1.00x103/µL or 1.00 GI/L)
  - Absolute neutrophil count <500 cells/µL (0.50x103/µL or 0.50 GI/L)
  - Lymphocyte count <200 cells/µL (0.20x103/µL or 0.20 GI/L)
  - Hemoglobin <6.5 g/dL (<65.0 g/L)

Temporary interruption rules (see Section 8.1.1) must be followed where applicable. For lab values that meet permanent discontinuation thresholds, investigational product should be discontinued. However, if in the opinion of the investigator, the lab abnormality is due to intercurrent illness or another identified factor, lab tests may be repeated. The investigator may be able to restart investigational product after consultation with the Lilly-designated medical

monitor, only when the lab value meets resumption thresholds (Table JAIM.4) following the resolution of the intercurrent illness or other identified factor.

- **Discontinuations due to other circumstances:**
  - Pregnancy
  - Malignancy (except for successfully treated basal cell or squamous epithelial skin cancers)
  - Hepatitis B virus DNA is detected with a value above the lower limit of quantitation (see Section 9.4.6).
  - Occurrence of a VTE (DVT/pulmonary embolism [PE]) during the study
  - Serious infection, that in the opinion of the investigator merits the investigational product being discontinued
  - If the patient, for any reason, requires treatment with another therapeutic agent that may be effective for treatment of SLE that is noncompliant to the concomitant therapy requirements (see Section 7.7) during the study. Discontinuation from the investigational product must occur prior to introduction of the new agent.

Throughout the trial, investigators should continue to assess benefit-risk for patients to remain in the trial, and should consider discontinuing patients if sufficient clinical benefit is not observed with protocol allowed treatments.

Patients discontinuing from study treatment prematurely for any reason, should complete AE and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol and proceed to the post-treatment follow up period.

### *8.1.3. Discontinuation of Inadvertently Enrolled Patients*

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment, unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the sponsor-designated medical monitor agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor-designated medical monitor to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product. Safety follow up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

## 8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

- Enrollment in any other clinical study 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
- Investigator decision
  - The investigator decides that the patient should be discontinued from the study
- Subject decision
  - The patient requests to be withdrawn from the study

Patients discontinuing from the study prematurely for any reason, should complete AE and other safety follow-up as indicated in the Early Termination Visit per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol and proceed to the post-treatment follow up period.

## 8.3. Lost to Follow-Up

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. 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.

# 9. Study Assessments and Procedures

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

Appendix 2 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.

## 9.1. Efficacy Assessments

### *9.1.1. Secondary Efficacy Assessments*

#### 9.1.1.1. Systemic Lupus Responder Index

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 British Isles Lupus Assessment Group (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. The SRI-4 response is defined as follows:

- Reduction of ≥4 points from baseline in SLEDAI-2K score (Section 9.1.1.2); and
- No new BILAG A or no more than 1 new BILAG B disease activity scores (Section 9.1.1.3); and
- No worsening (defined as an increase of ≥0.3 points [10 mm] from baseline) in Physician's Global Assessment of Disease Activity (Section 9.1.1.4).

#### 9.1.1.2. Systemic Lupus Erythematosus Disease Activity Index-2000

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, Cerebrovascular attack; 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.

#### 9.1.1.3. British Isles Lupus Assessment Group 2004 Index

The BILAG-2004 Index is a validated global disease activity index designed on the basis of the physician's intention to treat, 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 intravenous 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 that the system was never involved.

#### 9.1.1.4. 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.

#### 9.1.1.5. Systemic Lupus Erythematosus Responder Index

The SRI-5, -6, -7, and -8 will also be assessed, and are similar to the SRI-4, except that they require a reduction of ≥5, 6, 7, or 8 points (respectively) from baseline in SLEDAI-2K score. For assessment description, see Section 9.1.1.1.

#### 9.1.1.6. Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) Flare Index

The SELENA-SLEDAI Flare Index (SFI) uses the SLEDAI 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.

#### 9.1.1.7. Cutaneous Lupus Erythematosus Disease Area and Severity Index

The Cutaneous Lupus Erythematosus Disease Area and Severity Index 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.

#### 9.1.1.8. Lupus Low Disease Activity State

The LLDAS is defined as a low level of disease activity attained with or without use of low-dose steroids and/or tolerated standard maintenance doses of SoC medications.

#### 9.1.1.9. Tender/Swollen Joint Count (28 Joints)

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.

#### 9.1.1.10. Systemic Lupus International Collaborating Clinics/American College of Rheumatology 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.

#### 9.1.1.11. Health Outcomes and Quality of Life Measures

The self-reported questionnaires will be administered via an on-site electronic clinical outcome assessment device as specified in the Schedule of Activities (Section 2) in countries where the questionnaires have been translated into the native language of the region and linguistically validated.

##### *9.1.1.11.1. Worst Pain Numeric Rating Scale*

The Worst Pain numerical rating scale (NRS) is a single-item, patient-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "pain as bad as you can imagine." Overall severity of a patient's pain is indicated by selecting the number that best describes the worst level of pain during the past 7 days. Data will be captured on an electronic tablet collected at site visits.

##### *9.1.1.11.2. Worst Joint Pain Numeric Rating Scale*

The Worst Joint Pain NRS is a single-item, patient-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no joint pain" and 10 representing "joint pain as bad as you can imagine." Overall severity of a patient's joint pain is indicated by selecting the number that best describes the worst level of joint pain during the past 7 days. Data will be captured on an electronic tablet collected at site visits.

##### *9.1.1.11.3. Worst Fatigue Numeric Rating Scale*

The Worst Fatigue NRS is a single-item, patient-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no fatigue" and 10 representing "as bad as you can imagine." Overall severity of a patient's fatigue is indicated by selecting the number that best describes the worst level of fatigue during the past 7 days. Data will be captured on an electronic tablet collected at site visits.

##### *9.1.1.11.4. Patient's Global Impression of Severity*

The Patient's Global Impression of Severity is a single-item question asking the patient how they would rate their overall lupus symptoms over the past 7 days. The 5 categories of response range from "no symptoms" to "severe". Data will be captured on an electronic tablet collected at site visits.

#### *9.1.1.11.5. Medical Outcomes Short-Form 36-Item Health Survey Version 2 (SF-36v2)*

The Short-Form 36-item Health Survey version 2 (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 physical component score and the mental component score, 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). Data will be captured on an electronic tablet collected at site visits.

#### *9.1.1.11.6. Functional Assessment of Chronic Illness Therapy–Fatigue Scale*

The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale (Cella and Webster 1997) is a brief, 13-item, symptom-specific questionnaire that specifically assesses the self-reported severity of fatigue and its impact upon daily activities and functioning. The FACIT-Fatigue uses 0 ("not at all") to 4 ("very much") NRS to assess fatigue and its impact in the past 7 days. Scores range from 0 to 52, with higher scores indicating less fatigue. Data will be captured on an electronic tablet collected at site visits.

#### *9.1.1.11.7. Work Productivity and Activity Impairment Questionnaire–Lupus*

The Work Productivity and Activity Impairment Questionnaire-Lupus (WPAI-Lupus) records impairment due to Lupus during the past 7 days. The WPAI-Lupus consists of 6 items grouped into 4 domains: absenteeism (work time missed), presenteeism (impairment at work/reduced on-the-job effectiveness), work productivity loss (overall work impairment/absenteeism plus presenteeism), and activity impairment. Scores are calculated as impairment percentages (Reilly et al. 1993), with higher scores indicating greater impairment and less productivity. Data will be captured on an electronic tablet collected at site visits.

#### *9.1.1.11.8. European Quality of Life-5 Dimensions-5 Levels*

The European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) is a standardized measure of health status in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of 2 components: a descriptive system of the respondent's health and a rating of his/her current health state using a 0- to 100-mm VAS. The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his or her health state by ticking (or placing a cross) in the box associated with the most appropriate statement in each of the 5 dimensions. It should be noted that the numerals 1 to 5 have no arithmetic properties and should not be used as an ordinal score. The VAS records the respondent's self-rated health on a vertical VAS where the endpoints are labeled "best imaginable health state" and "worst imaginable health state." This information can be used as a quantitative measure of health outcome. The EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single summary index by applying a formula that

essentially attaches values (also called weights) to each of the levels in each dimension (EuroQol Group 2015 [WWW]). Data will be captured on an electronic tablet collected at site visits.

### *9.1.2. Appropriateness of Assessments*

All assessments and/or concepts included in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant.

## 9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee of 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 or stabilizes with appropriate diagnostic evaluation. 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 informed consent form (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 any change in the condition(s) and any new conditions as AEs. Investigators should record the following via eCRF for each AE: start date, stop date (if applicable), severity, and their assessment of the potential relatedness of each AE to protocol procedure 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.

### *9.2.1. 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
- Important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor 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, the SAE should be reported to the sponsor according to SAE-reporting requirements and timelines, 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 paper SAE form. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. The SAE form should be completed by the investigator, and submitted via fax to the sponsor's global patient safety department. This form includes a fax cover page that is pre-populated with the appropriate fax number. The 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Patients with a serious hepatic AE should have additional data collected using the eCRF.

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 disposition CRF 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 or she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

#### 9.2.1.1. 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

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

### 9.2.2. Adverse Events of Special Interest

Adverse events of special interest (AESIs) will include the following:

- Infections (including TB, herpes zoster, or opportunistic infections)
- Malignancies
- Hepatic events (see Section 9.4.7)
- MACE (see Section 9.4.8)
- VTE (DVT/PE) (see Section 9.4.9).

Sites will provide details on these AEs as instructed on the eCRF and may be asked for additional description by Lilly.

### 9.2.3. 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.

## 9.3. Treatment of Overdose

Refer to the IB.

## 9.4. Safety

Any clinically significant findings from physical examination, vital signs measurements, or laboratory measurements that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via eCRF.

### 9.4.1. Vital Signs

For each patient, vital signs measurements (sitting blood pressure, heart rate, and temperature) should be conducted according to the Schedule of Activities (Section 2). Subjects should be seated and relaxed with both feet on the floor for at least 5 minutes prior to taking measurements. Three replicate blood pressure readings should be made at each time point at approximately 30- to 60-second intervals. A single-pulse measurement should be taken simultaneously with at least 1 of the blood pressure readings. Blood pressure and pulse measurements should be made using either automated or manual equipment. If measurements are machine averaged, the average blood pressure reading should be recorded on the CRF. If measurements are manual or the machine does not provide an average reading, then each individual reading should be recorded on the CRF. Measurements should be made before any scheduled blood draws. Additional measurements of vital signs may be performed at the discretion of the investigator.

### 9.4.2. Physical Examination

For each patient, symptom-directed physical examinations will be conducted according to the Schedule of Activities (Section 2).

### 9.4.3. Laboratory Tests

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

With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

### 9.4.4. Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) captures the occurrence, severity, and frequency of suicidal ideation and/or behavior during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if suicidal ideation and/or behavior occurred. The C-SSRS is administered by an appropriately trained health care professional with at least 1 year of patient care/clinical experience. The tool was developed by the National Institute of Mental Health trial group for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. For this study, the scale has been adapted (with permission from the scale authors) to include only the portion of the scale that captures the occurrence of the 11 preferred ideation and behavior categories.

The nonleading AE collection should occur prior to the collection of the C-SSRS. If a suicide-related event is discovered during the C-SSRS but was not captured during the nonleading AE collection, sites should not change the AE form. If an event is serious or leads to discontinuation, this is an exception where the SAE and/or AE leading to discontinuation should be included on the AE form and the process for reporting SAEs should be followed.

Suicide-related events (behavior and/or ideations) will be assessed and evaluated at every visit with the administration of the C-SSRS and the Self-Harm Supplement Form. The Self-Harm Supplement Form is a single question to enter the number of suicidal behavior events, possible suicide behaviors, or nonsuicidal self-injurious behaviors. If the number of behavioral events is greater than zero, it will lead to the completion of the Self-Harm Follow-Up Form. The Self-Harm Follow-Up Form is a series of questions that provides a more detailed description of the behavior cases.

### 9.4.5. 16-Item Quick Inventory of Depressive Symptomatology-Self Report

The 16-item Quick Inventory of Depressive Symptomatology-Self Report is a self-administered, 16-item 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, 5th Edition (APA 2013). A patient is 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: (1) sad mood, (2) concentration, (3) self-criticism, (4) suicidal ideation, (5) interest, (6) energy/fatigue, (7) sleep disturbance (initial, middle, and late insomnia or hypersomnia), (8) decrease/increase in appetite/weight, and (9) psychomotor agitation/retardation.

### *9.4.6. Hepatitis B Virus (HBV) DNA Monitoring*

Patients who were hepatitis B core antibody positive at screening for the originating study will continue to require Hepatitis B virus (HBV) DNA monitoring approximately every 3 months up to Week 60, thereafter reducing to every 6 months, regardless of their hepatitis B surface antibody status.

The following actions should be taken in response to HBV DNA test results:

- If a single result is obtained with a value "below limit of quantitation," the test should be repeated within approximately 2 weeks.
- If the repeat test result is "target not detected," monitoring may resume according to the study schedule.
- If the patient has 2 or more test results with a value "below limit of quantitation" during the study, HBV DNA testing should be performed approximately once per month for the remainder of the study and referral to a hepatologist is recommended.
- If a result is obtained with a value above limit of quantitation at any time during the study, the patient will be permanently discontinued from investigational product (see Section 8.1.1) and 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 after evaluation of individual patient risks and benefits.

### *9.4.7. Hepatic Safety Monitoring*

If a study patient experiences elevated ALT ≥3 x ULN, ALP ≥2 x ULN, or elevated TBL ≥2 x ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days, including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Discontinuation criteria of investigational products, either temporary interruption or permanent discontinuation, due to abnormal ALT, AST, TBL, or ALP, are detailed in Section 8.1.

**Hepatic Safety Data Collection**
Additional safety data should be collected via the eCRF if 1 or more of the following conditions occur:

- Elevation of serum ALT to ≥5 x ULN on 2 or more consecutive blood tests
- Elevated serum TBL to ≥ 2 x ULN (except for cases of known Gilbert's syndrome)
- Elevation of serum ALP to ≥2 x ULN on 2 or more consecutive blood tests
- Patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- Hepatic event considered to be a SAE

### *9.4.8. Safety Monitoring*

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

The Lilly-designated medical monitor will monitor safety data throughout the course of the study. Lilly will review SAEs within time frames mandated by company procedures. The Lilly-designated medical monitor 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.

Investigators will monitor vital signs and carefully review findings that may be associated with cardiovascular events. Adverse event reports and vital signs will be collected at each study visit. The cardiovascular monitoring plan includes the following:

- Regular monitoring of lipid levels
- Potential MACE (cardiovascular death, myocardial infarction, stroke), other cardiovascular events (such as, hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, coronary interventions), venous thrombotic events and noncardiovascular deaths will be identified by the investigative site or through medical review and will be sent to a blinded Clinical Event Committee for adjudication at regular intervals.

### *9.4.9. Venous Thromboembolic Events*

If a patient develops clinical features of a DVT or PE, appropriate local laboratory tests and imaging should be performed, as necessary, for the diagnosis of the event. For confirmed cases,

the patient will be discontinued from study treatment and additional laboratory testing is recommended as outlined in Appendix 5. All suspected VTE events will be independently adjudicated by a blinded Clinical Event Committee.

## 9.5. Pharmacokinetics

Not Applicable.

## 9.6. Pharmacodynamics

Samples collected to measure PD markers, including, but not limited to, anti-dsDNA and complement will be identified by the patient number (coded) and retained at a facility selected by Lilly or its designee for a maximum of 1 year following last patient visit for the study.

## 9.7. Pharmacogenomics

### *9.7.1. Whole Blood Samples for Pharmacogenetic Research*

Not applicable.

## 9.8. 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 proteins, lipids, and other cellular elements.

Serum, plasma, and urine samples for biomarker research will be collected at the times specified in the Schedule of Activities (Section 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, 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 at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs/IRBs impose shorter time limits. 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. Any samples remaining after 15 years will be destroyed.

## 9.9. Medical Resource Utilization and Health Economics

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

# 10. Statistical Considerations

## 10.1. Sample Size Determination

It is expected that 80% of patients will complete Study JAHZ or JAIA and approximately 90% of patients who complete will enter Study JAIM; therefore, planned enrollment into JAIM from these originating studies will be approximately 1100 patients. Additional patients may enroll from addenda or other studies.

## 10.2. Populations for Analyses

For purposes of analysis of Study JAIM, the following populations are defined:

| Population | Description |
|---|---|
| Modified intent to treat (mITT) Population | All patients who receive at least 1 dose of investigational product in Study JAIM will be included in the mITT population. |
| Safety Population | The safety population for JAIM is defined as all patients who receive at least 1 dose of investigational product in Study JAIM and who did not discontinue from the study for the reason 'Lost to Follow-up' at the first postbaseline visit. |

## 10.3. Statistical Analyses

### *10.3.1. General Statistical Considerations*

Statistical analysis of this study will be the responsibility of Lilly or its designee. A detailed SAP describing the statistical methodologies will be developed by Lilly or its designee.

Depending on the efficacy and health outcomes analysis, baseline may be defined as the last assessment prior to the first dose of active study drug in Study JAIM or as baseline from the originating study. Depending on the analysis, treatment groups can be based on assignment in JAIM, or could be further subdivided based on treatment group assignment in the originating studies.

Some of the efficacy and safety endpoints may be better assessed in the context of integrating data from the originating studies (and possibly other relevant studies). The SAP for this study and the SAPs which specify integrated analyses, will include details of which analyses will be performed on JAIM alone and which will be performed in an integrated fashion (including originating studies and possibly other studies). The exact definition of baseline, populations, and treatment groups will depend on the particular analysis (integrated vs. JAIM alone).

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. Adjustment for multiple comparisons will not be made.

Any change to the 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. Additional exploratory analyses of the data will be conducted as deemed appropriate.

## *10.3.2. Treatment Group Comparability*

### 10.3.2.1. Patient Disposition

A detailed description of patient disposition by treatment will be summarized with reasons for discontinuation. Frequency counts and percentages will be presented for each treatment group. All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported along with their reason for discontinuation.

### 10.3.2.2. Patient Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group. Descriptive statistics, including number of patients, mean, standard deviation, median, minimum, and maximum, will be provided for continuous measures, and frequency counts and percentages will be tabulated for categorical measures. No formal statistical comparisons will be made among treatment groups unless otherwise stated. A complete list of patient characteristics and baseline clinical measures will be provided in the SAP.

### 10.3.2.3. Concomitant Therapy

Concomitant medications will be coded and descriptively summarized by treatment group in terms of frequencies and percentages using the safety population.

### 10.3.2.4. Treatment Compliance

Compliance with investigational product treatment will be assessed through counts of returned investigational product tablets. A patient will be considered significantly noncompliant if he or she misses more than 20% of the prescribed doses during the study, that is, compliance <80%. Similarly, a patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

## *10.3.3. Efficacy Analyses*

Efficacy and health outcomes analyses will generally be summarized using descriptive statistics. The number and percentage of patients maintaining or achieving a categorical efficacy or health outcomes response will be summarized. The mean change from baseline of continuous measures will be summarized using mixed model repeated measures (MMRM), except for SLICC/ACR which will be analyzed using analysis of covariance (ANCOVA). The MMRM model will include treatment, region, visit, treatment-by-visit interaction as fixed categorical effects, and baseline value and baseline value-by-visit interaction as fixed continuous effects to estimate change from baseline across postbaseline visits. Additional factors, such as originating study (JAHZ, JAIA) and originating study stratification factors, may also be included in the model. The ANCOVA model for analyzing SLICC/ACR will be based on the same model factors as the MMRM analyses, excluding visit and value-by-visit interaction terms. Additional details, including any outcomes that will utilize statistical inference and use of originating study data, will be provided in the JAIM SAP or the integrated efficacy analysis plan (IEAP), which will define how the efficacy and health outcomes data from the Phase 2 and 3 studies will be analyzed when combined.

#### 10.3.3.1. Missing Data Imputation

Missing data will be imputed at specified time points utilizing methodologies, including the following:

- Modified Last Observation Carried Forward: The last observed value (non-missing value) is used to fill in missing values at a later time point.
- Nonresponder imputation: Patients who discontinue treatment early will be defined as nonresponders.

The SAP will stipulate which methodology will be utilized for specific analyses.

### *10.3.4. Safety Analyses*

Safety assessments will include AEs, laboratory analytes, vital signs, and questionnaires to assess the existence and severity of depression.

The primary endpoints of safety and tolerability will be analyzed as part of the integrated safety analyses for SLE. All details of these integrated analyses will be contained in the integrated safety analysis plan for SLE.

Categorical safety measures for JAIM alone will be summarized with percentages, and incidence rates where appropriate. The following summaries will be reported specifically for JAIM:

- patients who permanently discontinue from study drug due to adverse events,
- patients reporting SAEs during the treatment period,
- patients with at least 1 temporary interruption of study drug
- patients who permanently discontinued study drug prior to full study completion

Additional details, including any measures that will utilize inferential statistics, will be specified in the SAP and/or iSAP.

#### 10.3.4.1. Adverse Events

Adverse events are classified based upon the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are defined as AEs that first occurred or worsened in severity on or after baseline. The number of TEAEs, as well as the number and percentage of patients who reported 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.

Serious adverse events (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. Potential AESIs will be identified by a standardized MedDRA query or a Lilly-defined MedDRA query. Details of the AESIs (including but not limited to those listed in Section 9.2.2) and analysis will be documented in the iSAP.

#### 10.3.4.2. 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, variables obtained at the baseline to postbaseline visits will be summarized as changes from baseline. Categorical variables, including the incidence of abnormal values and incidence of AESIs, will be summarized by frequency and percentage of patients in corresponding categories.

#### 10.3.4.3. Vital Signs, Physical Findings, and Other Safety Evaluation

Observed values and changes from baseline (predose or screening if missing) for vital signs and physical characteristics, and other continuous safety measures will be descriptively summarized by treatment group and time point. Shift tables will be presented where appropriate.

Summary tables or listings for the C-SSRS and the Self-Harm Supplement Form will be produced as needed.

The incidence and average duration of investigational product interruptions will be summarized and compared descriptively among treatment groups. Various techniques may be used to estimate the effects of investigational product interruptions on safety measures.

### *10.3.5. Subgroup Analyses*

Subgroup analyses for selected safety, efficacy or health outcomes parameters may be performed if needed. Details will be provided in the SAP, iSAP or IEAP.

### *10.3.6. Interim Analyses*

A data monitoring committee (DMC) will oversee the conduct of all the Phase 3 clinical trials evaluating baricitinib in patients with SLE. The DMC will consist of members external to Lilly. This DMC will follow the rules defined in the DMC charter, focusing on potential and identified risks for this molecule and for this class of compounds. Data monitoring committee membership will include, at a minimum, specialists with expertise in rheumatology and statistics. This DMC for studies of patients with SLE may be coordinated with the DMC(s) for other ongoing studies of baricitinib in other indications. Details of the DMC will be documented in a DMC charter.

Periodic data cut offs are planned, and efficacy and safety analyses will be conducted for the purpose of regulatory submission or publication.

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# 12. Appendices

# 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. |
| **AESI** | adverse events of special interest |
| **ALP** | alkaline phosphatase |
| **ALT** | alanine aminotransferase |
| **ANCOVA** | analysis of covariance |
| **anti-dsDNA** | anti-double-stranded deoxyribonucleic acid |
| **AST** | aspartate aminotransferase |
| **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. |
| **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. |
| **compliance** | Adherence to all study-related, good clinical practice, and applicable regulatory requirements. |
| **CSR** | clinical study report |
| **C-SSRS** | Columbia-Suicide Severity Rating Scale |
| **DMC** | data monitoring committee |
| **DVT** | deep vein thrombosis |
| **eCOA** | electronic clinical outcome assessments |
| **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 study are those who have been assigned to a treatment. |
| **enter** | Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives. |
| **EQ-5D-5L** | European Quality of Life-5 Dimensions 5 Levels |
| **ERB** | ethics review board |
| **FACIT** | Functional Assessment of Chronic Illness Therapy |
| **GCP** | good clinical practice |
| **GPS** | Global Patient Safety |
| **HBV** | Hepatitis B virus |
| **IB** | Investigator's Brochure |
| **ICF** | informed consent form |
| **ICH** | International Council for Harmonisation |
| **IEAP** | integrated efficacy analysis plan |
| **IFN** | interferon |
| **IL** | interleukin |
| **Informed consent** | A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form. |
| **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. |
| **IRB** | institutional review board |
| **iSAP** | integrated SAP |
| **IVRS** | interactive voice-response system |
| **IWRS** | interactive web-response system |
| **JAK** | Janus kinase |
| **LLDAS** | lupus low disease activity score |
| **MACE** | major adverse cardiovascular events |

| | |
|---|---|
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **MMRM** | mixed model repeated measures |
| **NRS** | numerical rating scale |
| **NSAID** | nonsteroidal anti-inflammatory drug |
| **PD** | pharmacodynamics |
| **PE** | pulmonary embolism |
| **PK** | pharmacokinetics |
| **PRO/ePRO** | patient-reported outcomes/electronic patient-reported outcomes |
| **PSAP** | program safety analysis plan |
| **QD** | once daily |
| **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-36v2** | Short-Form 36-item Health Survey version 2 |
| **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-4** | Systemic Lupus Erythematosus Responder Index-4 |
| **STAT** | signal transducers and activators of transcription |
| **SUSARs** | suspected unexpected serious adverse reactions |
| **TB** | tuberculosis |
| **TBL** | total bilirubin level |
| **TEAE** | treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment. |
| **TYK** | tyrosine kinase |

| | |
|---|---|
| **ULN** | upper limit of normal |
| **VAS** | Visual Analog Scale |
| **VTE** | venous thromboembolic event |
| **WPAI-Lupus** | Work Productivity and Activity Impairment Questionnaire-Lupus |

# Appendix 2. 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 platelet volume | Alkaline phosphatase (ALP) |
| Mean cell hemoglobin (MCH) | Alanine aminotransaminase (ALT)/serum glutamic pyruvic transaminase |
| Mean cell hemoglobin concentration (MCHC) Leukocytes (WBC) | Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase |
| Absolute count of | Blood urea nitrogen (BUN) |
| Neutrophils, segmented | |
| Neutrophils, juvenile (bands) | Creatinine |
| Lymphocytes | Estimated glomerular filtration rate (eGFR)[c] |
| Monocytes | Uric acid |
| Eosinophils | Calcium |
| Basophils | Glucose[d] |
| Platelets | Albumin |
| Cell morphology | Creatine phosphokinase (CPK) |
| Differential and blood smear[e] | Total protein |
| | **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 | |
| Urine Protein | |
| Glucose | **Other Tests** |
| Ketones | Urine pregnancy test (females only)[g] |
| Blood | HBV DNA[i] |
| Bilirubin | Serum immunoglobulins (IgG, IgA, IgM) |
| Urobilinogen | Stored serum, plasma, and urine samples for exploratory biomarker analyses |
| Leukocyte esterase | Lupus anticoagulant (dRVVT) |
| Nitrite | Complement C3 and C4 |
| Microscopic examination of sediment[h] | Anti-beta2 glycoprotein-I (IgG, IgM) |
| Urine creatinine | |
| Urine protein | |
| Urine protein-creatinine ratio | |

| |
|---|
| **Autoantibodies** |
| Anti-nuclear antibody (ANA) |
| Anti-double-stranded DNA (anti-dsDNA) antibody |
| Autoantibodies (anti-RNP, anti-Sm, anti-SSA/Ro, anti-SSB/La) |
| Anti-cardiolipin antibodies IgG, IgA, IgM |

Abbreviations: anti-dsDNA = anti-double-stranded deoxyribonucleic acid; dRVVT = Dilute Russell's Viper Venom Time; HBcAb = hepatitis B core antibody; HBV DNA = hepatitis B virus deoxyribonucleic acid; Ig = immunoglobulin; RBC = red blood cells; SSA/Ro = Sjögren's-Syndrome-related antigen A; SSB/La = Sjögren syndrome type B antigen/Lupus La protein; WBC = white blood cells.

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

[b] Unscheduled blood chemistry hematology, and urinalysis panels may be performed at the discretion of the investigator.

[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, Weeks 12, 24, 48, 108 and 156. Patients should not eat or drink anything except water for 12 hours prior to test. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation.

[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, urine pregnancy tests (local laboratory) will be performed at each study visit per the Schedule of Activities.

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

[i] HBV DNA testing will be performed in patients who tested positive for HBcAb in the originating study

# Appendix 3. Study Governance Considerations

# Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

## *Appendix 3.1.1. Informed Consent*

The investigator is responsible for:

- Ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- Ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (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 study.
- Ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- Ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

## *Appendix 3.1.2. Recruitment*

Eli Lilly and Company (Lilly) or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

## *Appendix 3.1.3. Ethical Review*

The investigator or an appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for 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 Good Clinical Practice (GCP).

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

- The protocol and related amendments and addenda, current Investigator Brochure (IB) and updates during the course of the study
- Informed consent form
- Other relevant documents (for example, curricula vitae, advertisements)

### *Appendix 3.1.4. Regulatory Considerations*

This study will be conducted in accordance with the protocol and with the:

- Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences 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.

### *Appendix 3.1.5. 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 systemic lupus erythematosus may also participate as investigators.

### *Appendix 3.1.6. 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.

### *Appendix 3.1.7. Final Report Signature*

The clinical study report (CSR) coordinating investigator 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.

## Appendix 3.2. 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 CRFs, 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 CRF 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.

### *Appendix 3.2.1. 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 (e.g., a rating scale) and electronic clinical outcome assessments (eCOAs) are entered into an ePRO/eCOA 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/eCOA instrument record will serve as the source.

If ePRO/eCOA 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/eCOA instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Case report form data collected by a third-party will be encoded by the third-party and stored electronically in the third-party's database system. Validated data will subsequently be transferred to the sponsor's data warehouse, using standard Lilly file transfer processes.

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.

## Appendix 3.3. Study and Site Closure

### *Appendix 3.3.1. Discontinuation of Study Sites*

Study site participation may be discontinued if Lilly or its designee, 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.

### *Appendix 3.3.2. Discontinuation of the Study*

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

### *Appendix 3.4. Publication Policy*

The publication policy for Study I4V-MC-JAIM is described in the Clinical Trial Agreement.

# 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, clinical research physician.

**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 |
| Alkaline phosphatase | |
| ALT | **Anti-nuclear antibody[a]** |
| AST | |
| GGT | **Alkaline Phosphatase Isoenzymes[a]** |
| CPK | |
| | **Anti-smooth muscle antibody (or anti-actin antibody)[a]** |

Abbreviations: 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.

# Appendix 5. Monitoring Tests for Confirmed VTE

Selected tests may be obtained in the event of a confirmed venous thromboembolic event (VTE) and may be required in follow-up with patients in consultation with Lilly, its designee, or the Lilly-designated medical monitor. The choice and optimal timing of these tests will be directed by the patient's management and may require ongoing follow-up after study discontinuation.

| |
|---|
| Protein C Functional |
| Protein S Clottable |
| Antithrombin III |
| APC Resistance |
| PT |
| APTT |
| Fibrinogen |
| Cardiolipin Antibodies |
| PT Gene |
| Factor VIII C Assay |
| Hexagonal Phase Phospholipid Neutralization |
| C-Reactive Protein |
| PTT Incubated Mixing |
| Dilute Russell Viper Venom |
| Platelet Neutralization |
| Factor V Leiden |
| MTHFR |
| Thrombin Time |
| Reptilase |
| Fibrinogen Antigen |
| Protein C Immunologic |
| Protein S Immunologic |
| Heparin fXa Inhibition |

Abbreviations: APC = activated protein C; APTT = activated partial thromboplastin time; MTHFR = methylene tetrahydrofolate reductase; PT = prothrombin time; PTT = partial thromboplastin time.

# Appendix 6. Protocol Amendment I4V-MC-JAIM (a) Summary - A Phase 3, Double-Blind, Multicenter Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Patients with Systemic Lupus Erythematosus (SLE)

## Overview

Protocol I4V-MC-JAIM, A Phase 3, Double-Blind, Multicenter Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Patients with Systemic Lupus Erythematosus (SLE) has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table. Editorial revisions with no impact on protocol design or implementation were also made. These revisions are not noted in this protocol amendment summary except where contained in a section with substantive changes.

## Amendment Summary for Protocol I4V-MC-JAIM Amendment (a)

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Table JAIM.2. – Objectives and Endpoints | Secondary endpoints describing the proportion of patients receiving prednisone at baseline able to decrease dose by a specified amount that is maintained for at least 12 weeks through Week 156 and the proportion of patients taking corticosteroids at baseline able to discontinue use through Week 156 were removed. | It was determined that these categorical endpoints were not appropriate for such a long-term study. |
| Section 2 - Schedule of Activities | Several assessments and study visits were removed:<br>• Study visits (V) V8, V10, V12, and V14 have been removed.<br>• Iron assessments for V1, V6 and V15 have been removed.<br>• Autoantibodies (anti-Sm/RNP/SSA/SSB) assessments for V4 have been removed.<br>• Anti-cardiolipins assessments for V3, V4, V5, V7, V9 (now V8), V11 (now V9), and V13 (now V10) have been removed.<br>• Anti-beta2 glycoprotein-I assessments for V3, V4, V5, V7, V9 (now V8), V11 (now V9), and V13 (now V10), have been removed.<br>• Lupus anticoagulant assessments for V3, V4, V5, V7, V9 (now V8), V11 (now V9), and V13 (now V10), have been removed.<br>Clarified that both the C-SSRS and Self-Harm Supplemental Form are completed at each visit. | To reduce patient burden with less study visits and venipuncture, assessments that are unlikely to produce additional meaningful data beyond what is already known for baricitinib were removed.<br><br>Added text to clarify that both the C-SSRS and Self-Harm Supplemental Form are required to reduce risk for missing data. |
| Section 5.1 – Figure JAIM.1. | Figure was updated to remove visits as above. | Updated to be consistent with updated Schedule of Activities. |
| Section 6.1 – Inclusion Criteria | Hormonal contraception dosage forms were corrected from oral, intravaginal, or transdermal to oral, injectable, or implantable | Updated to correct a typographical error |
| Section 7.1.1 - Packaging and Labelling | It was clarified that patients will be instructed to | Text was clarified to minimize potential risk for |

| | | |
|---|---|---|
| | take 2 tablets, 1 tablet from 2 different bottles, each day. | errors |
| Section 7.2.1 – Selection and Timing of Doses | Text specifying 1 tablet from each bottle was removed. | Text was removed to reduce potential confusion particularly at longer visit intervals when more than 2 bottles of study drug may be provided. |
| Section 7.3 - Blinding | Text was added to include site personnel and patients and to specify the continuation of the blind relative to additional trials | Text was added to specify that site personnel and patients would remain blinded after database lock of trials JAHZ and JAIA |

**Amendment Summary for Protocol I4V-MC-JAIM Amendment (a)**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 8.1.1 - Temporary Interruption of Investigational Product; Table JAIM.4. Criteria for Temporary Interruption of Investigational Product | Delete interruption criterion based on eGFR <30. | Because of study blinding, "baseline" eGFR will not be known to investigators (For patients assigned to baricitinib in originating study, eGFR from baseline in the originating study is used. For patients assigned to placebo in originating study, eGFR from baseline in JAIM is used). The more conservative criteria (eGFR <40) will be used. |
| Section 9.4.6 - Hepatitis B Virus (HBV) DNA Monitoring | Text was modified to describe HBV monitoring every 6 months after W60. | Text was added to account for the increased interval of HBV testing after Week 60 due to the removal of study visits V8, V10, V12, and V14. |
| Section 10.3.1 – General Statistical Considerations | Text was updated to include efficacy and specify that integrated data will be assessed. | Updated to clarify that the safety and efficacy data would be (in addition to) assessed in the context of integrated data |
| Section 10.3.3 – Efficacy Analyses | Wording was updated to include the ANCOVA model. | ANCOVA model was needed to analyze SLICC/ACR responses. |
| Section 10.3.3.1 – Missing Data Imputation | Last Observation Carried Forward was changed to Modified Last Observation Carried Forward. | Text was changed to specify the methodology used in which to impute missing data. |
| Section 10.3.4 – Safety Analyses | Text added specifying how the endpoints of safety and tolerability would be analyzed and to outline safety measures to be reported specifically for JAIM. | To specify that the primary endpoints would be analyzed as a part of the integrated safety analyses for SLE and as such, will be reflected in the integrated safety analysis plan for SLE and to outline the categorical safety measures to be reported specifically for JAIM. |
| Section 10.3.4.1 – Adverse Events | PSAP analysis was removed | PSAP and iSAP are redundant terminology. |
| Section 10.3.4.3 - Vital Signs, Physical Findings, and Other Safety Evaluation | Text specifying that further analysis will be planned in the SAP iSAP was removed | Upon review of the section, the text was deemed unnecessary and was removed. |

# Revised Protocol Sections

| | |
|---|---|
| **Note:** | Deletions have been identified by ~~strikethroughs~~.<br>Additions have been identified by the use of underscore. |

# 1. Synopsis

## Objectives and Endpoints

| | |
|---|---|
| • To evaluate the long-term corticosteroid sparing effect of baricitinib 4-mg or 2-mg QD. | • ~~Proportion of patients receiving >7.5 mg prednisone (or equivalent) at baseline able to decrease dose by ≥25% to a prednisone equivalent dose of ≤7.5 mg/day maintained for at least 12 weeks through Week 156.~~<br>• Change from baseline in prednisone dose through Week 156.<br>• ~~Proportion of patients taking corticosteroids at baseline able to discontinue use through Week 156.~~ |

**Table JAIM.1. Schedule of Activities**

| | Baseline | Treatment Phase: Study Drug Administration | | | | | | | | | | | | | | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **~~V8~~** | **V9~~8~~** | **~~V10~~** | **V11~~9~~** | **~~V12~~** | **V~~13~~1 0** | **~~V14~~** | **V~~15~~1 1** | **ET[a]** | **V801[b]** |
| **Study Week** | **W0** | **W4** | **W12** | **W24** | **W36** | **W48** | **W60** | **~~W72~~** | **W84** | **~~W96~~** | **W108** | **~~W120~~** | **W132** | **~~W144~~** | **W156** | **Any** | **W160 or last dose + 4 weeks** |
| **Study Day** | **1** | **29 ± 4** | **85 ± 7** | **169 ± 10** | **253 ± 10** | **337 ± 10** | **421 ± 10** | **~~505 ± 14~~** | **589 ± 14** | **~~673 ± 14~~** | **757 ± ± 14** | **~~841 ± ± 14~~** | **925 ± ± 14** | **~~1009 ± 14~~** | **1093 ± 14** | **Any** | **Last dose + 28 ± 5 days** |
| **Procedure** | | | | | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | | |
| Abbreviated patient demographics | X | | | | | | | | | | | | | | | | |
| Symptom-directed physical examination | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| Weight | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| Waist circumference | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| Vital signs (BP[d], pulse, temperature) | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| Review JAIM inclusion/exclusion criteria | X | | | | | | | | | | | | | | | | |
| Adverse events | X[e] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| Concomitant medications | X[f] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| C-SSRS[g] & /Self-Harm Supplement Form | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| Self-Harm Follow-up Form[h] | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| QIDS-SR16[i] | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |

| | Baseline | Treatment Phase: Study Drug Administration | | | | | | | | | | | | | | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **~~V8~~** | **V9~~8~~** | **~~V10~~** | **V11~~9~~** | **~~V12~~** | **V~~13~~1 0** | **~~V14~~** | **V~~15~~1 1** | **ET[a]** | **V801[b]** |
| **Study Week** | **W0** | **W4** | **W12** | **W24** | **W36** | **W48** | **W60** | **~~W72~~** | **W84** | **~~W96~~** | **W108** | **~~W120~~** | **W132** | **~~W144~~** | **W156** | **Any** | **W160 or last dose + 4 weeks** |
| **Study Day** | **1** | **29 ± 4** | **85 ± 7** | **169 ± 10** | **253 ± 10** | **337 ± 10** | **421 ± 10** | **~~505 ± 14~~** | **589 ± 14** | **~~673 ± 14~~** | **757 ± ± 14** | **~~841 ± ± 14~~** | **925 ± ± 14** | **~~1009 ± 14~~** | **1093 ± 14** | **Any** | **Last dose + 28 ± 5 days** |
| Log in IWRS | X | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| Randomization[j] | X | | | | | | | | | | | | | | | | |
| Investigational product dispensed | X | | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | | | |
| Investigational product returned and compliance assessed | | X[k] | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | |
| **Physician-Completed Scales[l]** | | | | | | | | | | | | | | | | | |
| SLEDAI-2K | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| BILAG2004 | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| Physician's Global Assessment of Disease Activity | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| SLEDAI Flare Index | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| SLICC Damage Index | X[c] | | | | | X | | | | ~~X~~ | | | | ~~X~~ | X | X | |
| CLASI | X[c] | X | X | X | X | X | | ~~X~~ | | ~~X~~ | | ~~X~~ | | ~~X~~ | X | X | X |
| 28-Tender and Swollen Joint Counts | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| **Patient-Reported Questionnaires** | | | | | | | | | | | | | | | | | |
| Worst Pain NRS[i] | X | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| Worst Joint Pain NRS[i] | X | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| Worst Fatigue NRS[i] | X | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |

| | Baseline | Treatment Phase: Study Drug Administration | | | | | | | | | | | | | | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **~~V8~~** | **V9~~8~~** | **~~V10~~** | **V11~~9~~** | **~~V12~~** | **V~~13~~1 0** | **~~V14~~** | **V~~15~~1 1** | **ET[a]** | **V801[b]** |
| **Study Week** | **W0** | **W4** | **W12** | **W24** | **W36** | **W48** | **W60** | **~~W72~~** | **W84** | **~~W96~~** | **W108** | **~~W120~~** | **W132** | **~~W144~~** | **W156** | **Any** | **W160 or last dose + 4 weeks** |
| **Study Day** | **1** | **29 ± 4** | **85 ± 7** | **169 ± 10** | **253 ± 10** | **337 ± 10** | **421 ± 10** | **~~505 ± 14~~** | **589 ± 14** | **~~673 ± 14~~** | **757 ± ± 14** | **~~841 ± ± 14~~** | **925 ± ± 14** | **~~1009 ± 14~~** | **1093 ± 14** | **Any** | **Last dose + 28 ± 5 days** |
| Patient's Global Impression of Severity (PGI-S)[i] | X | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| SF-36v2[i] | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| FACIT-Fatigue[i] | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| WPAI-Lupus[i] | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| EQ-5D-5L[i] | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| **Laboratory Tests** | | | | | | | | | | | | | | | | | |
| HBV DNA[m] | X[c] | | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| Urine pregnancy test[n] | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| Clinical chemistry[o] | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| Fasting lipid panel[p] | X[c] | | X | X | | X | | ~~X~~ | | ~~X~~ | X | ~~X~~ | | | X | | |
| Hematology | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| ~~Iron studies (iron, TIBC, and ferritin)~~ | ~~X~~[e] | | | | | ~~X~~ | | | | ~~X~~ | | | | | ~~X~~ | | |
| Urinalysis | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| Urine Creatinine and Protein, Ratio | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| ANA | X[c] | | | | | X | | | | ~~X~~ | | | | | X | | |
| Anti-dsDNA | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |

| | Baseline | Treatment Phase: Study Drug Administration | | | | | | | | | | | | | | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **~~V8~~** | **V9~~8~~** | **~~V10~~** | **V11~~9~~** | **~~V12~~** | **V~~13~~1 0** | **~~V14~~** | **V~~15~~1 1** | **ET[a]** | **V801[b]** |
| **Study Week** | **W0** | **W4** | **W12** | **W24** | **W36** | **W48** | **W60** | **~~W72~~** | **W84** | **~~W96~~** | **W108** | **~~W120~~** | **W132** | **~~W144~~** | **W156** | **Any** | **W160 or last dose + 4 weeks** |
| **Study Day** | **1** | **29 ± 4** | **85 ± 7** | **169 ± 10** | **253 ± 10** | **337 ± 10** | **421 ± 10** | **~~505 ± 14~~** | **589 ± 14** | **~~673 ± 14~~** | **757 ± ± 14** | **~~841 ± ± 14~~** | **925 ± ± 14** | **~~1009 ± 14~~** | **1093 ± 14** | **Any** | **Last dose + 28 ± 5 days** |
| Autoantibodies (anti-Smith, anti-RNP, anti-SSA/Ro, anti-SSB/La) | X[c] | | | ~~X~~ | | X | | ~~X~~ | | ~~X~~ | | ~~X~~ | | | X | | |
| Anti-cardiolipin antibodies IgG, IgA, IgM) | X[c] | | ~~X~~ | ~~X~~ | ~~X~~ | X | ~~X~~ | ~~X~~ | ~~X~~ | ~~X~~ | ~~X~~ | ~~X~~ | ~~X~~ | ~~X~~ | X | X | X |
| Anti-beta2 glycoprotein-I (IgG, IgM) | X[c] | | ~~X~~ | ~~X~~ | ~~X~~ | X | ~~X~~ | ~~X~~ | ~~X~~ | ~~X~~ | ~~X~~ | ~~X~~ | ~~X~~ | ~~X~~ | X | X | X |
| Lupus anticoagulant (dRVVT) | X[c] | | ~~X~~ | ~~X~~ | ~~X~~ | X | ~~X~~ | ~~X~~ | ~~X~~ | ~~X~~ | ~~X~~ | ~~X~~ | ~~X~~ | ~~X~~ | X | X | X |
| Complement (C3 and C4) | X[c] | X | X | X | X | X | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | ~~X~~ | X | X | X |
| Immunoglobulins (IgG, IgA, IgM) | X[c] | | | | | X | | | | ~~X~~ | | | | | X | X | X |
| ~~Lymphocyte subsets (T, B, NK, and T-cell subsets)~~ | ~~X~~[e] | | | | | ~~X~~ | | | | ~~X~~ | | | | | ~~X~~ | ~~X~~ | ~~X~~ |
| Exploratory storage samples (serum and plasma) | X[c] | | | | | X | | | | ~~X~~ | | | | ~~X~~ | X | | |
| Exploratory storage samples (urine) | X[c] | | | | | X | | | | ~~X~~ | | | | ~~X~~ | X | | |

Abbreviations: ANA = antinuclear antibody; BILAG = British Isles Lupus Assessment Group; BP = blood pressure; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; C-SSRS = Columbia-Suicide Severity Rating Scale; dRVVT = Dilute Russell's Viper Venom Time; dsDNA = double-stranded deoxyribonucleic acid; EQ-5D-5L = 5-level EuroQol-5 Dimensions; ET = early termination; FACIT = Functional Assessment of Chronic Illness Therapy; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBV DNA = hepatitis B virus deoxyribonucleic acid; Ig = immunoglobulin; IWRS = interactive web-response system; ~~NK = natural killer;~~ NRS = numerical rating scale; PGI-S = Patient's Global Impression of Severity; RNP = ribonucleoprotein; QIDS-SR16 =16-Item Quick Inventory of Depressive Symptomatology-Self Report; SF-36v2 = Short-Form 36-item Health Survey version 2; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC = Systemic Lupus Erythematosus International Collaborating Clinics; SSA/Ro = Sjögren's-Syndrome-related antigen A; SSB/La = Sjögren syndrome type B antigen/Lupus La protein; ~~TIBC = total iron binding capacity;~~ V = visit; W = week; WPAI = Work Productivity and Activity Impairment.

[a] Patients who discontinue from investigational product (IP) early should complete the ET visit and proceed to post-treatment follow-up.

[b] All patients should return for Visit 801, a post-treatment follow-up visit, 28±5 days after the last dose of IP. Patients who discontinue IP but remain in the study for at least 28±5 days without IP, can combine their Visit 11~~15~~/ET with their Visit 801 (post-treatment follow-up visit).

[c] Visit 1 of Study JAIM should occur on the same day as the final visit of the originating study. Assessments/procedures required for both Visit 1 of Study JAIM and the final visit of the origination study should only be performed once.

[d] At each time point, 3 replicate readings should be made at approximately 30- to 60-second intervals. Blood pressure is recorded as the average of these 3 readings. A single pulse measurement should be made simultaneously with at least 1 of the readings at each time point (Section 9.4.1. for details on vital signs).

[e] Adverse events that are ongoing at the completion of the originating trial should be reported as pre-existing conditions at Visit 1 for Study JAIM.

[f] Concomitant medications ongoing at the completion of the originating trial should be reported as concomitant medications at Visit 1 for Study JAIM.

[g] Suicidal ideation and behavior subscales excerpt; adapted for the assessment of 11 preferred ideation and behavior categories. C-SSRS and Self-Harm Supplemental Form should be completed after collection of unsolicited adverse events.

[h] The Self-Harm Follow-up Form is only required if triggered by the Self-Harm Supplement Form.

[i] Patient-reported questionnaires will be administered via an on-site electronic clinical outcome assessment (eCOA) device and should be administered prior to any clinical assessments.

[j] At Visit 1, patients randomized to active treatment during the originating study will be assigned to the same, blinded dose of baricitinib in Study JAIM. Patients randomized to placebo during the originating study will be randomized 1:1 to blinded baricitinib 2-mg or baricitinib 4-mg. Dose adjustment for patients newly randomized to baricitinib, if necessary, will be based on the last available estimated glomerular filtration rate (eGFR) from the originating study.

[k] New bottles of study drug tablets will NOT be dispensed at Week 4 (Visit 2) unless the patient requires additional tablets for the next visit window. Patients will continue to take tablets from the bottles dispensed at Week 0 (Visit 1). Compliance will be checked, and the bottles with remaining tablets will be returned to the patient for dosing the following visit window. If new bottles are required, the patient will not have their previous bottles returned.

[l] SLE assessments must be completed by a physician and will be documented on an eCOA (electronic clinical outcome assessment) device.

[m] Patients who were enrolled in the originating study with positive HBcAb and negative HBV DNA, regardless of HBsAb status or level, must undergo HBV DNA testing per the schedule of events (see Section 9.4.6 for details of HBV DNA monitoring).

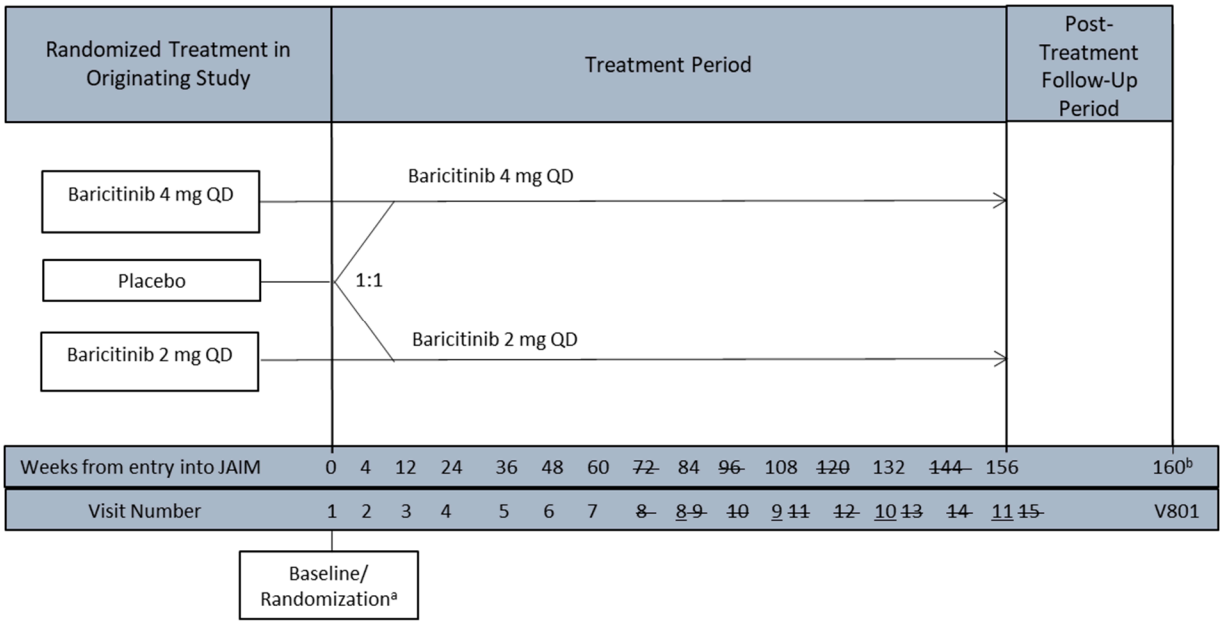
[n] For all women of childbearing potential, urine pregnancy tests (local laboratory) will be performed at all study visits. If required per local regulations and/or institutional guidelines, pregnancy testing can occur more frequently during the study treatment period. Unscheduled urine pregnancy tests may also be performed if a regular monthly menstruation is absent in a woman of childbearing potential.

[o] Clinical chemistry will include the following value calculated from serum creatinine: eGFR (calculated using the Modification of Diet in Renal Disease [MDRD] isotope dilution mass spectrometry traceable method).

[p] 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, the sample should still be collected. This will not be considered a protocol violation.

## 5.1. Overall Design

…




…

## 6.1. Inclusion Criteria

…

**Patient Characteristics**

…

- Progestogen-only containing hormonal contraception associated with inhibition of ovulation: oral, ~~intravaginal~~ injectable, or ~~transdermal~~ implantable

### 7.1.1. Packaging and Labelling

…

**Patients will be instructed to take 2 tablets, 1 tablet from 2 different ~~each~~ bottles, each day**.

All investigational products will be stored, inventoried, reconciled, and destroyed according to applicable regulations. Investigational products will be supplied by Lilly or its representative in accordance with current Good Manufacturing Practices and will be supplied with lot numbers, expiry dates, and certificates of analysis (as applicable).

### 7.2.1. Selection and Timing of Doses

Investigational product will be provided to patients at Visit 1.

Two tablets ~~(1 tablet from each bottle)~~ should be taken orally each day, without regard to food and, if possible, at approximately the same time every day.

### 7.3. Blinding

This is a double blind study. After database lock of trials JAHZ and JAIA, site personnel and patients will remain blinded to treatment assignment. ~~To preserve the blinding of the study, a minimum number of Lilly personnel who are not directly involved with investigational sites will see the randomization table and treatment assignments before the study is complete.~~

### 8.1.1. Temporary Interruption of Investigational Product

…

**Table JAIM.4. Criteria for Temporary Interruption of Investigational Product**

| Hold Investigational Product if the Following Abnormalities Occur: | Investigational Product May be Resumed When: |
|---|---|
| WBC count <2000 cells/µL (<2.00 x $10^3$/µL or <2.00 GI/L) | WBC count ≥2500 cells/µL (≥2.50 x $10^3$/µL or ≥2.50 GI/L) |
| ANC <1000 cells/µL (<1.00 x $10^3$/µL or <1.00 GI/L) | ANC ≥1200 cells/µL (≥1.2 x $10^3$/µL or ≥1.2 GI/L) |
| Lymphocyte count <300 cells/µL (<0.30 x $10^3$/µL or <0.30 GI/L) | Lymphocyte count ≥500 cells/µL (≥0.50 x $10^3$/µL or ≥0.50 GI/L) |
| Platelet count <25,000/µL (<25 x $10^3$/µL or <25 GI/L) | Platelet count ≥50,000/µL (≥50 x $10^3$/µL or ≥50 GI/L) |
| eGFR <40 mL/min/1.73 $m^2$ for patients with eGFR ≥60 mL/min/1.73 $m^2$ | eGFR ≥50 mL/min/1.73 $m^2$ |
| ~~eGFR <30 mL/min/1.73 $m^2$ for patients with eGFR ≥40 to <60 mL/min/1.73 $m^2$~~ | ~~eGFR ≥40 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 |
| Infection that, in the opinion of the investigator, merits the IP being withheld[a] | Resolution of infection that, in the opinion of the investigator, merits the IP being restarted |

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.

[a] Permanent discontinuation of IP should be considered for patients who develop a serious infection that, in the opinion of the investigator, would pose an unacceptable risk if IP were resumed.

### 9.4.6. Hepatitis B Virus (HBV) DNA Monitoring

Patients who were hepatitis B core antibody positive at screening for the originating study will continue to require Hepatitis B virus (HBV) DNA monitoring approximately every 3 months up to Week 60, thereafter reducing to every 6 months, regardless of their hepatitis B surface antibody status.

### 10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. A detailed SAP describing the statistical methodologies will be developed by Lilly or its designee.

Depending on the efficacy and health outcomes analysis, baseline may be defined as the last assessment prior to the first dose of active study drug in Study JAIM or as baseline from the originating study. Depending on the analysis, treatment groups can be based on assignment in JAIM, or could be further subdivided based on treatment group assignment in the originating studies.

Some of the efficacy and safety endpoints may be better assessed in the context of ~~combining the safety data~~ integrating data from the originating studies (and possibly other relevant studies). The SAP for this study and the ~~integrated~~ SAPs which specify integrated analyses, ~~(iSAP; which will detail how all Phase 2 and 3 studies will be combined)~~ will include details of which analyses will be performed on JAIM alone and which will be performed in an integrated fashion (including originating studies and possibly other studies). The exact definition of baseline, ~~safety population~~ populations, and treatment groups will depend on the particular analysis (integrated vs. JAIM alone).

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. Adjustment for multiple comparisons will not be made.

Any change to the 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. Additional exploratory analyses of the data will be conducted as deemed appropriate.

### 10.3.3. Efficacy Analyses

Efficacy and health outcomes analyses will generally be summarized using descriptive statistics. The number and percentage of patients maintaining or achieving a categorical efficacy or health outcomes response will be summarized. The mean change from baseline~~s~~ of ~~the~~ continuous measures will be summarized using mixed model repeated measures (MMRM), except for SLICC/ACR which will be analyzed using analysis of covariance (ANCOVA)~~mixed model repeated measures~~. The MMRM model will include treatment, region, visit, treatment-by-visit interaction as fixed categorical effects, and baseline value and baseline value-by-visit interaction

as fixed continuous effects to estimate change from baseline across postbaseline visits. Additional factors, such as originating study (JAHZ, JAIA) and originating study stratification factors, may also be included in the model. The ANCOVA model for analyzing SLICC/ACR will be based on the same model factors as the MMRM analyses, excluding visit and value-by-visit interaction terms. Additional details, including any outcomes that will utilize statistical inference and use of originating study data, will be provided in the JAIM SAP or the integrated efficacy analysis plan (IEAP), which will define how the efficacy and health outcomes data from the Phase 2 and 3 studies will be analyzed when combined.

#### 10.3.3.1. Missing Data Imputation

Missing data will be imputed at specified time points utilizing methodologies, including the following:

- Modified Last Observation Carried Forward: The last observed value (non-missing value) is used to fill in missing values at a later time point.
- Nonresponder imputation: Patients who discontinue treatment early will be defined as nonresponders.

The SAP will stipulate which methodology will be utilized for specific analyses.

### 10.3.4. Safety Analyses

Safety assessments will include AEs, laboratory analytes, vital signs, and questionnaires to assess the existence and severity of depression.

The primary endpoints of safety and tolerability will be analyzed as part of the integrated safety analyses for SLE. All details of these integrated analyses will be contained in the integrated safety analysis plan for SLE.

~~The c~~Categorical safety measures for JAIM alone will be summarized with percentages, and incidence rates where appropriate. The following events will be reported specifically for JAIM:

- patients who permanently discontinue from study drug due to adverse events,
- patients reporting SAEs during the treatment period,
- patients with at least 1 temporary interruption of study drug
- patients who permanently discontinued study drug prior to full study completion

~~The mean changes of the continuous safety measures will be summarized using descriptive statistics. Shift tables for select categorical safety analyses (for example, 'high' or 'low' laboratory results) will also be produced.~~ Additional details, including any measures that will utilize inferential statistics will be specified in the SAP and/or~~, program safety analysis plan (PSAP) or~~ iSAP.

### 10.3.4.1. Adverse Events

…

Serious adverse events (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. Potential AESIs will be identified by a standardized MedDRA query or a Lilly-defined MedDRA query. Details of the AESIs (including but not limited to those listed in Section 9.2.2) and analysis will be documented in the ~~SAP,~~ iSAP ~~or PSAP.~~

…

### 10.3.4.3. Vital Signs, Physical Findings, and Other Safety Evaluation

…

The incidence and average duration of investigational product interruptions will be summarized and compared descriptively among treatment groups. Various techniques may be used to estimate the effects of investigational product interruptions on safety measures.

~~Further analyses may be performed and will be planned in the SAP or iSAP.~~

## Appendix 1 Abbreviations and Definitions

| | |
|---|---|
| **ANCOVA** | analysis of covariance |
| **MMRM** | mixed model repeated measures |

## Appendix 2 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 platelet volume | Alkaline phosphatase (ALP) |
| Mean cell hemoglobin (MCH) | Alanine aminotransaminase (ALT)/serum glutamic pyruvic transaminase |
| Mean cell hemoglobin concentration (MCHC) Leukocytes (WBC) | Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase |
| Absolute count of | Blood urea nitrogen (BUN) |
| Neutrophils, segmented | |
| Neutrophils, juvenile (bands) | Creatinine |
| Lymphocytes | Estimated glomerular filtration rate (eGFR)[c] |
| Monocytes | Uric acid |
| Eosinophils | Calcium |
| Basophils | Glucose[d] |
| Platelets | Albumin |
| Cell morphology | Creatine phosphokinase (CPK) |
| Differential and blood smear[e] | Total protein |
| ~~Lymphocyte subsets (T, B, NK, and T-cell subsets)~~ | ~~Iron studies (iron, TIBC, and ferritin)~~ |
| | **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 | |
| Urine Protein | |
| Glucose | **Other Tests** |
| Ketones | Urine pregnancy test (females only)[g] |
| Blood | HBV DNA[i] |
| Bilirubin | Serum immunoglobulins (IgG, IgA, IgM) |
| Urobilinogen | Stored serum, plasma, and urine samples for exploratory biomarker analyses |
| Leukocyte esterase | Lupus anticoagulant (dRVVT) |
| Nitrite | Complement C3 and C4 |
| Microscopic examination of sediment[h] | Anti-beta2 glycoprotein-I (IgG, IgM) |
| Urine creatinine | |
| Urine protein | |
| Urine protein-creatinine ratio | |

**Autoantibodies**
Anti-nuclear antibody (ANA)
Anti-double-stranded DNA (anti-dsDNA) antibody
Autoantibodies (anti-RNP, anti-Sm, anti-SSA/Ro, anti-SSB/La)
Anti-cardiolipin antibodies IgG, IgA, IgM

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Abbreviations: anti-dsDNA = anti-double-stranded deoxyribonucleic acid; dRVVT = Dilute Russell's Viper Venom Time; HBcAb = hepatitis B core antibody; HBV DNA = hepatitis B virus deoxyribonucleic acid; Ig = immunoglobulin; ~~NK = natural killer;~~ RBC = red blood cells; SSA/Ro = Sjögren's-Syndrome-related antigen A; SSB/La = Sjögren syndrome type B antigen/Lupus La protein; ~~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 hematology, and urinalysis panels may be performed at the discretion of the investigator.

[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, Weeks 12, 24, 48, 108~~, 72, 96, 120~~ and 156. Patients should not eat or drink anything except water for 12 hours prior to test. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation.

[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, urine pregnancy tests (local laboratory) will be performed at each study visit per the Schedule of Activities.

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

[i] HBV DNA testing will be performed in patients who tested positive for HBcAb in the originating study